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Biological Effects and Exposure Criteria for Radiofrequency Electromagnetic Fields

Recommendations of the
NATIONAL COUNCIL ON RADIATION PROTECTION AND MEASUREMENTS

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Preface

This report is the second of a series concerning radiofrequency electromagnetic (RFEM) radiation that constitutes an extension of the NCRP interest into the subject of non-ionizing radiation. The first report, NCRP Report No. 67, *Radiofrequency Electromagnetic Fields—Properties, Quantities and Units, Biophysical Interaction, and Measurements*, was published in 1981. The report provided a comprehensive discussion of fundamentals, especially those that relate to radiation protection. It provided the basis for future reports, including this one.

Soon after the work on Report No. 67 was begun, the NCRP formed Scientific Committee 53 to prepare a report on the biological effects of RFEM radiation. This scientific committee was also requested to consider the development of recommendations for exposure criteria if the committee felt that such recommendations could be justified on the basis of the adequacy of the biological information. The scientific literature on the biological effects of RFEM radiation is voluminous but of varying scientific quality, and it has taken considerable time to assess it. On the basis of a detailed evaluation, which is reflected in this report, the committee concluded that exposure criteria could be developed in spite of the limitations of the biological information and these too are included in this document.

It needs to be recognized that our understanding of the biological effects of RFEM radiation is still evolving, based on continuing research on this important subject. As a result, it is to be expected that the exposure criteria set out in this report will be evaluated periodically in the future, and possibly revised as new information becomes available. This is a continuing challenge for those involved in radiation protection and one to which the NCRP expects to respond.

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1. Introduction

The radio-frequency electromagnetic (RFEM) spectrum (Table 1.1) is formally defined as waves that range in frequency from >0 to 3×10^{12} Hz (Sams, 1968; ITU, 1981). This report addresses the biological effects of exposure to RFEM fields that range in frequency from 3×10^5 to 10^{11} Hz and in *in-vacuo* wavelength from, respectively, 1000 to 0.003 meters. Included in this range are all shortwave and most microwave frequencies. Waves longer than 1000 m have scattering and absorption properties with respect to the human body that differ greatly from those of waves that approximate the body's physical dimensions; such waves should and will receive independent analysis by other assemblies of experts. RFEM fields that lie near the upper limit of the microwave spectrum (3×10^{11} Hz), and fields of even higher frequency in the sub-millimeter spectrum (3×10^{11} to 3×10^{12} Hz), i.e., fields at wavelengths that range from 3 mm to 300 μm, have received relatively little study in the biological laboratory and are not addressed in this report. However, exposure to far-infrared radiations, which overlap the RFEM spectrum and are defined as wavelengths from 300 to 20 μm (frequencies from 10^{12} to 1.5×10^{13} Hz), has been studied extensively in the laboratory and is covered by separate exposure criteria, at least in the industrial sector.

The lack of quantitative data on the biological effects of RFEM fields has resulted in widespread concern that such exposure poses the risk of injury to health regardless of intensity. Although there are several thousands of reports—scientific papers, books, articles, and newspaper accounts—of widely varying scientific quality that present data or opinion on the biological response to RFEM radiations, no consensus has emerged regarding thresholds and mechanisms of injury at specific absorption rates (*SAR*s) below a few watts per kilogram (W/kg). The wide variation in RFEM-radiation exposure criteria around the world reflects this absence of consensus. An objective analysis of the scientific literature and recommendations for exposure limits by a qualified and unbiased group of experts is sorely needed.

To address this need, the National Council on Radiation Protection and Measurements (NCRP) decided in 1973 to extend its scope of activities to the publication of reports that provide evaluations of the biological effects of non-ionizing radiations and to the publication of

TABLE 1.1—*Frequency bands of the RFEM spectrum*[a]

Band number	Frequency range	Metric subdivision (waves)	Adjectival description	Acronym
1	>0 to 30 Hz	—	Sub-extremely[b] low frequency	SELF[b]
2	30 to 300 Hz	Megametric	Extremely low freqency	ELF
3	0.3 to 3 kHz	—	Voice frequency	VF
4	3 to 30 kHz	Myriametric	Very-low frequency	VLF
5	30 to 300 kHz	Kilometric	Low frequency	LF
6	0.3 to 3 MHz	Hectometric	Medium frequency	MF
7	3 to 30 MHz	Decametric	High frequency	HF
8	30 to 300 MHz	Metric	Very-high frequency	VHF
9	0.3 to 3 GHz	Decimetric	Ultra-high frequency	UHF
10	3 to 30 GHz	Centimetric	Super-high frequency	SHF
11	30 to 300 GHz	Millimetric	Extremely high frequency	EHF
12	0.3 to 3 THz	Decimillimetric	Supra-extremely high frequency[c]	SEHF

[a] From Sams (1968), based on international treaty involving participants in the International Telecommunications Union (ITU, 1981).

[b] Band 1 is a designated band with no official adjectival description and symbol. Suggested entries are shown for this band.

[c] Band 12 has no official adjectival description. A suggested entry is shown for this band.

recommendations aimed at limiting exposures. Because there was very little standardization of quantities and units relating to this field, and because there was considerable confusion between ionizing and non-ionizing radiation, the NCRP felt that, as a prerequisite to the report on biological effects and exposure criteria, a publication was needed on properties, quantities, units, biophysical interactions, and measurements relating to RFEM fields. This first report, NCRP Report No. 67, published in March 1981 (NCRP, 1981), provides a background on the physical parameters and mechanisms of interaction of RFEM fields with matter, a background essential for the interpretation and understanding of the present report. The complexity of the interaction of these fields with biological systems makes it difficult to interpret the large volume of literature on the subject, because a substantial fraction of the research reported in the literature lacks the essential quantitation discussed in NCRP Report No. 67. The biological effects of exposure to RFEM fields depend on many factors that complicate

the interpretation of the literature and the specification of appropriate exposure limits.

Unlike ionizing radiation, RFEM radiation must be specified in terms of carrier frequency, modulation, electric-field and magnetic-field strengths (or power density when applicable), and zone of irradiation (near or far field). Also complicating the task of recommending exposure guides is the fact that unrestricted exposure of the body to a plane-wave or a multipath field at a given intensity can have results far different from those of partial-body exposure at the same intensity. Unlike ionizing radiation, the spatially averaged field strength, depending on the volume of space over which the fields are averaged, may vary for a given body from practically zero to levels far exceeding any proposed limit on exposure. This wide variation of field strengths necessitates the use of exclusion clauses in the specified exposure criteria, as discussed in Section 17.

This report, which begins with a discussion of fundamental studies at the molecular level in Section 2, presents a review of the subject matter covered in NCRP Report No. 67 on mechanisms of interaction of RFEM fields with tissue. The discussion continues to progressively larger scales of interaction, beginning with macromolecular and cellular effects in Section 3, chromosomal and mutagenic effects in Section 4, and carcinogenic effects in Section 5. The scope of the subject matter is then expanded to include systemic effects such as those on reproduction, growth, and development in Section 6, hematopoiesis and immunology in Section 7, endocrinology and autonomic nervous function in Section 8, cardiovascular effects in Section 9 and cerebrovascular effects in Section 10. The discussion in Section 10 places strong emphasis on the blood-brain barrier, which has received considerable attention in recent years.

Another controversial area based on many conflicting reports—the interaction of electromagnetic fields with the central nervous system and special senses—is discussed in Section 11. Some of the more interesting and controversial effects that have received widespread attention, such as frequency and intensity "windows," are discussed. Section 11 concludes with a discussion of neurological effects, which include the peripheral neuromuscular system. Some of the more sensitive biological end points, those associated with behavior, are discussed in Section 12; these end points contrast greatly with the apparently insensitive biological endpoint of cataractogenesis discussed in Section 13. In Section 12, a thermoelastically mediated interaction, which has received widespread attention over the past decade, is discussed as an auditory neural effect, and it is a phenome-

non that deserves special attention. This interesting phenomenon would never have been clearly understood without the development of a quantitative argument based on the material presented in NCRP Report No. 67.

Probably of greatest importance in terms of the effects of RFEM radiations on human populations are the epidemiological studies discussed in Section 14. Thermoregulation is discussed in Section 15 and is an especially important subject because irradiation of an organism can result in hyperthermia, which is responsible for many reported effects. Hyperthermia, as such, is also extremely important because it is the basis for the use of shortwave or microwave radiation as an adjunct to the treatment of cancer, as reviewed in detail in Section 16.

Because the major purpose of this report is to interpret the literature in terms of health and safety of human beings in an RFEM environment, the human exposure criteria and rationale provided in Section 17 contain significant conlusions. It was necessary to make difficult decisions in arriving at these conclusions. Because the biological data base is drawn from reports varying in quality from poor to excellent, one must be aware that the data forming the basis of this chapter also vary in quality. Thus, value judgments had to be made concerning the data base discussed in the preceding chapters. Also, practical problems that relate highly localized exposures of the body to low-power radio devices essential to the quality of life and to public safety had to be dealt with by recommending maximal energy-absorption levels in addition to exposure levels.

The history of therapeutic applications of RFEM fields, which is reviewed in Section 16, is important because it covers a period when large numbers of human beings were exposed to highly intense RFEM fields. The history is also illuminating, in relation to today's controversies, in that it points out how misconceptions, that still exist today, were recognized early.

The cutoff date for the literature review of this report is the end of 1982. A few references have 1983 dates. These references were originally abstracts dated 1982 or earlier, but, because the references became available in early 1983 as peer-reviewed reports, these have been included as preferable to the abstracts when it has been possible to do so. Section 17.6, "Considerations possibly influencing the criteria in the future," is included in order to alert the reader about these new developments. References to this subsection are, of course, current references for the period 1983 to 1985.

2. Mechanisms

2.1 Introduction

Interpretation of mechanisms of biological effects of RFEM fields is clouded by a host of conflicting reports and opinions, especially when incident fields are at intensities that fail discernibly to elevate the temperature of the *in-vivo* or *in-vitro* preparation. Even when fields are at intensities associated with reliable elevations of the temperature of the preparation, the possibility that observed effects are due in part to field-specific events cannot be excluded. *Direct* interactions by electric and magnetic fields with biological materials not only are possible but are demonstrable, both *in vitro* and *in vivo* (*cf.* e.g., Saito and Schwan, 1961; Presman, 1970; Walcott *et al.*, 1979).

There is an inherent difficulty in distinguishing and discriminating between thermal and athermal[1] effects, a difficulty borne both of a methodological problem and of faulty inference. When, for example, a complex organism exhibits a behavioral or physiological response to irradiation by an RFEM field, the phenomenological character of the response provides no definitive leverage on which mechanism of three possible classes is operative: thermal, athermal (field-specific), or the two in some combination. This threefold set of possibilities defines the methodological—some would say epistemological—problem. The issue of faulty inference is exemplified by the widely held view in the bioelectromagnetics community that biological responses to weak fields are *a priori* evidence of athermal causation. The hot tip of a small soldering iron that made accidental contact with the epidermis of an unsuspecting technician would result in a dramatic behavioral response. An outside observer equipped with even the most sensitive of thermometric or calorimetric devices would be unable to detect the average elevation of body temperature or the quantity of energy imparted by the brief contact—and if not aware of the instrument of

[1] An athermal effect, referred to as a "field-specific" effect, is an effect not attributable to changes of temperature when RFEM energy is imposed on or absorbed by a medium or system. The term "athermal" is to be preferred over that of "non-thermal". On the basis of newer knowledge, the above definition supersedes that in NCRP Report No. 67 (NCRP, 1981) where this effect is described as a non-thermal effect and is defined as a change in a medium or system that is not directly associated with heat production when electromagnetic energy is absorbed.

stimulation, would doubtless interpret the response as an athermally inspired event. This is not to argue that all "weak-field" responses are provoked by thermal "hot spots"—although some so-called weak-field effects are probably of thermal-hot-spot origin—only that the strength of the incident field has no *a priori* bearing on the question of mechanisms.

An ideal methodology in elucidating mechanisms of interaction is one in which independently detectable thermal and field-specific responses are elicited from the same biological system by the same field. Although this ideal has not been fully realized, Pickard and colleagues have articulated testable theory, have developed novel techniques, and have performed innovative experimentation that collectively exemplify the ideal approach (see, e.g., Pickard and Rosenbaum, 1978; Pickard and Barsoum, 1981; Barsoum and Pickard, 1982a, b).

The biological specimens selected by Pickard and colleagues are algae of the characean family, primitive plants with membranes that exhibit excitability, action potentials, and graded responses to mechanical or electrical stimulation (*cf.* Pickard, 1973; Pickard and Barsoum, 1978). A single, elongate cell is maintained in a circulating fluid medium in a holding device so constructed that part of the cell can be exposed to an RFEM field while a distal part, not exposed, is contacted by electrical recording electrodes. A burst of CW RFEM energy at frequencies ranging from tens of kilohertz to tens of gigahertz has been found to elicit a relatively prolonged electrical response of ostensibly thermal origin, one that persists for some seconds after a burst of radiation is absorbed. An earlier response, an offset of the membrane's resting potential that occurs within a few milliseconds, is a field-specific potential that is elicited by the burst of RFEM energy, but only at carrier frequencies below 10 MHz (Pickard and Barsoum, 1981).

Ironically, the thermal basis of the prolonged response has not been unequivocally demonstrated, but the early offset potential is unarguably the result of non-linear—rectifying—properties of the characean membrane. The quantity of absorbed energy required to elicit the field-specific, offset response is relatively large, a requirement also in the earlier demonstration of pearl-chain formations by Saito and Schwan (1961). Were it not for the continuous cooling of the characean preparations by circulating fluids during periods of irradiation, the preparation would be rapidly denatured by marked elevations of temperature.

Although exemplifying an ideal experiment, the work on the characean organism is of unknown generality. The data are extremely

important, however, in revealing unequivocally that a field-specific effect can and does attend exposure of a biological preparation to an intense burst of CW RFEM radiation, at least at frequencies below 10 MHz, but these data shed little light on questions that attach to another class of athermal interactions, i.e., that observed after acute exposure to relatively very-low-intensity, sinusoidally modulated shortwave and microwave fields (*cf.*, e.g., Bawin *et al.* 1975; Blackman *et al.*, 1980; Adey, 1980). In experiments in which isolated chicken brains were exposed to CW fields or to fields modulated at 3 to 30 Hz, an exodus of calcium ions (Ca^{2+}) from brain materials was observed, but only to modulated fields within a narrow band of frequencies centered near 15 Hz—and only within a narrow range of power densities. Because the average amount of energy captured by brain materials was held constant across frequencies, thermal effects alone could not be responsible for the release of Ca^{2+}. These intriguing experiments are discussed in detail in Section 11.

As a point of departure in the discussion of mechanisms, it can be stated that there is ample evidence that athermal interactions in biological materials are not only possible but have been demonstrated for fields both strong and weak. It must also be stated that the biophysical mechanisms of these athermal events are but poorly understood. Summarized in this section are both data and theory that bear on thermal mechanisms and on the largely uncharted frontier of athermal interactions.

In addition to the discussion on mechanisms in this section, further discussion on mechanisms will be found in Section 11 on RFEM interactions with the nervous system. While this additional discussion could have been incorporated in this section, it has been kept in Section 11 to maintain continuity there.

2.2 Mechanisms of Interaction with Biological Materials

No one debates the potency of thermal effects of RFEM irradiation at high power densities ($\geq$100 mW/cm^2). Controversy arises, however, over interpretations of mechanisms at low power densities ($\leq$10 mW/cm^2) at which athermal biological effects have been demonstrated. Figure 2.1 summarizes data on dielectric dispersion, which have given rise to theories of interactions of RFEM fields with matter.

Schwan (1975, 1977) states that resonant interactions of biopolymers with electric fields are unlikely at frequencies below 100 GHz.

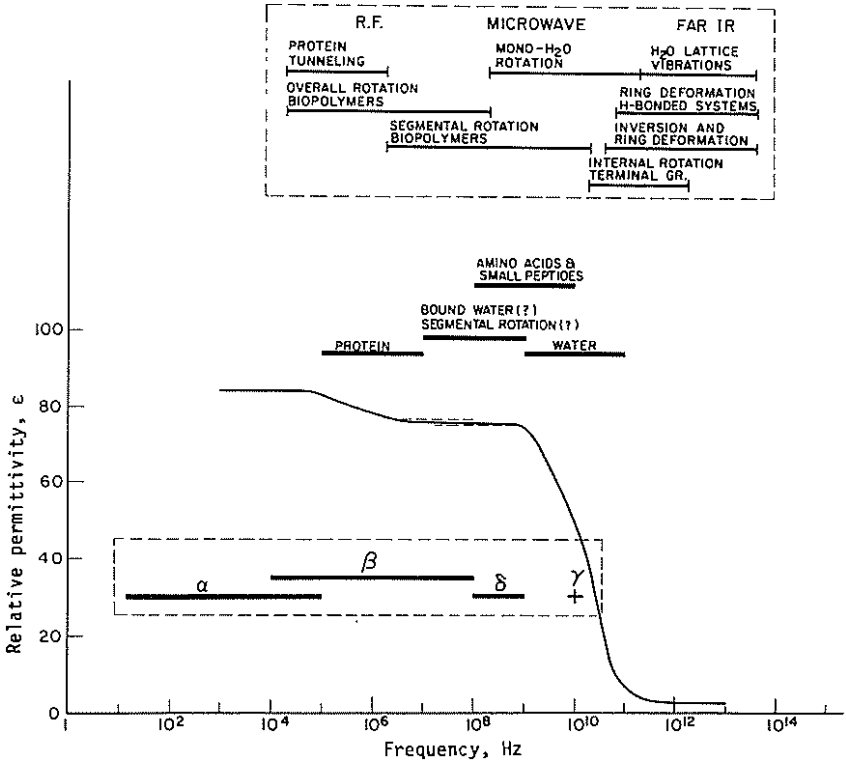


Fig. 2.1. Dielectric dispersion of a typical protein in aqueous solution. Principal dispersion regions for the protein and for water are shown. Dotted lines indicate limiting values for the principal dispersions, which illustrate the presence of the additional dispersion (Allis, 1975). Upper insert: Summary of the expected frequency domains of various types of field-induced interactions in biopolymers (Illinger, 1970). Lower insert: Ranges of characteristic frequencies for various biological systems (Schwan, 1975).

Instead, relaxation effects have been observed. These relaxation effects are degenerated resonances due to the highly viscous properties of the water that suspends the biopolymers *in vivo*.

Schwan (1975) discusses four regions of relaxation of the dielectric-constant curve over a range of frequencies from a few kHz to 20 GHz (Figure 2.2). The relationships in Figure 2.2 accounting for the three relaxation regions as described by Schwan are:

- α region—counter ion relaxation and electrophoretic relaxation
- β region—inhomogeneous structures (Maxwell-Wagner effect)
- γ region (and tail of β region)—Debye-type permanent dipole rotation

The β region dispersion is solely due to inhomogeneous structures, of which, in the cell, the cell membrane and its associated intra- and

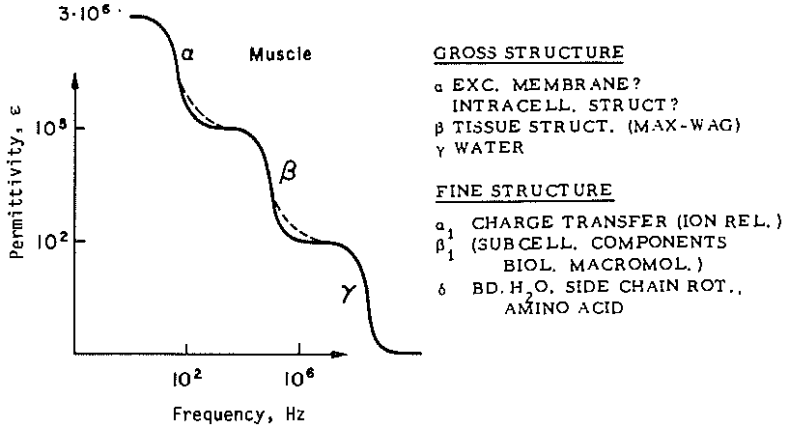


Fig. 2.2. Gross and fine structural relaxation contributions to the dielectric constant of muscle tissue. Dashed lines indicate fine structural contributions. The data and various structural contributions are typical for all tissues of high water content. (From Schwan, 1975.)

extracellular fluids are the most significant (the Maxwell-Wagner effect). The β region of anomalous dispersion was studied intensively in the 1920s through the 1940s, and a clear understanding was developed from Maxwell's theories as modified by Wagner (see, for example, Schwan, 1957). These efforts led to a reasonable explanation of anomalous dispersion in the β region which is centered around 1 MHz and extends downward to about 1 kHz and upward to a few MHz.

The γ dispersion in biological tissues is due solely to free water with its predictable relaxation behavior near 20 GHz. Some contributions are made from rotational motion of the smaller amino acids and from restricted rotation of charged functional groups in polypeptide chains. Protein-bound water has its relaxation region between 300 and 2000 MHz (Schwan 1957, 1975).

At lower frequencies, the α-region dispersion still remains to be completely clarified. However, most authors would prefer to explain α-region behavior as related to relaxation in large structures such as membranes and cellular structures (Takashima and Schwan, 1974). Electrophoretic mobility and counter-ion relaxation result from motion of charged particles in alternating fields. The magnitude of these effects is thought to be trivial.

DeLoor (1968) has summarized the dielectric losses in heterogeneous mixtures containing water (see Figure 2.3). These losses are similar to those described by Schwan (1957, 1975).

Illinger (1970) has summarized the expected frequency domains of various types of field-induced interactions in biopolymers (Figure 2.1). At the lower end of the spectrum (~10^4 to 10^6 Hz), proton tunneling is thought to be a possible mechanism. Figure 2.4 shows that there is

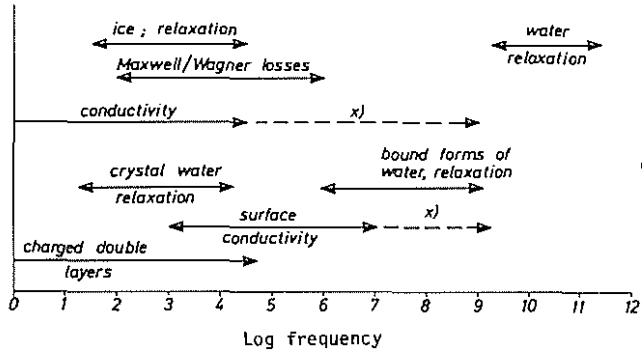


Fig. 2.3. Origin of dielectric losses in heterogeneous mixtures containing water. a. No surface effects. b. Losses due to surface effects. x. Extension for water containing ions. (From De Loor, 1968.)

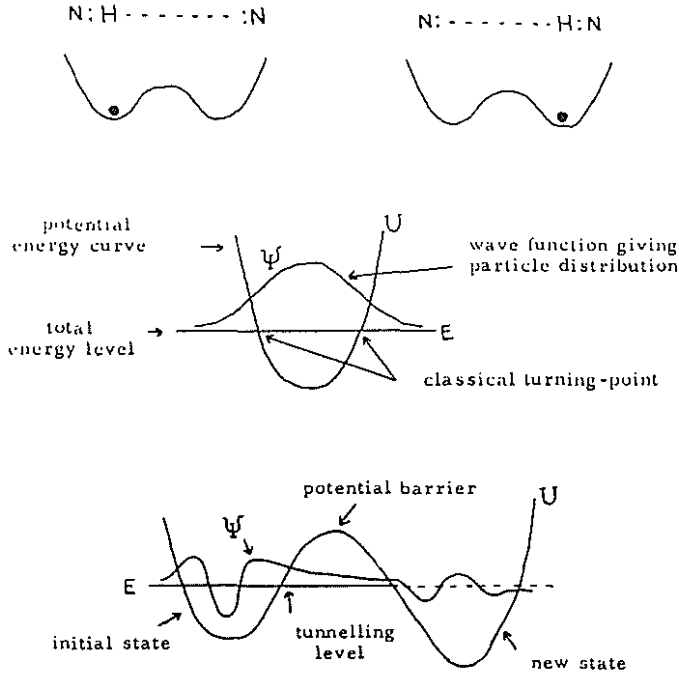


Fig. 2.4. Quantum-mechanical tunnel effect permitting a wave packet to penetrate from one potential well to another. (From Löwdin, 1964a.)

a small but finite probability that a particle may leak through a potential barrier from one "permitted" state to another. Löwdin (1963; 1964a, b) discusses possible mutagenic, carcinogenic, and aging consequences of this quantum mechanical effect, which may result in the transfer of one or two protons in, for example, the hydrogen bonds of the DNA helix.

The overall rotation of biopolymers would also be expected to occur at lower frequencies (10^4 to 10^8 Hz). This type of rotation would probably lead to no specific biological effects.

At slightly higher frequencies (10^6 to 10^{10} Hz), segmental rotation of the biopolymers may occur, which could lead to random-coil rotations that interfere with metabolism or replication, if these disorientations are sufficiently large and long-lasting.

In the 10^8- to 10^{11}-Hz range, mono-water rotation occurs. Most absorption results from the rotational relaxation of mono-water, which may lead to translational and vibrational excitation that ultimately results in an increase in temperature, but probably results in no other specific biological effects. The 2450-MHz frequency of the microwaves often used in radar, microwave ovens, and the majority of the experiments described in this report falls within this range.

Internal rotation of terminal groups would be expected in the 10^{10}- to 10^{12}-Hz range. Amino and hydroxyl groups may be so affected, but hydrogen bonding may hinder this rotation.

Inversion transitions ($-NH_2$) and ring deformations of non-planar ring systems may occur in the 10^{10}- to 10^{14}-Hz range, although in the far-infrared spectrum (10^{11} to 10^{14} Hz) ring deformation of hydrogen-bonded systems may occur.

Illinger believes water-lattice vibrations (quasi-rotational or vibrational motions) may be important in the labilization of the primary and secondary structure of the biopolymers in the frequency range of 10^{11} to 10^{14} Hz. Other researchers believe bound water has a principal dispersion region in the range of 3×10^8 to 2×10^9 Hz (Allis, 1975).

Athermal mechanisms of microwave interaction with matter have been suggested by a number of investigators. Heller and Teixeira-Pinto (1959), for example, observed orientation of subcellular particles and microorganisms along the lines of force when an RFEM field was turned on. They also observed "pearl-chain" formation in a variety of substances (Figure 2.5). However, this work has not been substantiated by other investigators at power densities below those associated with marked thermal effects (*cf.* Schwan, 1970; Michaelson, 1970). Significant effects arising from field-evoked forces require field strengths of about 1 V/cm in the medium, unless cellular dimensions are well in excess of 100 μm (Schwan, 1977).

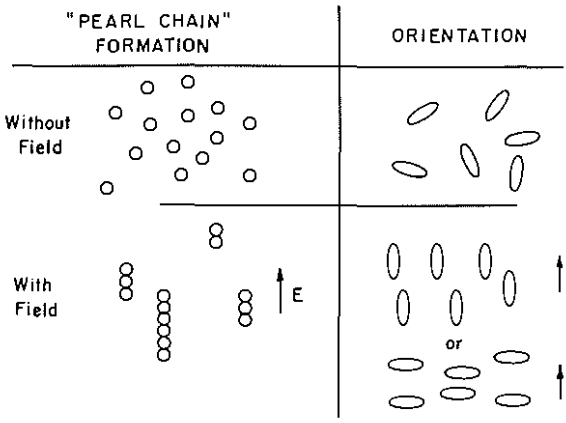


Fig. 2.5. Schematic presentation of some effects of alternating electrical fields on particle and cellular arrangements. (From Schwan, 1975.)

In the mid-microwave range, it appears that rotation is at least the primary, if not the sole, means of energy absorption (Schwan, 1957). At higher frequencies, other mechanisms have been hypothesized and much attention has been paid to the region of 10^{11} to 10^{12} Hz. Fröhlich (1968 a,b) was the first to apply quantum mechanical concepts to this domain. Since his reports were published, several experimenters have obtained data in support of his theories, most notably, Webb and his collaborator (Webb, 1976 abstract; Webb and Stoneham, 1977).

Basically, Fröhlich proposed that many biological systems have collective vibrational modes in the stated frequency region. A supply of energy to these modes (for example, from microwaves or metabolic energy) is channeled into the mode that has the lowest frequency when the rate of energy supply is larger than a critical threshold level. Therefore, some of this supplied energy is not completely thermalized but is stored in a highly ordered fashion. This energy channeling into a single mode shows a great similarity to the low-temperature, Bose-condensation phenomenon of a gas.

The vibrations postulated by Fröhlich are considered to involve regions of biological membranes or large sections of giant molecules such as the H bonds of proteins and DNA. This excitation of coherent modes could have important biological influences, especially if the excited mode represents a giant dipolar electric oscillation. One such consequence might be long- and short-range selective forces. These forces may initiate positional or conformational changes from which a variety of biological effects might result. For example, there may be the selective attraction of molecules (e.g., enzymes and substrates) or

the opening of a section of a DNA complex (Fröhlich 1970, 1975a, b).

Webb and Stoneham (1977) indirectly tested Fröhlich's theory by subjecting *E. coli* and *B. megaterium* to high-frequency RFEM fields. They reported resonances between 7.5×10^{10} and 5×10^{12} Hz in living bacteria with an active metabolism, but not in resting cells, in cell homogenates or in nutrient solutions. They concluded that these resonances are the result of active *in-vivo* metabolic processes. Webb and Dodds (1968) reported inhibition of cell growth in *E. coli* B when they used 136-GHz radiation, and in *E. coli* B_R at 61, 71, and 73 GHz, whereas 68-GHz fields stimulated growth (Webb and Booth, 1969). Grundler *et al.* (1977) reported a resonant effect in the growth rate of yeast cells irradiated by CW fields at power densities of a few mW/cm^2 at ~42 GHz. A spectral fine structure with a width of the order of 10 MHz was observed also. The temperature was in the range between 30.5 and 34 °C but it never varied by more than ±0.5 °C during a given experiment. The authors believe that these results confirm the existence of resonant influences of coherent millimeter waves on biological properties and show also the extreme narrowness of the frequency band for the response.

Further studies continue to confirm the existence of resonance phenomena in biological systems. One of the now more generally recognized of these responses is due to the work of Adey and coworkers (Adey, 1980) and has been confirmed by Joines and Blackman (1980) and Blackman *et al.* (1980). Others (Bush *et al.*, 1981) have not observed or sought for resonance phenomena.

Fröhlich's theories have been reviewed in some detail by Taylor (1981).

Several investigators have applied Fröhlich's concepts to explain other phenomena. Webb (1976) and Webb *et al.* (1976a, b) have reported differences in the Raman spectra of malignant and normal cells, which they relate to Fröhlich's theory of resonances. Cooper (1978) believes that the longer-than-normal ^{31}P and ^{1}H nuclear-magnetic relaxation times of malignant tumor cells, together with their softened phonon spectra, indicate that a condensed phonon state characterizes such cells. Furthermore, Holland (1972) proposes that coherent dipolar oscillations may be responsible for the early stage of the pairing process in meiosis. He further suggests that these oscillations might give rise to selective transport of proteins and RNA and to active transport of inorganic ions across membranes.

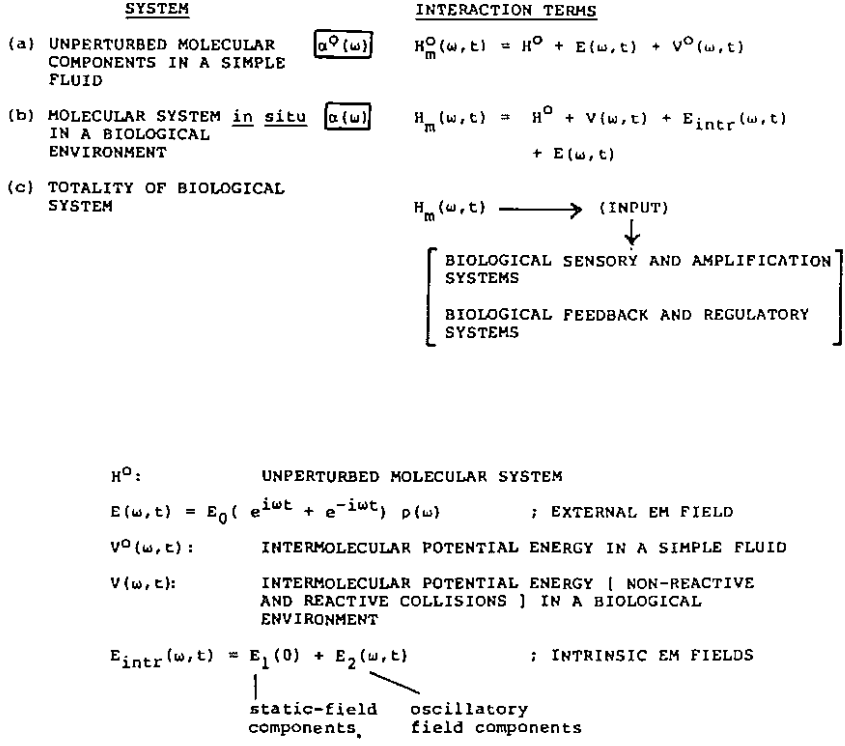
In addition to the work in the Western world, the USSR Academy of Science (1974) has published a number of reports that are supportive of Fröhlich's theories. Resonant effects were found in a wide variety

of organisms and organelles. The millimeter band in the region of 5–8 mm was studied, often at low power densities. Unfortunately, more detail is needed if most of these experiments are to be confirmed.

Illinger (1977) has analyzed the experimental data and theory relating to the millimeter and infrared range of frequencies and has suggested directions and caveats for future research. He categorized the interaction of RFEM fields with biological systems into a hierarchy of three levels as illustrated in Figure 2.6:

1. Unperturbed molecular components in a simple fluid [attenuation coefficient $\alpha^0(\omega)$],
2. The molecular system *in situ* in a biological environment [attenuation coefficient $\alpha(\omega)$], and
3. The totality of the system.

In his analysis of the total attenuation function $\alpha(\omega)$, Illinger has identified a number of contributing factors (Figure 2.7). There is an adiabatic regime up to about 6 GHz where there is the contribution



H^0: UNPERTURBED MOLECULAR SYSTEM

$E(\omega,t) = E_0(e^{i\omega t} + e^{-i\omega t})\, p(\omega)$; EXTERNAL EM FIELD

$V^0(\omega,t)$: INTERMOLECULAR POTENTIAL ENERGY IN A SIMPLE FLUID

$V(\omega,t)$: INTERMOLECULAR POTENTIAL ENERGY [NON-REACTIVE AND REACTIVE COLLISIONS] IN A BIOLOGICAL ENVIRONMENT

$E_{intr}(\omega,t) = E_1(0) + E_2(\omega,t)$; INTRINSIC EM FIELDS

$E_1(0)$: static-field components. $E_2(\omega,t)$: oscillatory field components

Fig. 2.6. Hierarchy of interactions of electromagnetic fields with biological systems. (From Illinger, 1977.)

from rotational relaxation. In the adiabatic (resonant) regime, coherent oscillations principally contribute to the attenuation coefficient. In the range of 600 to 6000 GHz, there are contributions from quasi-lattice vibrations (translational and vibrational). At still higher frequencies, there is a contribution from intramolecular vibrations and electronic transitions. The calculated attenuation function for water in the quasi-lattice region is shown in Figure 2.8.

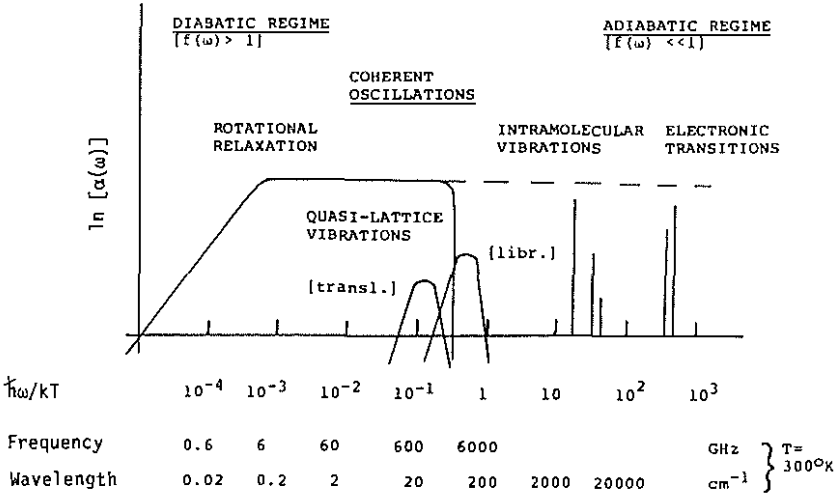


Fig. 2.7. Contributions to the total attenuation function, $\alpha(\omega)$, of a biological system. (From Illinger, 1977.)

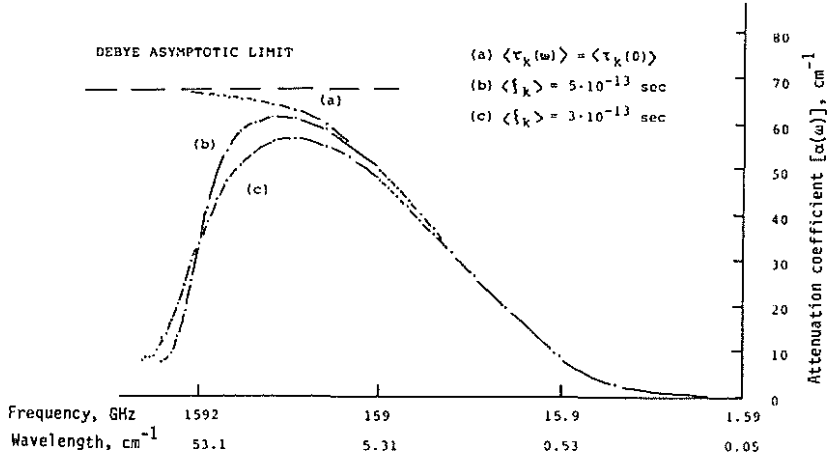


Fig. 2.8. Attenuation function, $\alpha(\omega)$, calculated for water. (From Illinger, 1977.)

The general radiative transfer problem in a biological system can be divided into three regimes: relaxation, quasi-resonance for coherent oscillations, and resonance. These regimes are illustrated in Figure 2.9.

Illinger has schematized three places of leverage for perturbations of the system as shown in Figure 2.10:

1. The membrane's intrinsic electric field, which establishes the metastable state(s),
2. The coherent-regime frequency branch (~10 to 1000 GHz), which is associated with long-range molecular interactions that lead to the coupled biochemical reactions, and
3. The low-frequency branch (~10 to 100 Hz), which is postulated to arise as a consequence of the above two places of leverage.

Illinger (1977) recognized that research in these frequency ranges must be done carefully and is difficult because of several sources of artifacts that cannot be overcome easily. He points out that a major experimental problem is internal reflections of (coherent) millimeter-wave radiation. Another difficulty is that absolute measurements of energy deposition are more difficult at increasingly higher frequencies

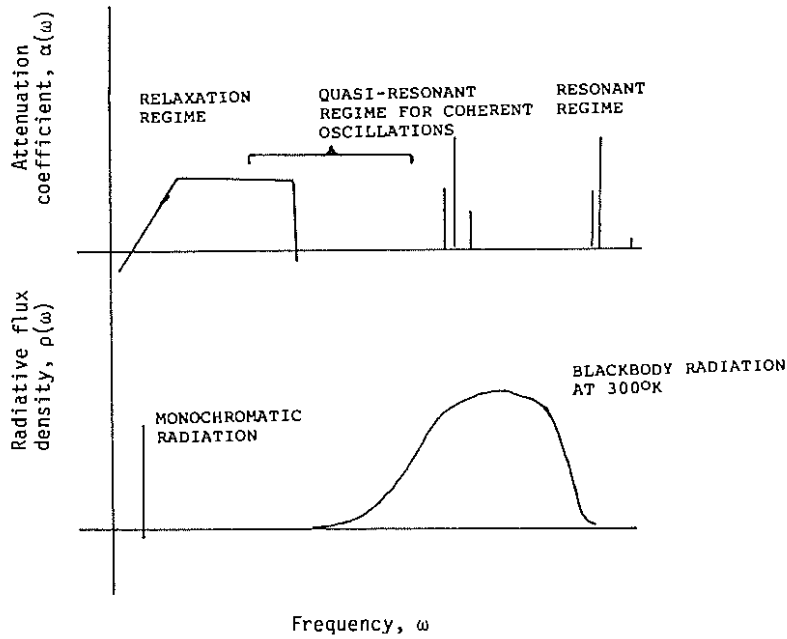


Fig. 2.9 Schematic representation of the general radiative transfer problem in a biological system. (From Illinger, 1977.)

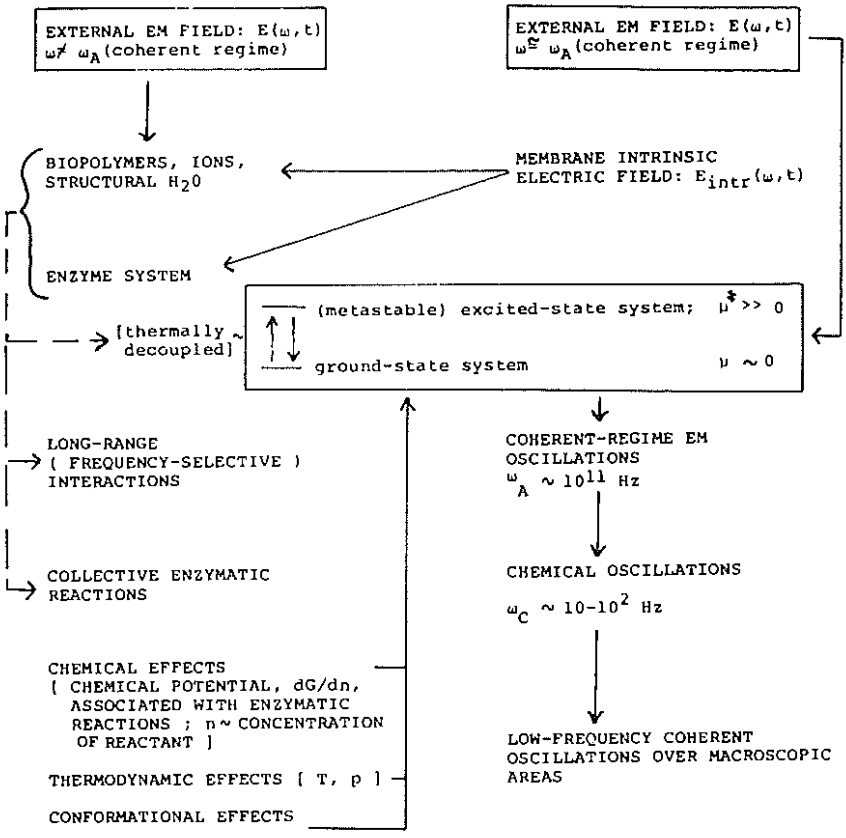


Fig. 2.10. Schematic representation of possible modes of interaction of electromagnetic fields with biological systems. (From Illinger, 1977.)

and that, in consequence, reported power densities may be considerably in error. A third source of difficulty is that the large quasi-resonant attenuations reported in some work may be artifacts because the intensity of absorption depends on the concentration of metastable states, and this concentration is typically small. Other studies (Webb and collaborators, for example) rely on the response spectra of cellular activity as functions of frequency and power density. Here, the quasi-resonant response is taken as evidence for the interaction of the external field with the metastable state. The metastable state is believed to be reflected in the perturbation of the chemical reactions in which the state is involved, and, finally, in an alteration of cellular activity.

Illinger (1977) recommends that direct spectroscopic information be

obtained on transition frequencies and intensities, and on photon-induced coherent-regime transitions. He believes that conventional spectroscopic theory needs to be expanded to give a meaningful analysis of transition probabilities and linewidths. Furthermore, he concludes that to determine reliably these quasi-resonant transitions, which arise from relatively low concentrations of absorbers as compared with the predominant absorption due to free water and structural water, refinement and development of spectroscopic techniques are necessary.

The non-equilibrium, steady-state subsystem determines in part the spectroscopic properties of *in-vivo* biological systems. Illinger (1979, abstract) has stated that of the three spectroscopic observables of this subsystem (the emissivity, the Raman-intensity ratio, and the attenuation function), the emissivity, despite experimental problems with its determination, provides the most direct experimental access to the quantification of the frequency of the Bose-condensation mode and to the measurement of the magnitude of the non-linear terms, which are the crucial parameters of Fröhlich's model.

3. Macromolecular and Cellular Effects

3.1 Effects on Macromolecules

A large body of information on the effects of RFEM radiation on bipolymers has been gathered. Much of this work has been done on the effect of microwaves on enzymes.

Ward (1975) exposed glucose-6-phosphate dehydrogenase from human red-blood cells and yeast, adenylate kinase from rat-liver mitochondria and rabbit muscle, and rat-liver microsomal NADPH cytochrome C reductase to 2450-MHz CW fields at an *SAR* of 42 ± 4 W/kg for 5 min at 25 °C. He found no difference in specific activity ($p \leq 0.005$) as monitored spectrophotometrically with a crossed-beam, exposure-detection system. The rate of energy deposition in the enzyme preparations was significantly higher than that which would be absorbed by man in a 10-mW/cm^2 field at this frequency.

Bini *et al.* (1978) exposed lactate dehydrogenase from beef heart to 3-GHz CW fields at *SAR*s from 30 to 1800 W/kg. The temperature ranged from 25 to 60 °C. In conducting the experiments both thermostatically and thermodynamically, he found no permanent or temporary changes when the energy absorption did not cause discernible elevations of temperature. At higher *SAR*s, the effects were purely thermal in nature.

Yeargers *et al.* (1975) also reported no significant differences in 50 independent measurements of enzyme performances with lysozyme (relatively heat insensitive) and trypsin (relatively heat sensitive). They used 2450-MHz fields at 50 to 100 W and a wide range of temperatures from 30 to 95 °C. After a desired temperature was reached and maintained for 1.5 h, the sample was cooled to room temperature for assaying. There was less than a 1-°C difference between conventionally and microwave-heated samples.

Allis (1975), in looking for field-induced changes in protein flexibility, found no differences in UV difference spectra of bovine serum albumin (Figure 3.1). Gel electrophoresis also showed no differences. He concluded that protein flexibility is not a sensitive indicator of irradiation at 1.7 and 2450 MHz and that relaxation of bound water

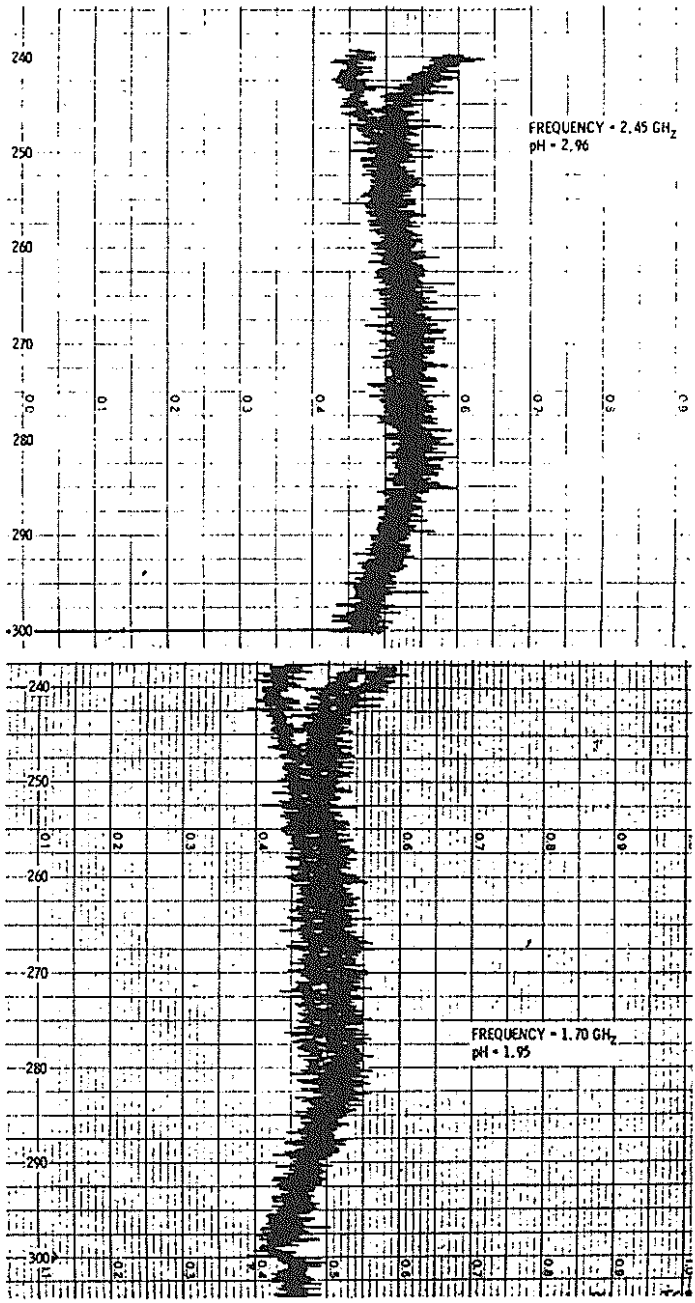


Fig. 3.1. Difference spectra under RFEM irradiation. Each of the 2 figures illustrates the actual scans of the three curves: unirradiated *vs* unirradiated (control), after start of irradiation *vs* unirradiated, after 30 min of irradiation *vs* unirradiated. Each set of three scans are within experimental reproducibility. Top: irradiation at 2.45 GHz with $SAR = 70$ W/kg, sample temperature 31.0 °C, pH 2.96. Bottom: irradiation at 1.70 GHz with $SAR = 57$ W/kg, sample temperature 29.7 °C, pH 1.95. Absorbance range is 0.1 units full scale, and wavelength range is from 300 to 240 nanometers. (From Allis, 1975.)

at the surface of proteins as excited by fields at these frequencies is not significant for protein structure. He concedes, however, that it would probably be better to use optical rotatory-dispersion techniques in attempts to detect these changes. The range of *SAR*s used by Allis was 30 to 100 W/kg during both a brief and a 30-min exposure. The sample and reference temperatures were within ±0.2 to 0.3 °C during most experiments.

Belkhode *et al.* (1974b) exposed three human serum enzymes to 2.8-GHz fields with 1000-pps square-wave modulation. The power density varied spatially from 400 to 1000 mW/cm^2 in the wave guide and the SAR was 230 ± 70 W/kg. Temperatures were maintained at 37 or 46.7 °C during 4.5-min exposures and at 49.7 °C during 18.5-min exposures. The control was run at 0 °C. Figures 3.2, 3.3, and 3.4 show the relative activity of the three enzymes (lactate dehydrogenase, acid phosphatase, and alkaline phosphatase) as a function of temperature. Belkhode *et al.* observed a thermally induced inactivation of all three enzymes but no effects unexplained by temperature alteration were apparent.

Under similar conditions, Belkhode *et al.* (1974a) also exposed human blood and yeast glucose-6-phosphate dehydrogenase to 2.8-

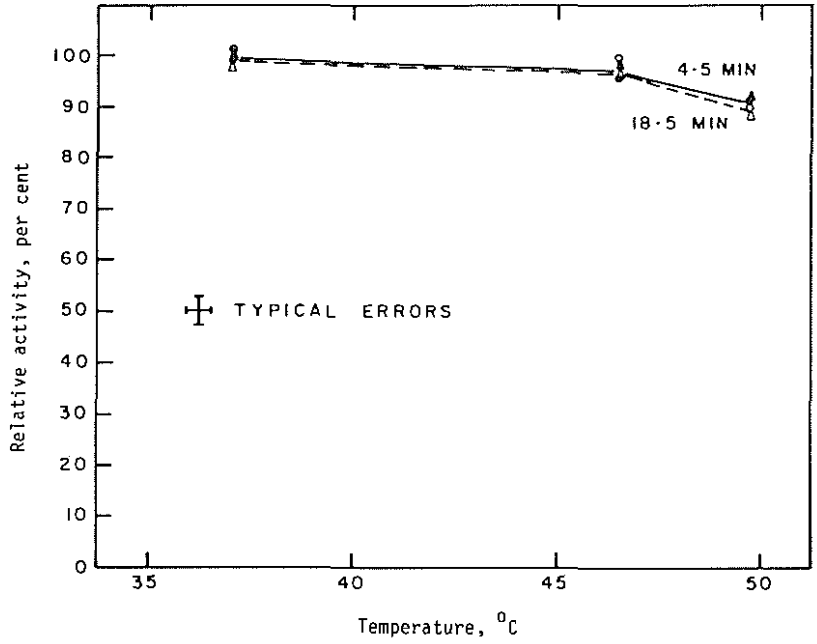


Fig. 3.2. Relative activity of human serum lactate dehydrogenase as a function of temperature: ○, 4.5-min treatment with microwave radiation; ●, 4.5-min treatment without microwave radiation; △, 18.5-min treatment with microwave radiation; ▲, 18.5-min treatment without microwave radiation. (From Belkhode *et al.*, 1974a.)

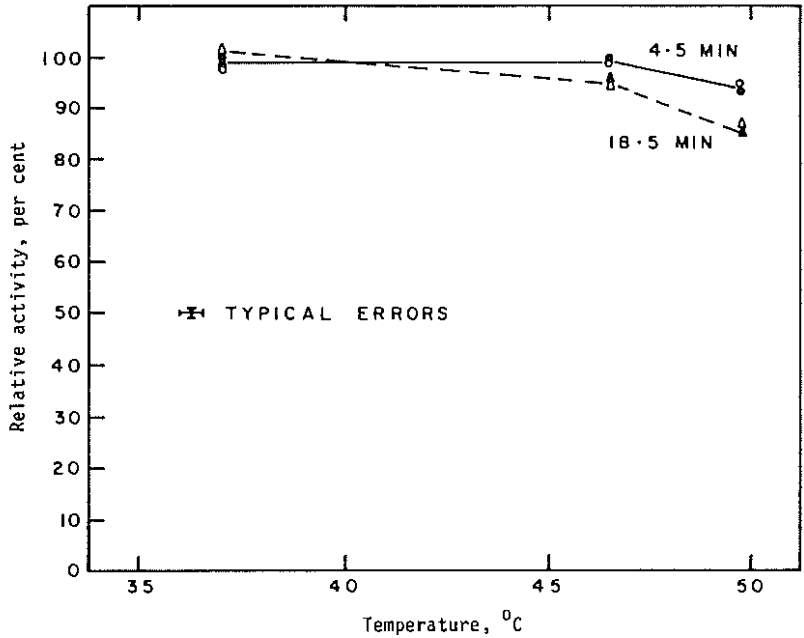


Fig. 3.3. Relative activity of human serum acid phosphatase as a function of temperature: ○, 4.5-min treatment with microwave radiation; ●, 4.5-min treatment without microwave radiation; △, 18.5-min treatment with microwave radiation; ▲, 18.5-min treatment without microwave radiation. (From Belkhode *et al.*, 1974a.)

GHz fields. Again, thermally induced reductions in relative activity were found—as much as 80 percent reduction—depending on the treatment period, but no statistically significant effects unrelated to temperature changes were observed (Figures 3.5 and 3.6).

Klainer and Frazer (1975) exposed glycine, ATP, *E. coli* tRNA, and electrophoretically homogeneous chymotrypsin to 100-MHz fields. They found no perturbations of glycine or ATP Raman spectra when thermal gradients were avoided. *E. coli* tRNA lost several peaks associated with intramolecular hydrogen bonding in the 800- to 2000-cm^{-1} Raman-spectrum region but only when irradiation was continued for one hour. The adenine-guanosine cross bonding showed the largest loss at 8 W, which corresponded to a field of approximately 400 V/cm in the solution. Chymotrypsin in the 209- to 600-cm^{-1} region of the spectrum showed a progressive loss of several of the prominent peaks at input powers of 3 W (approximately 150 V/cm) and 4 W (approximately 200 V/cm). At 5 W, the solution became turbid. The authors believe that alterations in the Raman spectra may show some of the information usually seen in dielectric-dispersion spectra and

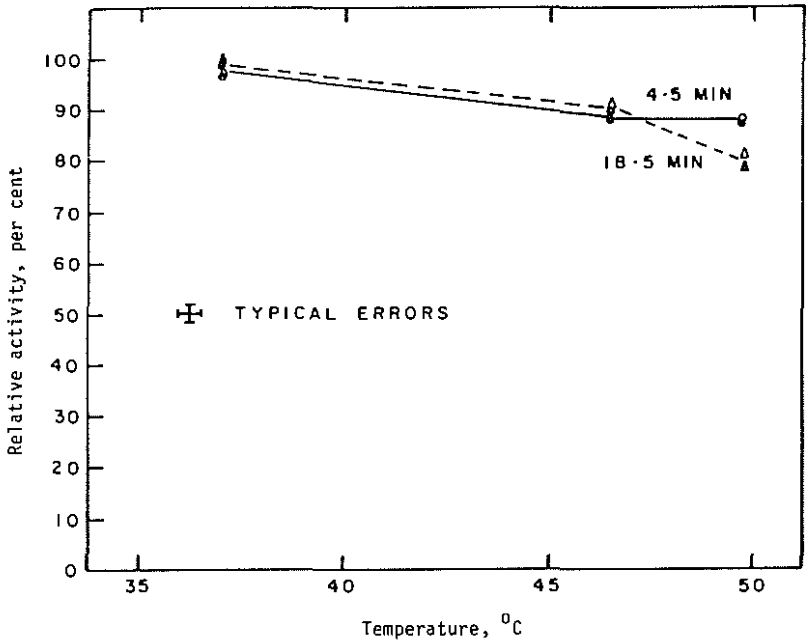


Fig. 3.4. Relative activity of human serum alkaline phosphatase as a function of temperature: ○, 4.5-min treatment with microwave radiation; ●, 4.5-min treatment without microwave radiation; △, 18.5-min treatment with microwave radiation; ▲, 18.5-min treatment without microwave radiation. (From Belkhode *et al.*, 1974a.)

also may provide information on effects of applied fields on the tertiary structure of larger molecules.

In summary, it appears that irradiation of the enzyme solutions in the experiments reported above had few effects not attributable to elevated temperature.[2]

3.2 Effects on Cell Organelles

Elder and Ali (1975) studied the effects of 2450-MHz CW fields on rat-liver mitochondria. The mitochondria were exposed at 10 and 50 mW/cm^2 (17.5 and 87.5 W/kg) for 3.5 h in an anechoic chamber. Irradiation was performed at 0 to 4 °C, and assays were made every 0.5 h at 25 °C. The respiratory-control ratio was used as an index of

[2] It is not surprising that interest in effects of RFEM exposure on macromolecules has waned greatly in recent years. An additional report in the peer reviewed literature (Millar, 1984) again confirms a lack of any detectable effect when the enzyme acetylcholine esterase was exposed to a 2450-MHz field.

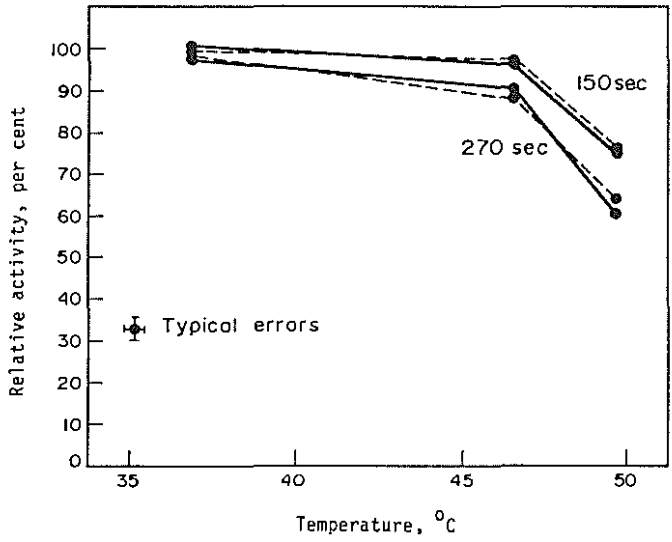


Fig. 3.5. Relative activity of human erythrocyte glucose-6-phosphate dehydrogenase as a function of temperature: – – –, treatment with microwave radiation; ——, treatment without microwave radiation. Upper lines, 150-s treatment; lower lines, 270-s treatment. (From Belkhode *et al.*, 1974b.)

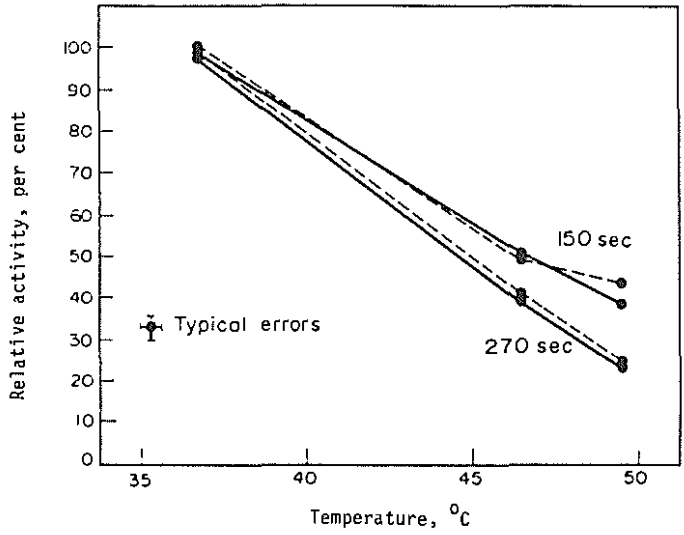


Fig. 3.6. Relative activity of yeast glucose-6-phosphate dehydrogenase as a function of temperature: – – –, treatment with microwave radiation; ——, treatment without microwave radiation. Upper lines, 150-s treatment; lower lines, 270-s treatment. (From Belkhode *et al.*, 1974b.)

the integrity of mitochondrial structure and function. This ratio is a measure of the dependence of the respiratory rate on ADP (adenosine 5′-diphosphate) and is defined as the rate of respiration in the presence of ADP divided by the rate after the expenditure of the ADP. No significant difference between control and irradiated mitochondria was found in respiratory control ratios of pyruvate, maleate, α-ketoglutarate, succinate, and β-hydroxybutyrate. Another ratio, ADP/O, was used to index the capacity of tightly coupled, intact mitochondria for oxidative phosphorylation. Again, no statistical differences were found with respect to pyruvate, α-ketoglutarate, β-hydroxybutyrate, and succinate (Figure 3.7).

No effect was seen in the respiratory response of the mitochondria to the addition of Ca^{2+} when different substrates were used as determined by the calcium-acceptor control ratio (the stimulated rate of oxygen consumption that results from the addition of Ca^{2+} divided by the rate that results after the binding of the cation to the mitochondrial inner membrane, an energy-dependent process). The calcium/oxygen ratio, the amount of added Ca^{2+} divided by the amount of oxygen consumed during activated respiration, was decreased slightly both in control and in irradiated mitochondria (Figure 3.8).

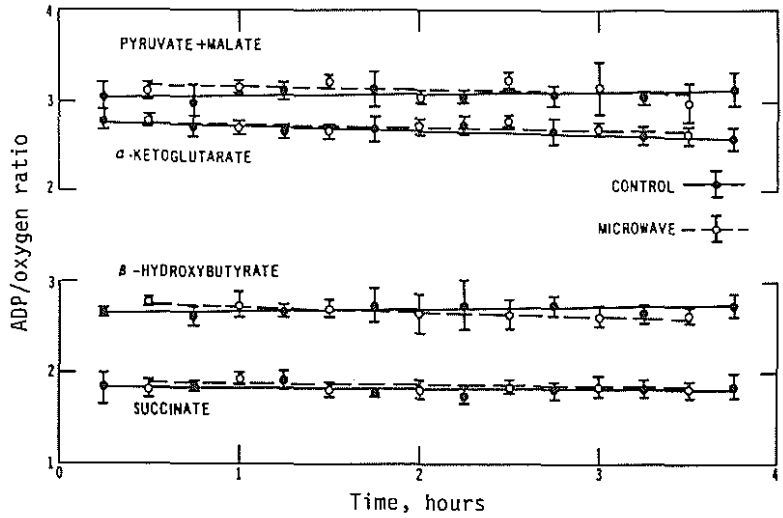


Fig. 3.7. ADP/oxygen ratios with succinate, β-hydroxybutyrate, α-ketoglutarate, and pyruvate and malate as substrates after exposure to a power density of 10 mW/cm^2. The ADP/oxygen ratio was calculated from the same ADP response as the respiratory control ratios. The error bars are equal to two standard errors of the mean. (From Elder and Ali, 1975.)

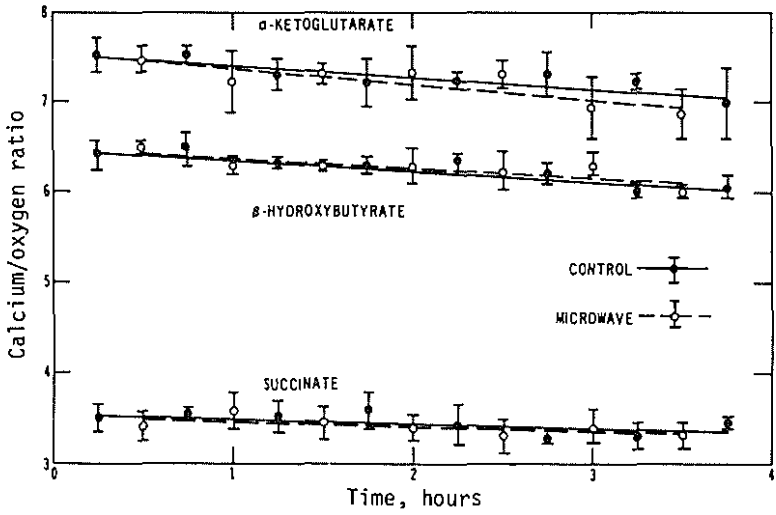


Fig. 3.8. Calcium/oxygen ratios of mitochondria exposed to a power density of 10 mW/cm^2 with succinate, β-hydroxybutyrate, and α-ketoglutarate as substrates. The Ca^{2+}/O ratios were determined from the same Ca^{2+} response as the Ca^{2+} acceptor control ratios. (From Elder and Ali, 1975.)

In summary, Elder and Ali found no effects on the molecular processes of substrate oxidation, electron transport, oxidative phosphorylation and Ca^{2+} transport on irradiation at 2450 MHz.

Straub and Carver (1975) conducted irradiations in waveguides at a variety of frequencies: 10 to 200 Hz and 1.6, 2.2, 2.86, 8, 10, and 12 GHz. They irradiated Na-K ATPase from guinea-pig brain microsomes at a power density of 2 mW/cm^2 and at 37 °C for 15 min, and found no effect in the ADP/O ratio. At the same power density and at 22 °C, they found no effects on oxidative phosphorylation in rat-liver mitochondria. The error range was approximately 20 percent. Frog-skin ion transport was studied with the skin arranged in such a way that the skin was part of a semi-infinite, water-plane surface, either parallel or perpendicular to the vector of the electric field, and no effects were found. The authors noted that the membrane fragments in the solution may shield the field and preclude the effect. Because the solutions were not heated by the field, they believe that the power density may have been less than the calculated value. Actual power densities and *SAR*s were not measured.

Straub (1977) has proposed that rotation of highly oriented assemblies of macromolecules that comprise the functioning units of mito-

chondria might disrupt the function of the assemblies if the rotation is to new stable states. However, current evidence does not support the occurrence of such a rotation in mitochondria.

Although the number of experiments is limited, over a wide range of frequencies and power densities there appear to be no effects of RFEM radiation on mitochondrial structure and function not attributable to changes of temperature.

3.3 Effects on Microorganisms

Baranski *et al.* (1976, abstract) exposed the fungus *Aspergillus nidulans* for 10 to 240 min to 2450-MHz fields at a power density of $\leq$10 mW/cm^2. They irradiated haploid spores in plastic containers before or during germination. They found no mutagenic effects as determined by morphological changes in the mycelium. They also saw no difference in the survival rates of irradiated and non-irradiated spores.

Algae (*Clamydomonas segnis*) in the log phase of growth in aqueous suspensions were irradiated by Hamid and Badour (1973) at 2450 MHz and at 35 to 40 °C for 10 seconds. Stimulation of photosynthesis and of growth was greater than that induced by conventional heating. At 4900 MHz, a 1-min exposure ($\geq$50 °C) resulted in proteolysis, loss of photosynthesis, and inhibition of growth. After other exposures (30 s or 5 min at double the power density and at 100 °C), there was a rapid degradation of chlorophyll that surpassed the effect of conventional heating. This study, like others reported by Blackman *et al.* (1975) and Robinson (1977), reveals the critical need for controlling and/or recording temperatures of organism and environment, because even small elevations can result in profound effects.

Several studies of RFEM fields on *E. coli* have been reported. Correlli *et al.* (1977) irradiated living *E. coli* B with 2.6- to 4.0-GHz CW fields for 10 to 12 h at a power density of 10 mW/cm^2 (*SAR*, $\leq$20 W/kg). The temperature was $\leq$26 °C during irradiation of suspensions. When cells in the log-phase of growth were exposed in nutrient broth, there was no effect on colony-forming ability. Irradiation of the cells in aqueous suspensions showed no effects in molecular structure as determined by infrared spectroscopy (Figures 3.9 and 3.10).

Hamrick and Butler (1973) found no effects on cell-replication rates not explainable as temperature effects in four strains of *E. coli* and in *Pseudomonas aeruginosa* in a 2450-MHz CW field when the cells were

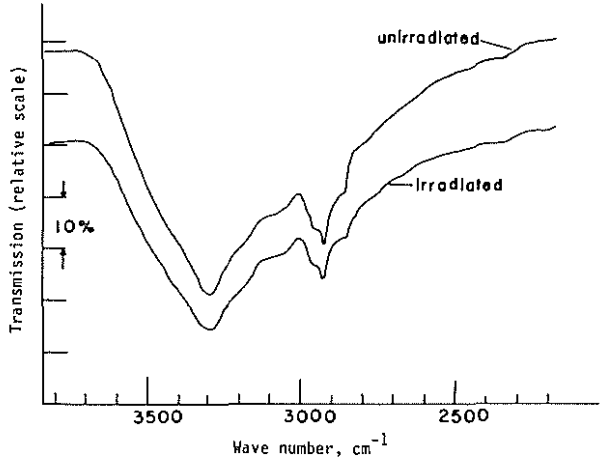


Fig. 3.9. Infrared spectrum (3800 to 2200 cm^{-1}) of live *E. coli* B after 11 h of irradiation at 3.2 GHz by 21 mW of absorbed power. The incident power was 121 mW, reflected power 73 mW, and transmitted power 27 mW. Also shown is the infrared spectrum of an unirradiated control sample. (From Corelli *et al.*, 1977.)

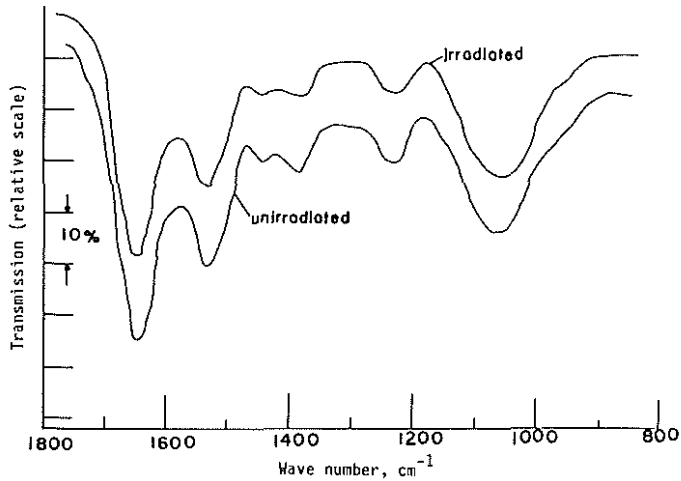


Fig. 3.10. Infrared spectrum (1800 to 800 cm^{-1}) of live *E. coli* B after 12 h of irradiation at 3.2 GHz by 16 mW of absorbed power. The incident power was 120 mW, reflected power 68 mW, and transmitted power 36 mW. Also shown is the infrared spectrum of an unirradiated control sample. (From Corelli *et al.*, 1977.)

irradiated for 12 h at 37 ± 0.5 °C at a power density of 60 mW/cm^2 (*SAR*, ~29 W/kg). In addition, they found no effect on the growth curve of *E. coli* at 259 and 450 mW/cm^2 (37 °C and 44 °C, respectively). The growth curves of *E. coli* (strain No. 9637) at 41 mW/cm^2 and 450 mW/cm^2 are shown in Figures 3.11 and 3.12. Figure 3.13 indicates the

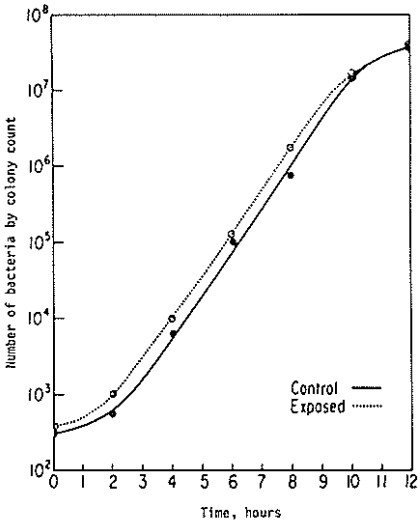


Fig. 3.11. Growth at 37 °C of *E. coli* (strain No. 9637) exposed to 2450 MHz radiation at a power density of 41 mW/cm^2. (From Hamrick and Butler, 1973.)

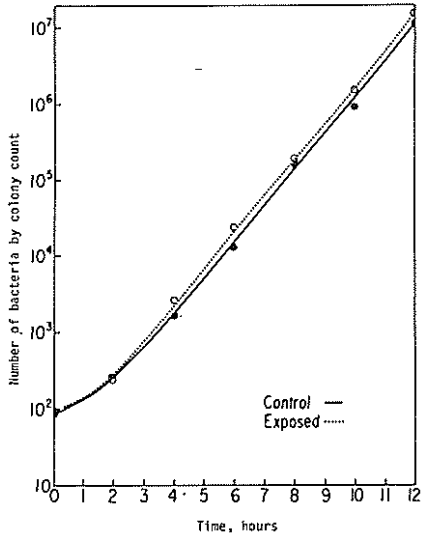


Fig. 3.12. Growth at 44 °C of *E. coli* (strain No. 9637) exposed to 2450 MHz radiation at a power density of 450 mW/cm^2. (From Hamrick and Butler, 1973.)

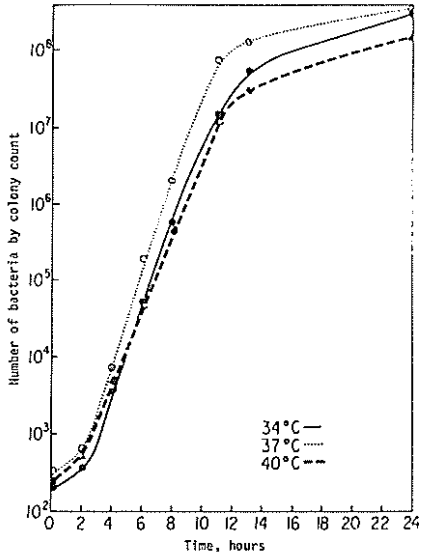


Fig. 3.13. Temperature dependence of growth of *E. coli* (strain No. 9637). (From Hamrick and Butler, 1973.)

temperature dependence of the growth of this strain under relatively small temperature changes (3 °C).

In the studies of microorganisms discussed here, irradiation did not result in genetic, cell-replication, colony-forming, molecular-structural or survival effects, with the possible exception of stimulation of photosynthesis in algae.

3.4 Effects on Somatic Mammalian Cells

Many somatic-cell experiments have been done at high power densities, but these shed little, if any, light on effects that might be attributable to RFEM irradiation at lower power densities.

Everts *et al.* (1972, abstract) found a statistically higher percentage of chromosomal aberrations relative to controls in cultured kidney, lung, and thyroid cells of 30-day-old Chinese hamsters that were exposed at a frequency of 2430 ± 4 MHz and at a power density of 200 ± 36.4 mW/cm^2. Exposure durations were 30, 60, 90, and 120 seconds. Unfortunately, little detail is available in their abstract, the only report of their study. At such high power densities, temperature alterations may be responsible for the chromosome aberrations.

Chen and Lin (1978) exposed Chinese hamster somatic cells (V-79) to 2450-MHz CW at a power density of 500 mW/cm^2 (*SAR*, 1059 W/kg). The cells were exposed for 20 min at a temperature of 37 ± 0.1 °C in a constant-temperature circulator within a waveguide exposure system. A 100-μl pipet held the suspension. Another suspension was sham-exposed under the same conditions. The authors reported a decrease of ~30 percent in the growth rate over 12 d of incubation and morphological changes in 10 percent of the exposed cells within 48 h after irradiation (Figure 3.14). They observed vacuoles that increased in volume and in irregularity during continued growth. Later, star-shaped, giant ruffle cells were formed. Finally, they observed a fibroblastic type of growth as shown in Figure 3.15. These changes appeared to be irreversible. Although the authors believe these effects were not due to temperature changes, they concede that intense thermal effects could occur and that there could be thermal microgradients. It has been suggested that thermal hot spots may have developed in the vacuoles because the vacuoles are surrounded by a membrane that may act to insulate the vacuole and to localize heating by retardation of heat exchange (Straub, 1977).

Yao and Jiles (1970) have done a number of experiments at 2450 MHz with kangaroo-rat cells. They irradiated cells in culture from

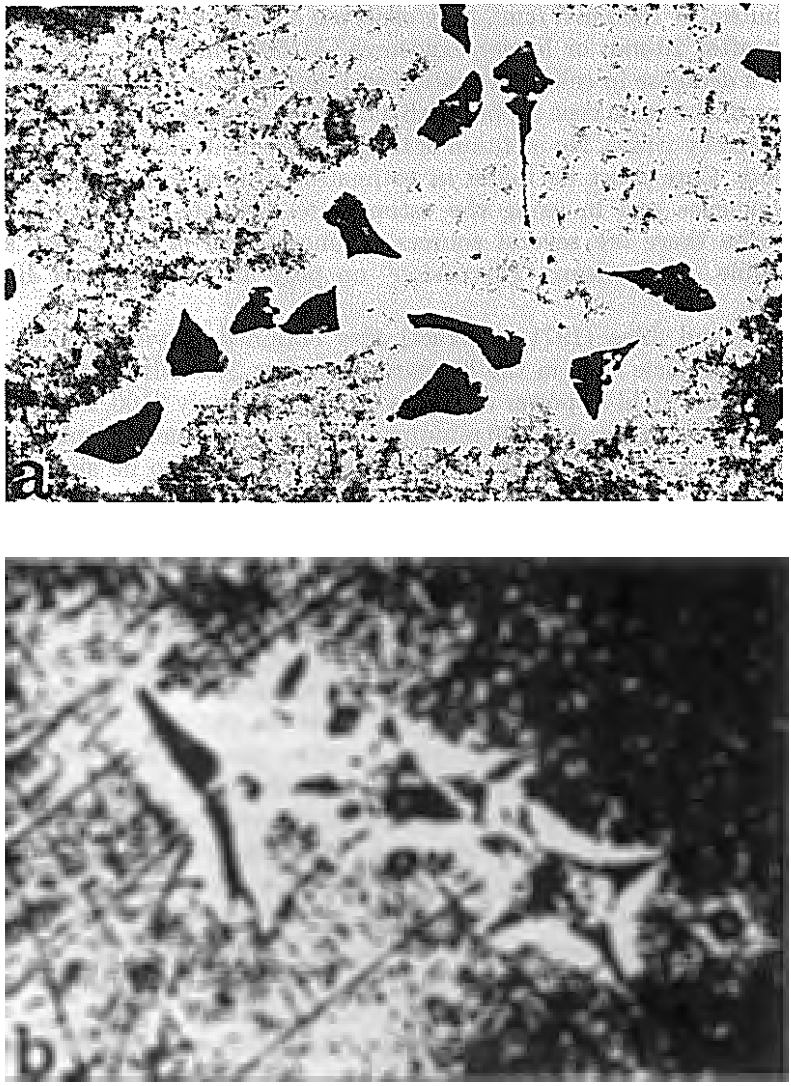


Fig. 3.14. Photomicrographs of Chinese hamster somatic cells after 3 d of incubation at 37 °C. (a) Control cells are shown in log phase of growth with an average generation time of 12 h. (b) The irradiated cells divide at a much slower rate, and the appearance of giant-ruffle cells is typical. (Both at magnification × 1,600.) (From Chen and Lin, 1978.)

choroid and bone-marrow tissues for 5 to 30 minutes. The flasks were placed in front of a microwave oven or in front of a microwave antenna in an anechoic chamber. At 200 mW/cm^2, they found an increase in cell proliferation after a 10-min exposure and a decrease after 30

minutes. At 1000 mW/cm^2, they observed a decrease in cell proliferation after 20-min or longer exposures. At 5000 mW/cm^2, there was also a decrease in cell proliferation and induced chromosomal aberrations of the same type as, but with a different distribution from, those induced by x rays. No mention of temperature controls is made in this report. Care must be taken in estimating chromosomal aberration frequencies and in using the estimate to evaluate such exposures because there are several sources of uncertainty or error that are possible (Michaelson: "Discussion" on page 133 in Yao and Jiles, 1970).

Yao and Jiles (1971, abstract) also obtained survival curves of ovarian follicle cells in the kangaroo rat after 2450-MHz irradiation in the near field at power densities of approximately 3100, 5600, and 12500 mW/cm^2 for 2 to 160 minutes. Using trypan blue, they observed survival curves of cells in the log phase of growth to be similar to curves observed after irradiation by x rays, except that the curves of the RFEM-irradiated cells had a shoulder and were more skewed. The cell death rates were 20.3, 2.6, and 1.1 percent at the three power densities and exposure times, but there was no association between power density and exposure period. Unfortunately, there is little information given on the controls for this experiment. These results are paradoxical and are unexplained by the authors. The high power densities make thermal effects highly probable, and it is important to note that hyperthermia also gives survival curves similar to those associated with x rays (Ross-Riveros and Leith, 1979). It has also been found that, when mammalian cells are elevated to temperatures above 40 to 41 °C for an appreciable period, irreversible damage and cell death will occur. At the high power densities used in the previously cited experiments, the temperature might be quite nonphysiological and damaging (Robinson, 1977; see also Section 15). Furthermore, the trypan-blue exclusion test is, at best, a primitive indicator of cell survival.

Valtonen (1966) exposed the mast cells of male rats to 1245 ± 25 MHz fields for 5 min at temperatures to 41 °C and at a power of 80 W. He found that 5 to 30 percent of the mast cells in the irradiated animals were giants, whereas there were no giants among the controls. He concluded that the giants are due to a disorder in the internal metabolism of the cells themselves, a disorder that is probably degenerative in nature. Because the staining properties did not change except to get weaker, he believes this response is probably not serious. Cells of other types were not affected. The control rats had a very high rectal temperature of 42 °C, which was maintained for 2 to 3 minutes. Valtonen believes that these results are not due to tempera-

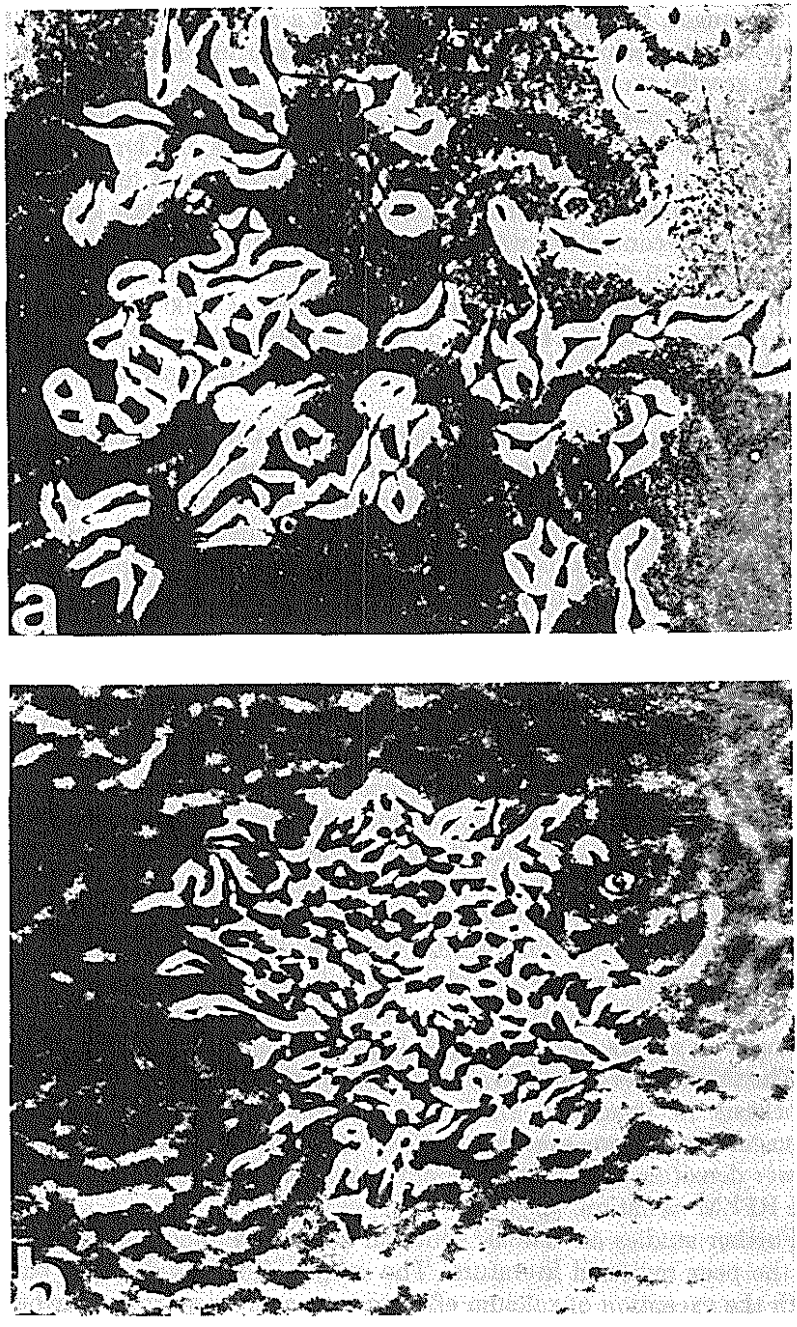


Fig. 3.15. The growth patterns and cone morphology of Chinese hamster cells *in vitro*. (a) Microwave-induced transformed cells exhibit a fibroblast type of growth and proliferate in matched parallel position to form irregular, single-layered masses of cells over the surfaces of a plate. (b) Normal cells grow in a relatively compact fashion with no particular orientation forming a multi-layered colony. (Both at magnification × 300.) (From Chen and Lin, 1978.)

ture changes. It should be mentioned that a rectal temperature of 42 °C does not preclude the possibility of hot spots in the organism that could greatly exceed 42 °C.

Lin and Peterson (1977) found that 2450-MHz CW radiation did not seem to have any effect on human fibroblasts and lymphoblasts in culture in the absence of a measurable elevation of temperature. They measured the growth and viability of cultured blast cells in a temperature-controlled, waveguide-exposure chamber. The cells were exposed for 15 min at power densities from 10 to 500 mW/cm^2. The *SAR*s corresponding to this range were as high as 1200 W/kg.

A number of studies has been done on the effects of RFEM radiation on the hematopoietic and immune systems and these are discussed in Section 7.

Considering the high power densities used in the studies cited above, temperature controls are essential to rule out thermal effects. In addition, it would be a welcome addition to the literature to see more studies done with somatic cells at low power densities. Specific absorption rates should be measured and reported in addition to measurements of power densities. Until these criteria are fulfilled and until experimental protocols are given in great detail, it will not be possible to elucidate the effects of fields at low power densities on somatic cells.

In 1981, the University of Utah group undertook a major study to attempt clarification of the effects of microwaves on cell function and survival (Partlow *et al.* 1981; Stensaas *et al.* 1981; Bush *et al.* 1981). The cell-exposure system was carefully designed for maximum dosimetric precision, and a range of power levels and frequencies was used to explore the possibility of "windows" of effectiveness in the power spectrum or the frequency spectrum. The ultrastructural studies led the authors to the conclusion that changes, when found, were always associated with temperature elevations. Stensaas *et al.* (1981) drew the conclusion that, at the two frequencies used, 41.8 and 74 GHz, the changes seen were associated with hyperthermia.

The third paper from this group (Bush *et al.* 1981) examined protein synthesis in irradiated BHK-21/C13 cells in the high-precision, waveguide-exposure system. A wide range of frequencies and two power densities were used. The authors failed to detect any effect of the RFEM radiation.

Further studies on cellular function have been almost nonexistent in the peer reviewed literature. The weight of the evidence is that, with the exception of calcium efflux experiments, reported elsewhere in this report, athermal effects of microwave power on cellular function are difficult to demonstrate.

3.5 Effects on Cell Transformation and Tumor Cells

The results of irradiation on cell transformation and on tumor cells are quite mixed.

Blackman *et al.* (1975) have done some of the most carefully controlled experiments with microwaves at low power densities. Suspensions of *E. coli* were irradiated at 1.70 GHz in the near field or at 2.45 GHz in the far field. Temperature was regulated to ±0.5 °C in a large chamber in an electrically shielded anechoic room. At 0, 0.005, 0.5, 5.0, and 50 mW/cm^2, effects on growth not explainable by temperature differences (0.2 to 0.3 °C) between the sham-irradiated and the irradiated bacteria were not observed. No reduction was observed in viral titers when *E. coli* was infected with ϕx 174 and irradiated at 32 ± 0.1 °C for 2 h at 5 mW/cm^2 by 68- to 74-GHz CW fields. No radiation-induced inhibition in heat-shock experiments was observed with respect to viral strain, growth medium, growth stage, temperature, frequency, carbon source, or nitrogen source. The only obvious effect of irradiation was an increase in rate of cell growth. Usually, differences of 20 percent in growth rate are easily detectable in this system.

Walker *et al.* (1974) studied the response of *E. coli* B to T4 rII phage under 2450-MHz fields (90-μs pulses at 8000 pps). Power density was not given but is estimated to be in the range of 1 to 10 mW/cm^2 (7-min exposure in an S-band waveguide). No statistically reliable effect on the infective capability of the phage was seen. The phage has a delicate tail structure that the authors believe would be a sensitive indicator of damage. No effect was seen on the bacteria or the phages in titration experiments. The results were analyzed using Student's *t* test, and fairly large errors were involved. It may, therefore, have been difficult to observe small effects.

Moody *et al.* (1979, abstract) irradiated *E. coli* C-600 lac II. This strain has a defect in the *ton-A* locus that normally confers resistance to bacteriophage T5. The bacteria became susceptible to infection by non-irradiated bacteriophage when virus was added immediately post exposure. This susceptibility was shown both by lysis of the bacteria and by production of viral particles, and indicates that a membrane-receptor site for T5 was uncovered during irradiation that elevated temperatures to 42 °C. Capacitor-coupled, 1.07-GHz fields were applied to bacteria in the log phase of growth. The field strength was at least 5 V/cm in solution. Both the bacteria and the phage were more susceptible to inactivation by the fields than by elevation of temperature alone.

Szmigielski *et al.* (1975) exposed a strain of human embryonic cells, labelled WISH cells (with and without infections of parainfluenza 3

virus), which were located on culture-flask surfaces, to 3-GHz CW fields. The cells were exposed for 30 min in the far field. Under these conditions they found no increase in temperature. With the use of morphological and virological techniques, they found reversible functional disturbances. At 5 mW/cm^2, they saw an increase in nitro-blue-tetrazolium reduction and an increase in myxovirus multiplication rates, both of which indicate that RFEM radiation at this intensity stimulates cell metabolism, especially because no change in the supravital staining and phase-contrast observations were found. Nitro-blue-tetrazolium reduction reflects the rate of O_2 consumption and the activity of the pentose-phosphate shunt. At 20 mW/cm^2, they observed an increase in membrane permeability as indicated by degree of staining, a decrease in nitro-blue-tetrazolium reduction rate, a decrease in succinic-dehydrogenase activity, a widespread cellular vacuolization, and an inhibition of myxovirus replication. These results indicate severe cellular injury and a possible disturbance of mitochondrial function. However, 24 and 48 hours after RFEM irradiation, partial regeneration of the cultures was observed and the viral replication rate had returned to normal. Little information, unfortunately, is given on the treatment of controls.

Luczak *et al.* (1976) also exposed WISH cells infected with myxoviral parainfluenza III at 3 GHz for 30 min in the far field. At 5 mW/cm^2 they found an increase in viral multiplication in cultures inoculated 2 h before, simultaneously, or 2 h after, irradiation. This increase indicates a stimulation of cell metabolism (protein and nucleic-acid synthesis) and not an increase in attachment of viruses to cell surfaces. At a higher power density (20 mW/cm^2), they found a decrease in the rate of multiplication of viruses in the cells irradiated for 2 h before or after inoculation. Cultures irradiated 24 h after inoculation showed a normal rate of multiplication. Luczak *et al.* also did *in-vivo* experiments on young CFW mice infected with *Vaccinia* or *Herpes* viruses. The effect was dependent on the schedule of irradiation. Exposure to RFEM radiation after infection decreased the rate of multiplication of *Herpes* viruses and enhanced the inhibitory effect of both Cytosar and ARA-C.

These experiments indicate that RFEM radiation may cause reversible functional disturbances in WISH cells infected with myxovirus parainfluenza by what appears to be a stimulation of cell metabolism. However, the negative findings of Blackman and Walker with phage-infected *E. coli* indicate that the effects may be due to small temperature changes (considering that Blackman found growth to be affected by temperature changes as small as 0.2 °C). Small temperature changes

must be considered in the analysis of data involving tumor cells because tumor cells are especially sensitive to elevations of temperature. Indeed, this selective sensitivity is being explored as a treatment modality for cancer (see Section 16).

3.6 Effects on Cellular Genetics

Within the topical bounds of this section on cellular effects, few reports on cellular genetics are available for review. Other aspects of genetic effects are discussed in greater detail in Section 4.

Everts *et al.* (1972, abstract) found chromosomal aberrations in Chinese hamster cells. However, at the power density used, 200 mW/cm^2, the resulting *SAR*s were so high that the aberrations could well be due to temperature increases. Yao and Jiles (1970) likewise found chromosomal aberrations in kangaroo-rat cells, and again a very high power density was used, 5000 mW/cm^2. Furthermore, no thermal controls were included in their study. On the other hand, Pay *et al.* (1972) found no increase at the $p = 0.01$ level in recessive lethal mutations in male *Drosophila* at power densities that also were very high, 5900 and 6500 mW/cm^2. Baranski *et al.* (1976) also found no mutagenic effects on *Aspergillus nidulans* at a low power density ($\leq$10 mW/cm^2).

Heller and Teixeira-Pinto (1959) observed chromosomal aberrations in onion root tips growing in water when exposed to 27-MHz fields for 5 minutes. Heller (1970) also found chromosomal aberrations in garlic cells, Chinese hamster cells, human lymphocytes, and male *Drosophila* germ cells at 27 MHz. He used intense, but short, pulses of radiation that he believed did not increase the temperature of the specimens significantly and, therefore, he ruled out effects of heating. However, no description is given of the methods of temperature measurements, and, hence, thermal effects cannot be convincingly eliminated as a causal agent for the aberrations observed.

Michaelson discusses a number of the potential problems associated with chromosome-aberration studies cited by cytogeneticists in a discussion of the report (page 133) by Yao and Jiles (1970). Among these problems are difficulties involved in chromosomal scoring techniques, the interpretation of chromosome stickiness, the uncertainties in estimating chromosomal-aberration frequencies, and the many variables in tissue-culture techniques.

3.7 Summary and Conclusions

It appears that RFEM fields, at least continuous waves at frequencies above 5 MHz, have little, if any, effect on bipolymers, cell organelles, and microorganisms other than effects associated with elevated tempertures. Likewise, the effects of RFEM fields on the genetic materials of cells have not been convincingly demonstrated to be unrelated to elevations of temperature. Unfortunately, the paucity of experimental data makes it difficult to draw definitive conclusions about mechanisms of field-cell interactions at *SAR*s below 1 W/kg. Although there may be metabolic effects of RFEM irradiation on viral multiplication, these results must be interpreted with caution given the lack of information on controls and given the finding of Blackman *et al.* (1975) that temperature differences as small as 0.2 °C can significantly influence growth.

One firm conclusion can be drawn: Temperature is a critical variable that needs to be considered in the execution of experiments and in the analysis of data irrespective of the intensity of the field. Implementation of adequate control of temperature is a major problem as is the need for complete descriptions of the experimental conditions and assays involved. The following are factors that are critical to the performance and reporting of experiments for assessing the effects of RFEM fields:

1. Power density (or E and H field strengths) and specific absorption rate
2. Duration of exposure and exposure schedule
3. Wavelength or frequency of the radiation
4. Mass and dimensions of the biological target
5. Thermoregulatory capabilities of the organism
6. Tissue thickness and composition
7. Orientation of the subject with respect to field vectors
8. Waveform (continuous or pulsed, and other modulation factors)
9. Electrical and biological shielding and shadowing
10. Environmental factors (e.g., heat, humidity, light, and air velocity)
11. Physiological and psychological status of subjects (anesthesia, restraint, handling, nutritional state, feeding and watering schedule)
12. Experimental design and instrumentation (RFEM source, monitoring equipment, etc.)
13. Adequate sample sizes and proper statistical analyses

There is ample evidence of thermal effects of RFEM fields at high power densities. Furthermore, it appears now that even small temperature changes can have significant cellular effects (Blackman *et al.*, 1975). However, until more data are obtained from carefully controlled and executed experiments, definitive conclusions on the cellular effects of microwaves at low power densities will have to wait.

4. Chromosomal and Mutagenic Effects

4.1 Chromosomal Effects

The ability of RFEM fields to induce chromosomal and mutagenic effects has been demonstrated in a limited number of biological systems under limited exposure conditions. Most investigations of chromosomal alterations in mammalian cells have been conducted in *in-vitro* systems and at microwave frequencies. For the purpose of comparison, studies of chromosomal effects may be categorized either as high-intensity studies in which the power density exceeds 10 mW/cm^2 (field strengths greater than 200 V/m) or low-intensity studies ($\leq$10 mW/cm^2 or $\leq$200 V/m).

Chromosomal alterations were reported by Leach (1976, abstract), who exposed Chinese hamsters *in vivo* to 200-mW/cm^2, 2.45-GHz CW RFEM fields for periods of 15 minutes. Exposure resulted in a decrease in the mitotic index of bone marrow cells and an increase in chromosomal stickiness at 5 h post exposure. Chromosomal stickiness was observed both between chromosomes and between sister chromatids. The observation of chromatin bridges between nuclei indicates that cells with chromosomal stickiness are able to escape the mitotic blocking effect of Colcemid. Cells examined one week post exposure showed reduced stickiness compared with immediate post-exposure samples, but structural aberrations, including breaks and rearrangements, occurred at significantly higher incidence in exposed cells. The nature of the chromosomal aberrations indicated that multiple mechanisms may be involved in the induction of chromosomal breakage by such exposure.

Exposure of cells of the meristem of garlic root tips to RFEM fields at frequencies of 5 to 40 MHz at field strengths of 0.25 to 600 kV/m for periods of 5 min to 8 h induced stickiness in chromosomes, which led to clumping, pyknosis, and the formation of bridges during anaphase and telophase (Mickey, 1963). Exposure also resulted in chromosomal fragmentation with loss of chromatin and the formation of micronuclei, which culminated in cell death.

Chen *et al.* (1974) exposed Chinese hamster and human amnionic cells *in vitro* to 2.45-GHz fields at intensities of 20 to 85 mW/cm^2 for durations of 4 to 20 minutes. Exposure resulted in temperature elevations to 6 °C (3-min exposure of cells initially at 37 °C to an 85-mW/cm^2 field resulted in a temperature rise to 43 °C). Thermal-control studies involving conventional heating of the cells to 45 °C produced no significant chromosomal aberrations, whereas aberrations were induced by microwave exposure under a variety of time-intensity combinations. A reduction in the number of chromosomal aberrations was noted in cells four generations post exposure, which might be evidence of cellular repair. Chromosomal damage to human amnionic cells was somewhat less than that to Chinese hamster amniotic cells under similar exposure conditions, indicating the possibility of species-specific chromosomal sensitivity to 2.45-GHz fields. Because the temperature of irradiated cells never exceeded 43 °C, whereas temperatures in excess of 45 °C were required to produce aberrations in conventionally heated cells, Chen and coworkers concluded that chromosomal damage induced by 2.45-GHz fields was not due solely to volume heating. These results do not indicate any consistent dose-response (or time-intensity-temperature) relationship for the induction of chromosomal aberrations under the conditions of this experiment.

The interaction of 2.45-GHz fields with temperature (of the cells) in the induction of chromosomal aberrations was also reported by Alam and co-workers (1978), who exposed Chinese-hamster ova in culture at various intensities with and without temperature control. Cells irradiated under hypothermic (i.e., 29 °C) conditions showed no significant chromosomal damage in contrast to cells irradiated without temperature control, in which case the temperature of the culture was elevated to 49 °C and the incidence of chromosome breakage was significantly increased. Cells exposed without temperature control also exhibited nuclear vacuoles and pyknotic and condensed chromosomes. These effects were attributed to heating, which ultimately resulted in cell death (Alam *et al.*, 1978).

In another investigation of the chromosomal effects of high-intensity 2.45-GHz fields, Yao and Jiles (1970) exposed kangaroo-rat bone marrow and choroid cells *in vitro* at 200 mW/cm^2 for periods of 10 to 30 minutes. Irradiation resulted in chromatid and isochromatid breaks, dicentrics and rings, and chromatid exchange. Exposures of 30-min duration caused cell lethality at the intensities used in this study. Yao and Jiles (1970) noted that exposure resulted in partial despiralization, a specific type of chromosomal change not reported to result from exposure to other agents such as ionizing radiation.

Huang *et al.* (1977) exposed Chinese hamsters to 2.45-GHz fields at power densities up to 45 mW/cm^2 for 15 min/d on 5 consecutive days and observed no detectable effect on the incidence of chromosomal aberrations in leukocytes. McLees *et al.* (1972) found no alterations in chromosome morphology in rat-liver cells following a 28- to 44-h exposure *in vivo* to 13.5-MHz CW fields at a field strength of 4.5 kV/m, or to fields with a pulse repetition rate of 50 Hz and a pulse width of 200 μs at an average field strength of 4.4 kV/m.

The effects of low-intensity electromagnetic fields on chromosomes have also been investigated. Mittler (1976) exposed *Drosophila melanogaster* for 12 h to 146-MHz radiation at a field strength of 0.625 V/cm or to 29-MHz fields at 600 V/m. No significant increases in genetic aberrations were observed in assays, which included measures of nondisjunction and recessive sex-linked lethal mutations.

The effects of low-intensity 27-MHz fields on human lymphocytes *in vitro* were reported by Holm and Schneider (1970), who exposed cells for periods of 1 to 84 h in a tuned-coil exposure system with an effective output power of 10 W. No significant effects on cell growth, DNA synthesis or mitosis were detected, but cultures irradiated for 72 h or longer had 7 times more chromosomal breaks than did non-irradiated controls, even though there were no other detectable alterations in cellular responses.

George (1978) reported that a specific type of chromosomal aberration referred to as "bandedness" was induced in germinated broad-bean seedlings (*Vicia faba*) exposed for 6 to 24 h to a 1.6-MHz field from a Tesla coil at a field strength of 450 V/m. The bandedness, which apparently was due to chromosomal fragmentation, was noted during all stages of mitosis, the effect apparently being due to the dispersal of chromatin material from specific regions, thus producing gaps in the chromosomes. The implications of the induced bands are unknown.

Chromosomal aberrations have also been reported to result from exposure to low-intensity RFEM radiation both *in vitro* and *in vivo*. Stodolnik-Baranska (1966), for example, reported damaging effects of three exposures of human lymphocytes *in vivo* to 3-GHz fields at intensities of 7 to 14 mW/cm^2. The chromosomal aberrations included chromatid breaks, dicentrics and exchanges. Such exposure also resulted in the activation of lymphocytes including lymphoblastoid transformations. The maximal cell temperature in this investigation was reported to be 38 °C. Chromosomal aberrations and alterations in the duration of particular phases of mitosis were reported following exposure of human lymphocytes and monkey kidney cells in culture

to 3-GHz CW and pulse-modulated fields at power densities of 3 to 7 mW/cm^2 (Baranski *et al.*, 1981). Effects on guinea pigs and rabbits exposed *in vivo* were investigated by Baranski (1967). Animals were exposed to fields at power densities of 3.5 to 7 mW/cm^2 for 3 h/d either for 2 to 3 weeks or for 3 to 4 months. Field-induced alterations in the nuclear structure of erythroblasts and lymphoid cells included fragmentation, micronuclei formation, non-uniform chromatin staining, and chromosome bridges between daughter nuclei. The authors noted that the alterations were detected in erythroblasts and lymphoid cells but not in granulocytic precursor cells, a difference that might indicate a cell-specific sensitivity to low-intensity RFEM exposure (Baranski, 1967; 1971a, b). The authors did not indicate whether the hosts were affected or whether cellular repair was assayed.

In summary, RFEM radiation, under certain conditions of exposure, has been shown to induce various types of chromosomal aberrations. Although the data are not extensive enough to classify chromosomal effects in terms of field intensity, there are some indications that highly thermalizing fields induce chromosomal stickiness and breakage, as contrasted to lower levels of exposure where this phenomenon has not been reported. The possibility that RFEM fields may cause specific chromosomal alterations is indicated by the induction of chromosomal banding and partial despiralization. Data derived from both *in-vitro* and *in-vivo* investigations also suggest the possibility of cell-specific chromosomal sensitivities to RFEM radiation although the data are not extensive enough for definite conclusions. A threshold power density or field strength for the induction of chromosomal aberrations cannot be specified but such effects do not appear to be induced at power densities helow 1 mW/cm^2 or at field strengths $\leq$200 V/m. It must be noted, however, that effects of chronic exposure have not been adequately investigated. There is an apparent involvement of thermal damage in the case of high-intensity irradiation, but conventional heating does not appear to cause equivalent levels or types of chromosomal damage as compared with those resulting from RFEM fields.

4.2 Mutagenic Effects

Mutagenic effects of RFEM radiation have been investigated in a limited number of biological systems. No effects on the incidence of sex-linked lethal mutations were detected by Mittler (1976), who

exposed *Drosophila melanogaster* either to 29-MHz fields at 600 V/m or to 146-MHz fields at 63 V/m for 12 hours. Mickey (1963) reported the induction of sex-linked recessive and dominant lethal mutations in *Drosophila* following 5-min to 1-h exposures to 3- to 40-MHz fields that were pulse-modulated at pulse repetition rates of 500 to 1000 pps (pulse durations 30 to 50 μs, field strengths 80 to 300 kV/m) followed 45 min later by exposure to ionizing radiation (3000 roentgens of ^{137}Cs gamma rays at an exposure rate of 1.2 to 1.5 kR/h). The percentage of sex-linked recessive lethal mutations was 7.92 percent in the combined-treatment flies as compared with 5.98 percent in the gamma-irradiated flies and 0.32 percent in the flies exposed only to RFEM radiation. Mickey (1963) concluded that the differences are highly significant and indicate that gamma radiation and RFEM radiation in combination are more mutagenic than either type of radiation alone.

Mutagenic effects of pulse-modulated X-band fields on *E. coli* have also been investigated by Dutta *et al.* (1978). Bacteria were exposed to 1-, 10-, or 20-mW/cm^2 fields for periods of 1, 5, 10, or 15 h at frequencies of 8.6, 8.8 or 9.0 GHz. No alterations in the mutagenic end point investigated, namely repair indices, were detected at an intensity of 1 mW/cm^2, whereas greater than 10-h exposures at 10 or 20 mW/cm^2 significantly retarded repair. Exposure at 10 mW/cm^2 resulted in temperature elevations of 2 to 4 °C in the culture medium whereas elevations of 6 to 8 °C occurred at 20 mW/cm^2. The authors concluded that temperature elevations below 2 °C do not induce genetic damage. Alterations induced by exposure to 20-mW/cm^2 fields were assumed to be due to a combination of thermal and athermal effects, but the effects at 10 mW/cm^2 were not attributed to thermal mechanisms.

Effects of 200-MHz fields at 1.5 V/m on the pollen of *Antirrhinum majus* exposed for periods of 4, 12, or 44 h have also been reported (Harte, 1975). Exposure resulted in an increase in embryonic lethality and in mutations for characters of the seedlings and young plants, findings that were reported to be consistent with those obtained following exposure of pollen as well as whole plants of *Onenothera hookeri* under similar conditions (Harte, 1973a,b).

Dutta *et al.* (1979) used the Ames test to investigate the mutagenic potential of 2.45-GHz CW fields. Different strains of the bacterium *Salmonella typhimurium* were exposed for 90 min at 20 mW/cm^2. *Salmonella* also were exposed to 8.6-, 8.8-, 9.0-, 9.2-, 9.4-, or 9.6-GHz fields pulse-modulated at a pulse repetition rate of 1000 pps (1-μs pulse width at time-averaged intensities of 10 and 45 mW/cm^2 and peak powers of 10000 and 45000 mW/cm^2). No increased incidence of

mutations was detected in this series of investigations. Blevins *et al.* (1980), who used the same assay to compare the effects of conventional heating and RFEM heating in the temperature range of 68 to 83 °C, concluded that short (i.e., 2- to 20-s) exposure to 2.45-GHz fields at an estimated power density of 5100 mW/cm^2 resulted in a significant increase in mutation rate relative to the effect of conventional heating.

The dominant-lethal test was used by Varma *et al.* (1976) to investigate mutagenesis in mice exposed to 2.45- and 1.7-GHz CW fields. An increase in the mutagenicity index was detected following a single 10-min exposure of male mice to 2.45-GHz fields at 100 mW/cm^2 or following 3 exposures for 10-min each at 2-h intervals on the same day at an intensity of 50 mW/cm^2. A 30-min exposure to 1.7-GHz fields at an intensity of 50 mW/cm^2 resulted in an increase in infertility, in pre-implantation losses, and in the mutagenicity index. This index was also increased in mice exposed to fields at the same frequency for 80 min at 10 mW/cm^2. Berman *et al.* (1980) found no significant increase in mutagenesis (as indexed by the dominant-lethal test) in rats exposed to 2.45-GHz fields 4 h/day from day 6 of gestation to 90 days *post partum* at 5 mW/cm^2, in mice exposed 5 h/d for 5 days beginning on day 90 at a power density of 10 mW/cm^2, or in mice exposed for 4 weeks beginning on day 90 at a power density of 28 mW/cm^2.

With the exception of mutagenic effects in pollen and plants reported by Harte (1973a, b; 1975), power densities in excess of 1 mW/cm^2 were required for the induction of mutations. The sensitivity of pollen to mutagenesis by microwave irradiation indicates the possibility of cell-specific effects, but the available data are too limited to draw such a conclusion at this time. For the same reason, it is not possible to ascertain the extent to which the mutagenic effects of RFEM radiation are temperature dependent. There are at present no known mechanisms for the induction of mutations or chromosomal aberrations by RFEM radiation at nonthermogenic intensities.

5. Carcinogenesis

There is no well-documented evidence that exposure to RFEM radiation increases the risk of cancer induction in human beings or in experimental animals. The few instances in which it has been alleged that low-intensity fields are carcinogenic have not yet been substantiated (see, however, Section 17.6.2).

A retrospective epidemiological study in which military and other records were utilized to assess morbidity and mortality in U.S. Naval personnel revealed no statistically significant increase in the incidence of cancer in a large group of individuals occupationally exposed to microwave radiation for indeterminate durations and at indeterminate intensities. Classification of exposure was based solely on military records, and, consequently, the actual extent of exposure of either the potentially exposed workers or the unexposed controls could not be determined (Robinette *et al.*, 1980).

In a study of 1827 employees and more than 3,000 dependents potentially exposed to low levels of microwave radiation in the U.S. Embassy in Moscow, the ratio of the number of deaths due to cancer to total deaths among females (8 deaths out of a total of 11 deaths) was numerically higher but not statistically different from the ratio in a comparably sized control group serving in other East European posts (i.e., 14 cancer deaths of a total of 31 deaths) (Lilienfeld *et al.*, 1978). There were, moreover, no statistically significant differences in total cancer or mortality when comparisons were made for all employees, male and female, at the Moscow Embassy and other East European stations. (For more details, see Section 14.)

An investigation of the chronic effects of RFEM exposure of mice, which also addressed neoplastic end points, was reported by Prausnitz and Süsskind (1962). A group of 200 male Swiss mice was exposed for 59 weeks, 5 d/week for 4.5 min per exposure to 9.27-GHz fields at 500 pps, with a pulse duration of 2 μs and at a power density of 100 mW/cm^2. The source of radiation was a horn antenna in an anechoic chamber, and 100 mice were sham-exposed in an identical system simultaneously with the other mice. Exposure induced a mean elevation of rectal temperature of ~3.3 °C. Myeloid leukemia or monocytic leukosis was reported in 21 of 60 irradiated animals (35 percent) that died during the experiment as compared with 4 of 40 (10 percent)

sham-irradiated controls. (See also Section 7.1.) The incidence of lung tumors in both experimental groups was similar (i.e., 10 to 12.5 percent).

An extensive study of the effect of RFEM fields on the growth of induced and spontaneous tumors has been reported by Szmigielski *et al.* (1982a). Survival time and the latent period for development of skin cancer in BALB/C mice that were topically treated daily with 1 percent 3,4-benzopyrene were significantly reduced by 2.45-GHz CW fields (2 h/d over a period of 3 or 6 months) at power densities of 5 or 15 mW/cm^2 (*SAR*s 2 to 9 W/kg; unrestricted exposure of the body). The development of skin cancer in treated mice was associated with a lowering of a delayed hypersensitivity reaction to oxazolone and a depression of phagocytosis. Szudzinski *et al.* (1980, abstract) and Szmigielski *et al.* (1982b) also reported that RFEM exposure prior to treatment with 3,4-benzopyrene also affected the rate of skin-cancer development. They interpret these findings as indicating that microwave exposure may, under certain conditions, act as a cancer promoter.

Promotion of malignant growth and reduction of survival time were also observed in irradiated mice with spontaneously occurring mammary cancer. Cancer promotion and life-span reduction were dose-rate dependent; both occurred more rapidly at *SAR*s of 7 to 9 W/kg than at 2 to 3 W/kg. Of interest, also, is that psychogenic stress in the form of prolonged isolation and confinement of mice of special control groups was about as effective in promoting skin and mammary cancer as was irradiation at 2 to 3 W/kg.

Data relating RFEM irradiation to cancer induction are very limited. Data reviewed in Section 4 of this report indicate that chromosomal damage and mutations may be induced as a consequence of acute exposure at equivalent free-field power densities in excess of 1 mW/cm^2. These data are not inconsistent with observations that thermal stress is known to increase both mutation rates and the probability of certain types of chromosomal aberrations, although it is not possible to attribute all such effects of RFEM fields to thermalization. The basic mechanisms of carcinogenesis and mutagenesis are not well enough understood to establish the relationship between chromosomal alterations or somatic mutations and the induction of malignant cell transformations. Consequently, it is not known if transformation of chromosomes or genes, induced by RFEM radiation, will result in cancer induction.

Based on the limited available data, power densities greater than 1 mW/cm^2 are required to produce detectable levels of chromosomal damage or to increase significantly spontaneous rates of mutation. It may therefore be tentatively concluded that exposure to low intensity

RFEM fields (i.e., less than 1 mW/cm^2) will not result in an increased risk of cancer in humans. This statement must, however, be qualified because, as noted in Section 4, available data are primarily restricted to acute or short-term exposure effects in a limited number of species and with limited durations of observation.

Exposure to RFEM fields has been demonstrated to produce a wide variety of effects on neurological, immunological, biochemical, hematologic, genetic, developmental, neuroendocrine and cellular end points in mammals. Although such effects are not known to be directly related to cancer induction, it has been suggested that, because they are associated with generalized physiological stress, exposure to RFEM fields could be related, directly or indirectly, to carcinogenesis under certain, as yet undetermined, exposure conditions. The absence of data indicating increased incidence of cancer induction in human beings or in experimental animals following RFEM exposure is inconclusive because adequate sample sizes and follow-up periods have not been employed. Only large increases in relative or absolute incidence of cancer could have been detected in previous studies of RFEM radiation as a possible cause.

6. Effects on Reproduction, Growth and Development

6.1 Introduction

Any environmental agent introduced during pregnancy that interferes with development of the conceptus is termed a teratogen. Two variables of considerable importance in teratogenic studies are the gestational stage during which the agent is introduced and the species used in the study. The day of gestation serves as a marker of the particular stage of development that the conceptus is undergoing. Those tissue and organ systems that are undergoing most rapid development or proliferation during a given stage are often susceptible to insult. Most teratogens operate within critical periods that are determined both by the type of agent and the time of its administration and by the species. Not all agents produce malformations at the same gestational stage and thus no single stage can be labeled as the most susceptible period for all teratogens. Although peak sensitivity differs for specific agents, the period of early development corresponding to implantation and early organogenesis is usually a highly sensitive time. During later stages of development the organism is reportedly immune to all but the most severe insult. A typical teratogen is thus an agent that produces species-specific malformations at species-specific stages of development. These statements refer to some common characteristics of known teratogens and specific examples, as well as exceptions, can be found rather easily.

6.2 Teratogenesis in Species Other than Mammals

6.2.1 *Fish and Insects*

When embryos of the zebra fish (*Lames*) were irradiated by pulsed 2.7-GHz fields (~1-μs pulses, typically 220 pps), the embryos developed small internal bulges that enlarged until they broke. All embryonic

material flowed into the chorionic space while the chorion itself remained intact (Pyle *et al.*, 1975). In early non-differentiating embryos, the animal pole was similarly affected, but in 12-h or older embryos, the yolk sac was affected. Pyle *et al.* believe one possible explanation for this is a difference in thermal conductivities: The yolk sac is much more homogeneous than the living part of the older embryo. The temperature-control embryos were disorganized and finally became opaque after 24 hours. Precise power levels were not known. One important concern is that localized hot spots might be formed in or near membranous structures (Straub, 1977).

No changes were found in generation times after male *Drosophila* were irradiated at 2450 MHz less than 24 hours after eclosion (Pay *et al.*, 1972). Irradiation was performed in the near field for 45 min at 21 and 22.5 °C. Power densities were 4600, 5900 and 6500 mW/cm^2. An increase in the male-to-female ratio was observed at the 4600-mW/cm^2 level. At the probability level of 0.01, no recessive lethal mutations were seen. The authors believe that a short-lived RFEM-sensitive stage in early spermatogenesis cannot be excluded.

In further *Drosophila* experiments, Pay *et al.* (1978) found that egg production was decreased in conventionally heated and field-irradiated females, but the difference was not statistically significant. On the other hand, flies from conventionally heated eggs exhibited longer survival times than did those from field-exposed eggs. Irradiation by 2450-MHz CW fields was carried out in a waveguide 100 h after hatching (i.e., on premeiotic germ cells). The exposures were for 10 min at an *SAR* of 0.64 W/g. The ambient temperature was 24 ± 0.5 °C at a relative humidity of 50 ± 1.5 percent. Survival of male *Drosophila* exposed under the same conditions did not differ from controls.

Several investigators have studied teratogenesis in pupae of *Tenebrio molitor*, the darkling beetle. Carpenter and Livstone (1971) irradiated individual pupae on the first or second day of pupation with 10.15-GHz fields for 20 or 30 minutes. Input power to a waveguide exposure system was either 80 mW for 20 or 30 min or 20 mW for 120 minutes. Of the animals exposed to radiation, 25 percent died, 50 percent were abnormal, and 25 percent were normal. An assessment of temperatures was also made. They found that, at 80 mW, temperature increased by as much as 12 °C. Pupae in the 20-mW condition exhibited temperature increases of 2.5 to 3 °C. In control studies, temperatures of pupae were elevated by conventional heating to 3 °C for 20 min or to 12 °C for 20 min; the two treatments resulted, respectively, in an incidence of defective pupae of 15 percent and 25 percent.

Lindauer *et al.* (1974) also observed teratogenesis in *Tenebrio molitor* by CW irradiation at 9 GHz in a waveguide. They found that a 2-h exposure at 20 mW did not produce differences with respect to exposures to pulsed fields at 20 mW for 2 hours; nor did effects of irradiation at either of these exposure conditions differ from that at 10 mW CW for 4 hours. Liu *et al.* (1975) confirmed the initial results of Carpenter and Livstone and demonstrated that the extent of teratological damage depended on the quantity of energy absorbed and the pupal age at the time of irradiation rather than on specimen orientation, power level, or pulsed versus CW radiation.

Green *et al.* (1977) reported results from eight experiments conducted at a frequency of 9 GHz in a waveguide and at power levels from 20 mW to 320 mW. The duration of exposure was 2 h in seven of the experiments and 16 hours in one experiment. They divided the pupae into three conditions prior to experimentation: ideal, non-ideal, and discards. The ideal pupae were free from any obvious defects, the non-ideal possessed some defects and the discards were damaged to the extent that survival was unlikely. Only ideal and non-ideal pupae were used in the microwave exposures. The authors reported that irradiation at 20 mW and above produced teratogenic effects in both sets of insects. The average temperature rise was less than 2 °C at 20 mW, and the non-ideal pupae suffered more damage from irradiation than ideal pupae. Irradiation at 320 mW for 2 h was invariably lethal, and irradiation at 160 mW for 2 h resulted in 10-percent lethality.

Because in all previous studies the electric and magnetic fields interacted simultaneously with the waveguide-mounted pupae, Olsen (1977) investigated them independently at frequencies of 4 GHz or 5.95 GHz; the pupae were oriented for maximal coupling of the electric field or of the magnetic field. The *SA* in the pupae ranged from 37.8 to 1526 kJ/kg. Exposures ranged from 5 min to 6 hours. In 200 sham-exposed insects only two abnormalities appeared. Olsen concluded that teratogenesis can result both from electric-field and magnetic-field exposures and that, for a given exposure, the differences in the effects seen in the two fields can be quite dramatic. Although no statistical analysis of the results was presented, the author stated that incidence of teratogenic effects correlated more highly with the *SA* than with the *SAR*.

Pickard and Olsen (1979) reported data from Olsen's earlier investigation (1977). Pupae from an in-house colony, as well as pupae purchased from an outside supplier, were used. The in-house colony (colony pupae) was maintained on ground Purina dairy meal and sliced potatoes, and the outside colony (K pupae) was maintained on

Kellogg's Special-K and sliced potatoes. All irradiation was administered in an anechoic chamber in the far zone of a standard-gain horn antenna at either 5.95 or 10.025 GHz. Exposures were performed under one of four conditions of pupal orientation: (1) a 3 × 4 array with the long axis of each pupa parallel to the electric vector in a standing-wave field; (2) a 3 × 4 array with the long axis oriented parallel to the magnetic vector in a standing-wave field; (3) a 3 × 4 array with the long axis oriented parallel to the electric vector in a travelling-wave field; and (4) pupae individually inserted in perforated capsules that were placed loosely into horizontal holes drilled through a vertical Styrofoam plank and the head of each pupa faced into the line of propagation of the field.

Exposure at 5.95 GHz with the long axes parallel to the electric field produced no significant differences. Exposure with the long axes parallel to the magnetic fields had an injurious effect on the K pupae but not on the colony pupae. The results showed clearly that the colony pupae and K pupae differ. Analysis of the additional exposure conditions produced results that are difficult to interpret in that the greatest differences occurred between the colony pupae and the K pupae. There was some indication that irradiation produced teratogenesis.

6.2.2 *Avian Species*

Several teratogenic and/or developmental effects also have been observed in investigations of chick embryos. Van Ummersen (1961) was one of the first to report abnormal development of chick embryos exposed to 2450-MHz CW fields. She irradiated the embryos *in ovo* at the 48-h stage of development in an anechoic chamber at power densities of 200 to 400 mW/cm^2. After irradiation, the embryos were allowed to grow for another 48 hours before removal and examination, followed by preservation, staining, and serial sectioning. There were 366 irradiated eggs and 109 non-irradiated controls. At 400 mW/cm^2, there were no appreciable deviations from the controls when the exposure lasted for 1 to 4 minutes. After 4.5 to 5 min of irradiation, abnormalities were observed. Irradiation for another 30 s was lethal. Of the 109 controls, 106 developed normally as did 142 of the 366 irradiated. One-hundred and three embryos died before 48 hours had elapsed after irradiation.

Van Ummersen indicated that lethality of embryos was associated with an *in-ovo* temperature of 59 °C. She didn't measure temperatures in eggs with embryos, but based her measurements on non-fertilized

control eggs that had been punctured before irradiation by a thermal probe. Maximal temperatures were recorded in that region of the punctured eggs proximal to the RFEM source.

More extensive work on teratogenic and developmental effects has been conducted on Japanese quail eggs by a second group of investigators. McRee *et al.* (1975) exposed Japanese quail eggs to 2.45-GHz fields at 30 mW/cm^2, which resulted in an *SAR* of 14 W/kg. Animals were exposed in an environment at a relative humidity of 40 percent, and the temperature of the eggs was 35 ± 2 °C. The irrradiation took place for 4 h at the end of days 1, 2, 3, 4, or 5 of the incubation period. One group was exposed on all five of these days. Although a large number of gross anatomical and hematological end points was assessed, the only statistically significant finding was a slight decrease in hemoglobin associated with exposure on day 2.

In further investigations of exposures on day 2 of the incubation period, Hamrick and McRee (1975) found no significant effects following irradiation of eggs at 2.45 GHz and at an *SAR* of 14 W/kg. This study did not elevate the temperatures of the eggs beyond those normally associated with incubation.

In addition to their acute studies, McRee and Hamrick (1977) reported on irradiation of eggs by 2.45-GHz fields at power densities of 5 mW/cm^2 throughout the first 12 days of development. The *SAR* was 4.03 W/kg. An initial study in which hyperthermia was induced by conventional heating resulted in only 5 percent of the eggs actually hatching. They lowered the temperature so that the exposed eggs were at 37.5 to 38 °C while the controls were maintained at 38 °C. At normal temperatures, no excess abnormalities were observed in the exposed quail at hatch, i.e., no differences in body mass, mass of the heart, liver, gizzard, adrenal gland, or pancreas were seen. No differences in hematocrit level, red blood cells, white blood cells, lymphocytes, heterophils, basophils, or eosinophils were observed. They did find that the titer of hemoglobin was increased by 4 percent in the exposed animals and that the monocyte count was decreased in the exposed animals. They hypothesized that the decreased monocyte count might indicate a change in immune responsiveness and, thus, an additional study was conducted (Hamrick *et al.*, 1977) to assess the development of immunological competence. One hundred twenty eggs were exposed throughout the first 12 days of development to 2.45-GHz fields at 5 mW/cm^2. During irradiation, the eggs were at temperatures between 37.5 and 38 °C. The chicks were observed from hatch to five weeks of age. The mean of body mass as assessed at hatch and weekly thereafter was numerically, but not statistically, lower in exposed than in control animals. Masses of immunologically important organs

(spleen and bursa of Fabricus) did not differ. No difference was observed in mortality. Both sexes developed normally, including immune competence. These studies were analyzed by multiple comparisons with Student's *t* test, even though the data are time dependent.

6.3 Teratogenesis in Mammals

The *in-utero* development of a mammal may be divided into three stages. The pre-implantation period is that time between fertilization of the egg and it's attachment to the uterine wall. The following stage is that during which the major organs are being formed and is termed "organogenesis". The final stage of growth is the fetal period. In general, an insult introduced during the pre-implantation phase results in a high proportion of embryonic death and resorption. The incidence of specific malformations is more likely to occur if the insult is introduced during organogenesis.

At high intensities, RFEM fields induce hyperthermia. Thermal stress has been shown to be teratogenic in several species and, therefore, is of specific interest to the study of RFEM radiation. Edwards and his colleagues have demonstrated not only that thermal stress can be injurious to fetal development but also that the nature, as well as the extent, of the teratogenic insult depends to a high degree on the mammalian species (Edwards, 1968; Edwards and Wanner, 1977; Edwards *et al.*, 1974, 1976; Johnson *et al.*, 1976; and Wanner *et al.*, 1976). For example, the guinea-pig embryo that survives severe hyperthermia will probably exhibit defects of the eyes, limbs, or brain. Also in the guinea pig, both abortions and fetal malformations tend to occur at lower elevations of temperature than those needed to produce maternal death. Rats, however, tend to resorb their thermally insulted embryos, and few fetal abnormalities have been observed at temperature elevations that do not produce a relatively high incidence of maternal death.

Of more recent concern is the identification of *behavioral* toxins or teratogens (Bari Kolata, 1978, 1979; Wilson, 1977), i.e., agents that produce deficits of behavior. Behavioral teratogenesis has been noted on a few occasions in conjunction with the production of structural abnormalities, but performance deficits that occur in the absence of more gross teratogenic anomalies have not been investigated widely. Indeed, the methodology typically employed to assess structural defects requires removal and necropsy of fetuses prior to normal parturition, and this procedure precludes postnatal assessment of behavior. This more recent concern can also be viewed as a broadening of the

field of teratology. The term, *terata* (monsters), defines a physical malformation, one induced, for example, by *in-utero* exposure to a toxic agent. Therefore, the conventional teratogenic study is associated with the tendency to restrict the term "teratology" to the study of structural malformations and histological anomalies.

6.4 Experimental Studies of Mammals

Most reports of RFEM-induced teratogenesis have appeared since the early 1970s. The reported studies differ considerably both in the teratogenic variables and in the irradiation parameters employed with the exception that most investigations were based on acute exposures to 2450-MHz fields at high intensities. Some studies are reviewed in which animals were exposed prenatally, but in which teratogenic end points were not the primary focus of investigation. In all reported studies of mammals, the mouse or rat has been used as the subject. Before beginning a detailed analysis of each study, it should be noted that the manner in which the pregnancy was timed is not indicated in a number of the reviewed studies. Kalter (1968) suggests that if the females are checked for vaginal plugs or sperm once per day, then the day on which the female is judged sperm-positive should be counted as day 1 of gestation. Studies not providing the information on timing of conception are presented as reported by the authors.

6.4.1 *Teratogenesis in the Rat*

Dietzel (1975) exposed 749 maternal rats, whose pregnancies were timed (7800 implantations), to 27-MHz fields that were generated by a Siemens diathermy machine at power settings of 55 W for 5 min, 70 W for 10 min, or 100 W for 10 minutes. His report does not include dosimetric information or field intensities, but the mean rectal temperatures associated with the three treatment conditions are, respectively, at 39.0, 40.5 and 42.0 °C. All exposures were acute and were given during a single day of gestation from the 7th to the 15th day. Most of the observed malformations occurred as a result of exposure on days 9, 13, or 14, and the highest incidence of abnormalities occurred in association with irradiation on days 13 and 14. The abnormalities observed were in the extremities. An increased incidence of resorption of conceptuses in irradiated animals also was reported. The percentage of fetuses with abnormalities was 0.25 percent for the control group, 0.27 percent for the 55-W condition, 12.4 percent for

the 70-W condition, and 46.1 percent for the 100-W condition. Dietzel attributed the malformations to excessive heating. He observed that RFEM irradiation at the higher levels often resulted in fetal death.

A study, in which teratogenic end points were not the primary focus, involved Long-Evans rats that were irradiated *in utero* on the 9th or 16th day of gestation by 2450-MHz CW fields (Michaelson *et al.*, 1976). Averaged power densities of incident radiation applied dorsally for 1 h were either 10 mW/cm^2 or 40 mW/cm^2. Controls were sham irradiated. At parturition, no change was noted in litter size, gestation time, growth rate, or development of pups. The pups were observed to time of weaning. Oxygen consumption of pups in a cold environment was measured, and increased consumption was observed in pups that had been exposed prenatally to 40 mW/cm^2 as compared with controls and with those whose dams were exposed to the 10-mW/cm^2 field. No differences in O_2 consumption were observed at normal environmental temperatures. In all three groups, comparable levels of corticosterone and thyroxine were observed.

Another investigation in which irradiation was administered prenatally was that of Shore *et al.* (1977). They reported on 24 Sprague-Dawley rats whose dams were exposed to 2450-MHz fields at 10 mW/cm^2 for 5 hours per day from day 4 through day 20 of gestation. During each exposure, 12 rats were oriented with the long axis of the body parallel to the electric-field vector while another 12 were oriented parallel to the magnetic-field vector. Environmental temperatures in the irradiation and sham-irradiation chambers were not controlled. Ambient temperatures during the sham exposures averaged 22.8 ± 0.2 °C compared with 25.5 ± 0.7 °C for the experimental chamber. At parturition, no differences were observed in litter size or in mortality rate. Body mass and brain mass of the pups were assessed on days 2, 3, 6, 7, 8, 9, 14, or 15 after birth. Exposed animals were significantly smaller in body mass on day 3 only. Coupling of energy is stronger in the case of exposure parallel to the electric-field vector, which is consonant with the finding that pups thrown by the dams so exposed were smaller than those of the dams exposed parallel to the magnetic-field vector. Based on comparison between fetally irradiated and sham-irradiated pups on each of the eight days by repeatedly applied t tests of two pairs of means, body masses were significantly smaller only on the third postpartum day. It should be pointed out, however, that such t tests can result in spuriously high probabilities of rejecting null differences.

Infrared-irradiated controls were employed by Chernovetz *et al.*, (1977) who exposed Holtzman-derived, Sprague-Dawley rats to 2450-MHz fields in a multi-mode cavity at an *SAR* of 31 ± 3 W/kg for 20

minutes. The RFEM exposure was matched to the infrared exposure on the basis of duration and of averaged increment of colonic temperature ($\Delta\overline{T} = 3.4$ °C). The animals were acutely exposed once on days 10, 11, 12, 13, 14, 15, or 16 of gestation. All results were analyzed by analysis of variance.

Day of treatment was not a statistically significant factor, but an increased number of fetal resorptions occurred in dams exposed to RFEM fields. The mean fetal mass of controls was significantly larger than the mean of fetuses whose dams had been subjected to RFEM or infrared irradiation. In addition to the standard anatomical analyses, fetal brains were removed and analyzed for content of norepinephrine and dopamine. Significantly less norepinephrine was observed in brains of fetuses whose dams had been exposed to RFEM radiation. Dopamine content of the fetal brains was reduced in RFEM-irradiated animals, but failed to differ significantly from that in control and infrared-irradiated animals.

The coefficient of correlation between post-treatment temperatures of surviving dams and percentages of living fetuses is high and negative ($r = -0.89$, $p \leq 0.01$). Although specific anatomical abnormalities were not observed in any of the fetuses, the RFEM irradiation was sufficiently intense to kill 23 percent of the dams. The authors speculated that the probability of teratogenic insult by RFEM radiation of the embryo or fetus is smaller than the dam's probability of lethality.

In a later study of rats, Chernovetz *et al.* (1979a) employed *SAR*s of 14 or 28 W/kg for 20 minutes, and reported no specific morphologic abnormalities or increase of resorptions from exposure of fetuses to 2450-MHz fields in a multimode cavity on days 8, 10, 12, or 14 of gestation. Once again, day of treatment was not a significant factor, and no lethality resulted from the treatment, although the post-treatment temperature of the dams in the 28-W/kg condition did reach 42 °C.

In a third study, irradiation at *SAR*s of 0, 17, or 31 W/kg in 2450-MHz fields for 20 minutes at gestational days 8, 10, 12, or 14 resulted in post-treatment means of temperatures of 43 °C and in a lethality rate of 21 percent for dams exposed at the 31-W/kg level (Chernovetz *et al.*, 1979b). As before, day of treatment was not a significant factor. The incidence of resorptions and of abnormalities was increased above that of controls at the *SAR* of 31 W/kg. Exencephaly was the most frequently observed abnormality. The mean of fetal body mass was smallest at 31 W/kg, but means of fetal brain mass differed little across levels of exposure. Regression analyses revealed that both peak temperature and *SAR* correlated positively with the incidence of resorptions and of abnormalities. The regression of fetal brain mass

on fetal body mass revealed a tendency for animals exposed at 31 W/kg to be macrocephalic, while animals exposed at 17 W/kg tended to be microcephalic.

Taken together, the three studies by Chernovetz *et al.* provide evidence that, in the laboratory rat, the *SAR* threshold of structural teratogenesis is near or even above the *SAR* threshold of lethality of the dam. In addition, the results of the three studies clearly parallel the heat-stress literature in the observation of a narrow range of temperatures at which damage occurs in fetuses of surviving dams.

This conclusion was subsequently confirmed by Berman *et al.* (1979). They exposed Sprague-Dawley rats to 2.45-GHz fields at a power density of 0 or 28 mW/cm^2 for 100 min daily on days 6 through 15 after breeding. Several additional animals were exposed at 40 mW/cm^2. The authors concluded that 2.45-GHz fields do not produce a strong teratogenic effect in the rat unless the dams are severely stressed thermally. Lary *et al.* (1979) reported data on exposures in 27-MHz fields of eight groups of gravid rats, each group containing 16 to 28 animals. The facility for exposing animals was a near-field synthesizer operating in the dominant magnetic-field mode at a field strength of 55 A/m. Dams were exposed on day, 2, 4, 6, 8, 10, 12, 14, or 16 for 20 to 40 min until rectal temperatures reached 43.0 °C. Eight groups of rats were sham irradiated for 30 min and another group of 29 rats served as reference controls. Dams irradiated on days 8 through 16 produced conceptuses that exhibited a significant increase in gross malformations and a significant decrease in fetal mass and fetal crown-to-rump length. No information was given about statistical tests used in the analysis of the data, nor was there any mention of maternal mortality.

Jensh *et al.* (1978b, abstract) reported on the effects of protracted prenatal exposure of Wistar derived rats to 2450-MHz fields for 8 h daily for 14 d during gestation at a power density of 20 mW/cm^2. No statistically significant differences were observed between control and exposed animals on the variables of maternal mass, embryonic or fetal resorption rate, abnormality rate, and the fetal and placental masses at term. These same authors reported similar experiments in which 915-MHz fields were employed (Jensh *et al.*, 1977, abstract; 1978a, abstract). They exposed 10 Wistar rats at 10 mW/cm^2 for 8 h daily during 14 d of the gestational period. Post-exposure rectal temperatures of dams showed no increase over baseline temperatures. No differences were observed in frequency of embryonic or fetal death, in incidence of abnormalities, and in fetal mass, litter size, placental mass, fetal sex ratio, maternal mass or maternal gain of mass.

In yet another study (Jensh *et al.*, 1978a), 11 gravid Wistar rats

were exposed about 8 h daily during pregnancy to 915-MHz fields at 10 mW/cm^2. The average of total exposure times was 109 hours. Within 3 d after natural birth, the reflexes of the pups were tested and found to be normal. After the pups were weaned, a series of performance tests was administered beginning on postpartum day 60 and completed by the 90th day. No detrimental effects were observed on performance in a water T-maze, on avoidance behavior, on open-field behavior, on forelimb hanging, or on daily revolutions of an activity wheel. More recently, Jensh *et al.* (1979a, b, abstracts) reported no observable teratology in rats exposed throughout gestation to 6000-MHz fields at 35 mW/cm^2. The authors of these studies state that the irradiation was "non-thermal," but no *SA*s or *SAR*s are reported for any of their exposure conditions.

Johnson, R. B. *et al.* (1977) exposed pregnant rats to 918-MHz CW fields at 5 mW/cm^2 for 20 h/d over 19 days of gestation. Groups of 8 rats each were exposed, sham-exposed, or served as reference controls. All rats were allowed to deliver their offspring, and no teratogenic assessment of possible structural anomalies was made. However, the pups were weighed and examined at birth and the authors reported no grossly discernable defects in the neonates. Additional information on the results of this study appears in the section on behavior (Section 12).

In summary of studies of the rat: Most of the significant results are based on exposure of dams to highly intense fields that frequently has proved fatal to the dam. Increases in incidence of resorptions and decreases of fetal mass are the most commonly reported effects.

6.4.2 *Teratogenesis in the Mouse*

The investigations that have produced the clearest demonstration of RFEM-induced teratogenesis have been conducted on the mouse. Most of these studies have been conducted on random-bred animals, although one study has been reported on an inbred mouse. A frequently cited report of teratogenesis as a result of RFEM irradiation is the 1974 study of Rugh *et al.* In this study, over 200 litters of CF-1 mice were exposed to 2450-MHz fields at varying *SA*s (12.5 to 33.5 kJ/kg) for a maximal duration of 5 minutes. The number of abnormalities (both specific malformations and resorptions) increased as the *SA* increased, and the authors stated that this indicated existence of a linear dose-response relationship. The data were reported only graphically, each point representing the percentage of abnormal fetuses in

a single litter. The percentage of litters at a given *SA* that contained abnormalities or the percentage of abnormalities per implantation were not reported. The most frequently observed anatomical abnormality was exencephaly. The percentage of fetuses in a litter that exhibited exencephaly appeared to increase as *SA* increased.

A 1975 report on 855 litters of CF-1 mice also described the environmentally controlled waveguide apparatus used in all exposures reported by Rugh and his colleagues (Rugh *et al.*, 1975). In this apparatus, temperature, relative humidity, and air flow were closely regulated. Temperature and humidity were maintained and monitored during the exposures at a T-H index (THI) of 71.6. The authors found that the average lethal *SA* decreased as the THI increased. Second, they found the LD_{50} of diestrous females to be ~48 kJ/kg as compared with ~44.5 kJ/kg for estrous females. The authors concluded that the female mouse is more susceptible to microwave radiation during estrous. In a third study, CF-1 mice were exposed on the 8th day of gestation for a maximum of 5 min at a THI of 71.6 and at an estimated power density of ~123 mW/cm^2. The incidence of exencephaly in the three studies increased as the level of radiation increased. The data of Rugh *et al.* are difficult to quantify because they are reported only graphically, each point representing the percentage of affected fetuses within a single litter.

Rugh and McManaway (1976a, abstract) irradiated individual CF-1 mice without anesthesia or restraint in a waveguide at 2450 MHz CW and at a mean *SAR* of 107 W/kg (range 71 to 136 W/kg). The mice were gravid and were exposed 4 min/d from day 0 through day 11 of gestation. Day 12 is the approximate end of the period of active organogenesis after which congenital anomalies of a gross nature can seldom be induced. Including resorptions and dead and anomalous offspring, 20 percent on days 3 and 4 were affected, 28 percent on day 10, and 68 percent on day 8. When only survivors with gross anomalies were counted, there were two peaks in survival: gestation days 4 and 8. Day 4 is the day of implantation, and day 8 is the beginning of organogenesis. Unfortunately, these results were reported in an abstract and no details were given on controls, temperatures attained, or on the numbers of animals involved.

In a more detailed report, Rugh and McManaway (1976b) described the combined effects of pentobarbital anesthesia and irradiation on 130 gravid CF-1 mice. The mice were exposed individually on the 8th day of gestation in a waveguide at 2450 MHz while being monitored for *SAR*. The exposure duration was 4 minutes. A total of 1328 offspring was examined, 327 of which were controls. On the 18th day of gestation each dam was euthanatized, and the fetuses were removed

and examined for stunting, anomalies and lethality. Also, each dam was examined for resorbed concepti. In controls (anesthetized but not irradiated) there were no dead or anomalous fetuses and only 4 percent were resorbed, well within the expected limits. In dams irradiated without anesthesia, the incidence of damaged fetuses was highest: 32 percent resorptions, 5.7 percent deaths, and 2.3 percent anomalies. In contrast, when dams were irradiated under anesthesia for 4 min, the incidences of morbidity and mortality in fetuses did not differ from those of non-irradiated controls. Controls restrained but not anesthetized showed a definite lack of protection against lethality. Anesthesia reduced the core temperature of these mice by 4 to 5 °C and irradiation elevated it by a similar amount, changes that provide further evidence that the primary effect of intense irradiation is thermal.

Chernovetz *et al.* (1975) reported on the C3H/HeJ mouse, an inbred, pigmented animal. In a series of studies, the authors extended the standard teratogenic investigation and included a report on the interaction of RFEM radiation with a known teratogen, cortisone. In addition, some irradiated dams were allowed to deliver their offspring, and survival rates, as well as functional deficits, were assessed in the pups after weaning. In the first study, 80 mice were exposed once for 10 min on day 11, 12, 13, or 14 of gestation to 2450-MHz fields at an *SAR* of 38 W/kg. This factorially designed study included irradiation versus sham irradiation and injection versus sham injection of cortisone. The cortisone was administered as a 5-mg intraperitoneal injection 37 ± 8 min before irradiation or sham-irradiation was initiated. Irradiation alone did not alter significantly the incidence of malformations. Some structural defects of the tail were observed in both irradiated and cortisone-treated mice, but the differences among the four groups were not statistically significant. The highest incidence of abnormalities was associated with the combined, irradiation-and-cortisone treatment on day 14 of gestation.

In the second study of the series to investigate *functional* teratology, 4 groups of 15 gravid mice each were treated in the factorial manner described above but only on day 14 of gestation. The animals were allowed to come to term, and the results indicated that cortisone treatment reduced the survival rate and that irradiation had no significant effects. The survival rate of pups whose dams had been given the combined treatment was significantly higher than that of pups from dams that received cortisone only. There were indications that irradiation ameliorated the toxic effects of cortisone.

In the third study, the functional competence of the prenatally exposed animals was also assessed. After weaning, the animals were challenged by a reversal-learning task in a modified Lashley-III water

maze. No statistical evidence of functional deficits resulting from RFEM radiation was observed.

Rugh *et al.* (1976) reported further studies on CF-1 mice exposed to 2450-MHz fields for 4 min at *SAR*s of 78.8 to 136.2 W/kg (average = 107.4 W/kg). Teratogenic effects were observed, the majority occuring in association with exposure on day 8 or 10 of gestation. In a later study (Rugh and McManaway, 1976c, abstract) in which the average *SAR* was 107.4 W/kg, the authors observed that 68 percent of the animals exposed on day 8 were either resorbed, dead, or abnormal as compared with 28 percent of the animals exposed on day 10, and with 20 percent of the animals exposed on days 3 or 4. The authors suggested two main peaks of teratogenic susceptibility: the first on day 4, which corresponds to the time of implantation of the embryo in the uterine horn, and the second at day 8, which corresponds to the beginning of organogenesis. In evaluating these results, it is important to note that 100 W/kg for 4 min (24 kJ/kg) is near the acute *SA* threshold for producing convulsions for the mouse.

Berman *et al.* (1978) have reported results of repeated exposure of the CD-1 mouse to 2450-MHz CW fields. Mice of more than 300 litters were exposed for 100 min daily during gestation (day 1 through day 18). The animals were exposed at power densities of 3.4 mW/cm^2 (*SAR*, 2 W/kg), 13.6 mW/cm^2 (*SAR*, 8.1 W/kg), or 28 mW/cm^2 (*SAR*, 22.2 W/kg). The anechoic chamber was maintained at 20.2 ± 0.5 °C and at 50-percent humidity. The authors reported that the irradiation resulted in no elevation of body temperatures. However, the exposed animals did exhibit and maintain a temperature approximately 1 °C above normal resting temperatures. The sham-exposed animals show this same 1-°C elevation before exposure but they do not maintain it—they return to the normal resting level (~37.5 °C) by the end of the 100-min sham exposure. The mean mass of live fetuses per litter was significantly decreased in the animals exposed at 28 mW/cm^2. The incidence of cranioschisis in the animals exposed to RFEM fields was not different from that of controls for any one of the three power densities, but, when the incidence of cranioschisis was summed across groups, a significantly higher number of fetuses with cranioschists occurred in the irradiated groups. The results of this study are similar to those of Rugh and McManaway (1976b), although the exposure conditions are considerably different. This study appears to represent the only published report of teratogenic effects resulting from long-term, relatively low-level exposure to microwave radiation.

Preskorn *et al.* (1978) reported retarded tumor growth and greater longevity in CFW mice following fetal irradiation by 2450-MHz fields.

The mice received radiation treatments at 35 ± 3 W/kg for 20 min on the 11th, 12th, 13th, and 14th days of gestation. The mice were implanted with a homogenate of a lymphoreticular cell sarcoma on the 16th day postpartum. Irradiation did not alter the incidence of tumors, but they developed at a slower rate in the fetally irradiated animals.

Nelson *et al.* (1979) repeatedly exposed 236 dams (C3H mice) at 148 MHz for 1 h daily from day 2 through day 19 of gestation. Exposures occurred in a rectangular coaxial exposure system at 0.5 mW/cm^2, which corresponds to an *SAR* of 0.013 W/kg. The experiment was conducted as three separate replications with 80, 40 and 80 animals, respectively. In each of the experiments some of the dams were allowed to come to term, and their fetuses were assessed for body mass at birth and again at 60 days of age. In the first two experiments, fetuses of the sham-irradiated groups weighed less than fetuses of the irradiated group under both Caesarean- and natural-born conditions. In the third experiment, the body mass of Caesarean-delivered fetuses did not differ, but that of the natural-born pups did. The irradiated pups weighed less than the sham-exposed pups both at birth and at 60 days postpartum. No statistically significant differences, in percentage of resorbed, stillborn, or abnormal fetuses were observed in any of the three experiments.

McRee and Nawrot (1979) exposed pregnant CD-1 mice to 2.45-GHz CW fields at power densities of 5 mW/cm^2 (*SAR*, 4.25 W/kg), and 30 mW/cm^2 (*SAR*, 25.5 W/kg), for 8 h daily. Dams of the 5-mW/cm^2 group were exposed daily from day 1 through day 15 of gestation, while dams of the 21-mW/cm^2 and 30-mW/cm^2 groups were divided into 2 groups and exposed either from day 1 through 6 or from day 6 through 15 of gestation. Both reference controls (non-handled) and sham-irradiated (handled) controls were employed as were handled and non-handled control groups that were subjected to elevated ambient temperatures. The results of the study indicated a decrease in pregnancy rate due merely to handling during days 1 through 6 of gestation (86 percent non-handled versus 72 percent handled). Dams exposed at 21 mW/cm^2 and 30 mW/cm^2 on gestational days 1 through 6 exhibited further reduction in pregnancy rates to 65 percent and 50 percent, respectively. Handling also produced significant retardation in the gain of dams' body mass. Average fetal mass for the combined, handling- and heated-groups was reduced but no differences were observed between irradiated-and-handled and conventionally heated-and-handled animals. In addition, 3.1 percent of the fetuses exposed at 30 mW/cm^2 on days 6 through 15 of gestation were malformed.

6.4.3 *Observations in Human Populations*

There are indirect reports of case studies of increases in congenital abnormalities in women working in RFEM fields in Eastern Europe (Marha, 1969), but there are no unequivocal reports of RFEM-induced malformations in the human being. However, as indicated in Section 14 on Studies of Human Beings, most surveys involving exposure of human beings have been conducted on men. Parturition has been studied by Daels (1973, 1976) in women who received 2450-MHz irradiation of the uterine wall as an analgesic during parturition. In his 1976 study, he compared 2000 irradiated patients with 2000 control patients. Radiation was applied intermittently to the abdomen during contractions and were sufficiently intense to increase fetal temperature by 1 °C. He found that 1,936 women indicated that the analgesic effect of the RFEM treatment was good; 64 indicated it was moderate. He reports that the temperature of the amniotic fluid was never raised above 36.5 °C and that the temperature of the newborn was never raised above 37.8 °C. He has now treated more than 10,000 women and has indicated that he has never seen any abnormalities as a result of this RFEM treatment (Justesen, 1978). However, the human fetus at parturition is almost fully developed, and gross structural defects would not be expected to result at such a late stage.

The use of diathermy in gynecology was first reported by Gellhorn in 1928. In more recent times, diathermy of pregnant women has been discouraged, and most reports of such exposure indicate that the pregnancy was not known at the time of treatment. Imrie (1971) reported case studies of three women who were treated with shortwave diathermy of the pelvic region during early stages of pregnancy. Two of the pregnancies proceeded normally and one woman aborted.

In an earlier and not-well-documented clinical report, Rubin and Erdman (1959) observed four pregnant women who received 2450-MHz diathermy treatments. Only the input power (100 W) was reported. Three of the women delivered normal infants and a fourth aborted on day 67. The same woman who aborted later delivered a normal infant following diathermy treatment during pregnancy. All four of these women were being treated for chronic pelvic inflammatory disease.

6.5 Discussion

With respect to basic design, procedure, and variables assessed, the studies reported to date have been more diverse than decisive. Wide

variation in exposure parameters makes it difficult to compare results; additional difficulty is generated because many of the reports do not contain information on critical variables. For example, some reports on mammals do not indicate the manner in which the day of gestation was timed. The day on which the animal is sperm or sperm-plug positive can be timed as day 0 or as day 1. The manner in which control animals were treated is often not given and, when specified, is highly variable; i.e., many kinds of controls have been employed including passive (caged) controls, sham-exposed controls, heated (infrared-irradiated) controls, and historic controls. In some reports, statistical or probability statements have been substituted for data from control animals. Multiple control procedures in single experiments have not been used extensively.

Prior to the 1970s, there was no consensual procedure for measuring and referring to *SA*s and *SAR*s in biological studies of RFEM fields (Justesen and King, 1970; Justesen, 1975; Guy, 1975; Süsskind, 1975; Johnson, 1975; Johnson, C. C. *et al.*, 1977). Many investigations have been reported that provided no information by which to calculate quantities and rates of energy absorption.

The problem of differentiating thermal from athermal effects is just as apparent in teratogenic studies as it is in other RFEM investigations. Specific to the teratogenic investigations is that many of the authors who reported defects have employed acute, highly intense irradiation that obviously has placed a thermal burden on the irradiated subject. Some investigators have attempted to control for temperature by including controls heated by infrared energy. In spite of all the difficulties, the teratogenic data resulting from thermal stress are quite similar. For example, the laboratory rat does not have a high incidence of specific anatomical defects in response to severe hyperthermia. Also, the elevations of temperature required to produce teratogenic effects in the rat embryo or fetus are frequently lethal to the dam.

Many of the teratogenic studies of RFEM radiation have been performed without a sufficient number of animals, and others lack rigorous design and, thus, do not allow for observation of low-probability events. One could argue that any increase in the incidence of fetal damage, regardless of how low, should be considered as a possible biologically significant event, even if it is not statistically significant. While few adequate and rigorous designs have been employed, more critical to the assessment of demonstrated teratogenic potential of microwaves is that statistical analyses are often not given in enough detail to permit evaluation.

If attention is focused not on procedural questions but only on

similarities in the results of the studies, several trends are apparent. The most common result of embryonic or fetal irradiation would appear to be a non-specific, general response, that of reduced, or retarded gains, of body mass. Without further study, it is impossible to know if this decrease is maintained after birth and when, if ever, the possibly stunted fetuses catch up. It is important to note that this inhibitory effect on body mass is the only observation that is commonly reported across the range of species that have been studied.

Only a few specific abnormalities have been reported. Both Dietzel (1975) and Chernovetz *et al.* (1975) observed evidence of tail abnormalities in the rat and the mouse. Rugh and McManaway (1976a) Conover *et al.* (1978), and Berman *et al.* (1978) reported increased incidence of exencephaly.

A deleterious response that is frequently seen in the intensely irradiated mammal is an increased incidence of fetal resorption. The increase may be indicative of malformed fetuses, but the resorption of fetal materials precludes a more detailed analysis and, thus, identification of which, if any, structures were damaged. The increased rate of resorption, and the range of exposures within which it occurs, are remarkably similar to those associated with thermal stress. Particularly in the rat, resorptions appear to occur within a rather narrow band of temperatures, the upper bound of which is hyperthermal death of the dam. Most defects have been observed following high-intensity, acute exposures that induce sizeable temperature differences. It is tempting to conclude that all of the observed effects are thermal in nature but there are a few investigations purporting defects in the absence of a measurable temperature increment (Berman *et al.*, 1978; Jensh *et al.*, 1978b). A strictly thermal conclusion would be premature because, at frequencies that are highly penetrating in human tissue and at levels that appear non-thermal, there are very few studies reported.

6.6 Summary and Conclusions

Although the incidence and dose-response relationship of radiation-induced teratogenesis cannot be clearly specified or outlined on the basis of the current literature, it is clear that RFEM radiation can produce teratogenic effects. Whether this teratogenic influence is derived primarily from thermal stress or from some frequency- or field-specific action of the RFEM radiation, or from a combination of

the two, has not been determined. The generality, as well as the implication, of the results for human exposure also have not been clearly demonstrated. Many of the studies have been conducted at 2450 MHz, one of the most commonly used frequencies, but one at which irradiation does not penetrate deeply into the human body. The question of possible teratogenic effects from low-level, long-term exposures has been addressed in only a few studies and the results are not conclusive. Most of the studies have used albino organisms and the species used most frequently, the albino rat, appears to be more resistant than other frequently studied rodents to heat-stress-induced teratogenesis (Edwards and Wanner, 1977).

The next step is to define more clearly the variables associated with damage to the conceptus and to begin to search for mechanisms of action. The preliminary work of determining whether RFEM radiation can be teratogenic at *any* level is completed. Studies now need to be developed that more closely parallel the conditions under which human organisms are most likely to encounter RFEM fields. A wider range of carrier frequencies needs to be explored to establish the generality of the findings based almost exclusively on 2450 MHz. There is an obvious need to look at long-term exposures to relatively weak fields. Studies are also needed to test a broader range of end points pertinent to behavioral toxicology and teratology. Environmental stresses in combination with RFEM fields are especially in need of exploration.

7. Effects on Hematopoietic and Immune Systems

Reports on the response of the hematopoietic system to RFEM radiation yield conflicting results. Early studies frequently involved fields at power densities now known to produce elevations of body temperature. In addition, many studies were done without adequate measurements of the fields, and most without any measurements of absorbed energy. Animals were often exposed in multiply-housed arrays that may have enhanced or attenuated the field, and sham-exposed controls were seldom included. Many of these deficiencies in experimental design have been overcome over the past few years because of more sophisticated instrumentation, greater appreciation of the importance of absorbed-energy measurements, and recognition of the need for sham-exposed controls.

There is a paucity of published data on effects of RFEM radiation on immune competence in intact animals. Most of the reports of potential effects are circumstantial and are based on changes observed in peripheral blood or in *in-vitro* tests of lymphocyte responses to mitogenic stimuli.

7.1 Effects on Blood and Blood-Forming Organs

There have been numerous studies to evaluate the effects of RFEM exposures on the mammalian hematopoietic system. Early on, the majority of these studies, particularly those relatively long in duration and/or at low power densities ($\leq$10 mW/cm^2), were performed by Eastern European investigators and have been reported in their literature. Many of these reports have been translated and summarized by Baranski and Czerski (1976). In general, the European scientists have reported hematologic effects at power densities much lower than those found to yield positive effects by Western investigators. However, many of their past studies failed to include appropriate sham-control groups, absorbed energy measurements were nonexistent or inade-

quate, exposed animals were group-housed, and/or the data were presented in a manner such that statistical evaluations were impossible.

Early studies of RFEM exposure of experimental animals were usually at high power densities for short periods. Moore (1968) cited hematologic findings based on both human and animal exposures in his review of hazards of RFEM irradiation. With the exception of an increased incidence of "neoplasms of white blood cells" in mice, no hematologic effects were noted in animals exposed to 9.27- to 24.0-GHz fields at power densities of 20 to 100 mW/cm^2. Retrospective studies of human beings exposed occupationally to radar for 2 to 48 months failed to reveal any effects on erythrocytic or leukocytic cell populations.

Experimental studies indicate that hematologic effects may be produced at moderately low levels of irradiation under controlled laboratory conditions. Deichmann *et al.* (1964) studied the hematologic effects of various acute exposures on three strains of rats at a frequency of 24.0 GHz. Rats exposed at a power density of 20 mW/cm^2 for 7.5 h had increased red cell counts and hemoglobin concentrations, but decreased leukocyte counts. Differential leukocyte counts revealed a neutrophilia and lymphopenia. The study was repeated, except that exposure times varied from 7 min to 5 h, and results were similar to those of the first study, i.e., increased erythrocyte concentrations and neutrophilia and lymphopenia occurred regardless of exposure time. Mere handling of control rats resulted in a modest increase in neutrophils and lymphocytes. In another study, these workers exposed rats to 24-GHz fields at 10 mW/cm^2 during a single 3-h exposure or during six 3-h exposures. The single exposure produced decreases in erythrocytes, whereas a modest increase occurred following the multiple exposures. Following both exposure regimens, the concentration of circulating leukocytes was markedly decreased, neutrophils increased, and lymphocytes decreased.

This series of experiments by Deichmann *et al.* (1964) is characteristic of many in the early literature and illustrates the problems involved in the evaluation of hematopoietic effects following RFEM exposure. Specifically, there were no sham-exposed controls, the animals were used as their own controls, and, unfortunately, baseline values of blood counts were obtained two days before exposure. It has become increasingly evident that with any insult that may questionably or minimally perturb any physiologic process, either an appropriate sham-exposed group must be used, or repeated measurements must be made on the same animals prior to and following exposure.

Only a few investigators have studied the effects of microwaves on a large animal such as the dog. Deichmann *et al.* (1963) exposed two beagles to 24.0-GHz pulsed fields at 20 mW/cm^2 for several hours daily over a period of 20 months and found no significant effects on hematologic or serum-chemistry parameters. Michaelson *et al.* (1961, 1964, 1968) studied the effects of lower-frequency irradiation on the hematopoietic system of dogs, which were exposed to 1.24- or 2.80-GHz pulsed fields for 6 h at 50, 100 or 165 mW/cm^2 in an anechoic chamber. The animals developed lymphopenia and eosinopenia. The cell concentrations returned to normal levels 24 h later, although neutrophil concentrations remained slightly elevated. Following exposure to microwaves at 165 mW/cm^2 for 2 h, which resulted in an increase in body temperature of 1.7 °C, there was a slight decrease in the concentration of all leukocytes and definite hemoconcentration. Results from ^{51}Cr and ^{59}Fe kinetic studies indicated a reduced red-cell life span following exposure, and a depressed plasma-iron clearance rate. Dogs exposed to whole-body x irradiation (300 R) were more sensitive to subsequent RFEM irradiation.

The results of these studies by Deichmann *et al.* and Michaelson *et al.* are consistent, at least partially, with a stress response possibly mediated thermogenically.

Many of the early studies of RFEM effects on the hematopoietic system of rodents involved very high power densities that were obviously in the thermal-effects range, although real-time temperature measurements were not done. Prausnitz and Süsskind (1962) exposed mice 4.5 min daily for 14 months at 100 mW/cm^2 to 9.27-GHz pulsed microwaves (2-μs pulses, 500 pps) and observed an increase in lymphocytes, with a 35 percent incidence of "leukemia" in the exposed mice as compared with 10 percent in the controls. These diagnoses were based on small samples and included monocytic and lymphatic leukosis and lymphatic or myeloid leukemia, whereby leukosis was defined as a non-circulating neoplasm of white blood cells, i.e., aleukemic leukemia. Based on these criteria, it is uncertain whether all of these cases would currently be diagnosed as "cancer of the white blood cells". Significantly, subsequent samples at later intervals revealed no significant differences between exposed and sham-exposed mice.

Spalding *et al.* (1971) exposed mice to 0.8-GHz fields in a waveguide at an estimated power density of 43 mW/cm^2, 2 h daily, 5 d/week for 35 weeks. Another group served as sham-exposed controls. No significant differences between the two groups were seen in red- or white-cell counts, volume of packed red cells, or hemoglobin concentrations. Kicovskaja (1964) exposed rats to 3.0-GHz fields at power densities of

10, 40, and 100 mW/cm^2 for 1 h daily for ~7 months. At 10 mW/cm^2, no effects were seen on peripheral blood parameters, whereas, at 40 and 100 mW/cm^2, there was a slight decrease in erythrocytes and either lymphocytosis or lymphopenia. The summary of this report, as is common in early studies, does not describe methods of exposure or the baseline used to compare these reported changes.

Ratkovska and Vacek (1972, 1975) exposed mice for 5 min to 2.45-GHz CW fields in a waveguide at a power density of 100 mW/cm^2, and compared the effects on hematopoietic stem cells and cellularity of the spleen and femur to those effects following external heating. Both sources of heating produced an increase in rectal temperature of ~2.5 °C. Following both RFEM exposure and conventional heating, there was an immediate increase in the leukocyte count that persisted in both groups for 6 to 7 days. However, 4 d after RFEM exposure, there was a fall in white-cell counts, followed by an increase the next 2 days. The authors interpret this as a biphasic effect, one that was not observed in the conventionally heated mice. However, the baseline or control values are not well defined, and it is unclear whether they represent a sham-exposed group. No effects were observed on erythrocyte counts of either group of mice.

The 6-h incorporation of ^{59}Fe into the spleen and bone marrow was evaluated by Ratkovska and Vacek until 20 d after RFEM or conventional heating. Incorporation of ^{59}Fe into the spleen increased immediately after exposure in both groups, then tended to remain above control values in the microwave-exposed mice, but oscillated randomly about the control mean in the conventionally heated group. No significant differences were observed in ^{59}Fe uptake in the femurs of either group. These authors also quantitated the cellularity of the spleen and femur as to total cells and nucleated cells. After RFEM exposure there was a decrease in nucleated cells in the spleen, and this effect remained apparent for 72 h, but was followed by a statistically significant increase during days 4 to 7 after exposure. The total number of cells in the femur was decreased for several days following RFEM exposure, and then significantly increased on days 5 and 7. No significant changes were seen in the nucleated cell population of the femur. The significance of these data is difficult to interpret, but, at the high power densities used, the results are related, at least partially, to thermal effects. Total cellularity, and even quantitation of the nucleated cells in the spleen and femur, are highly dependent on transient-cell populations. Although the authors imply that such changes reflect the status of the hematopoietic tissue, such an assumption is not valid without additional evidence. Indeed, during the period that

decreased nucleated cell counts in the spleen were observed, the authors reported enhanced ^{59}Fe uptake by that organ, and then later stated, based on this evidence, that RFEM exposure stimulates erythropoiesis more than conventional heating.

Ratkovska and Vacek also evaluated the hematopoietic stem-cell pool of the femur and spleen for several hours following RFEM or conventional heating. They used the *in-vivo*, colony-forming-unit (CFU) assay and found an increase in CFU numbers of both spleen and femur up to 6 h after RFEM exposure, followed by a return to control levels by 12 hours. Conventional heating produced a slight increase in CFUs within 5 min, and a non-significant decrease at 6 and 12 h afterward.

Huang and Mold (1980) investigated the hematopoietic stem-cell effects of RFEM exposure of mice at a power density that reportedly did not increase the rectal temperature. The mice were exposed for 9 d, 30 min/d, to 2.45-GHz CW fields at 15 mW/cm^2 (*SAR*, 11 W/kg). The ability of bone-marrow cells to form myeloid and erythroid colonies *in vitro* was reduced ~ 50 percent as compared with marrow from sham-exposed mice.

Lin *et al.* (1979a) studied the effects of 2450-MHz CW fields on the ability of mouse bone-marrow cells exposed *in vitro* to form granulocyte/macrophage colonies when grown in a methylcellulose-culture system. The bone-marrow cells were exposed for 15 min at 30 to 1000 mW/cm^2 (*SAR*s, 60 to 200 W/kg). At 30 mW/cm^2, there was no effect on the ability of hematopoietic stem cells to form colonies. As the exposure was increased in steps to 1000 mW/cm^2, there was a progressive reduction in the number of colonies formed by RFEM-exposed cells as compared with sham-exposed cells.

The effects of localized RFEM exposure was studied in rabbits by Yagi *et al.* (1974). They exposed the femoral region of rabbits to 2.45-GHz pulsed fields at 1300 mW/cm^2 for 2.5 h daily for 7 consecutive days. No effects on erythrocyte parameters were observed, but there was an increase in reactive lymphocytes in the blood. The bone marrow was extensively studied, and the authors observed marked vascular and inflammatory changes, followed by aplasia of the hematopoietic cells.

It is important to emphasize that the studies on hematopoietic effects of RFEM fields described to this point have, in general, involved high power densities. If fields indeed have an effect on hematopoiesis, the systemic thermal-loading at these power densities would likely mask the investigators' ability to discern such effects. In other words, hyperthermia is known to interfere with cellular metabolism and with

synthetic pathways, whereas the effects of RFEM exposure at nonthermal levels have not been unequivocally established. More recent studies at lower power densities and involving longer durations of exposure are more pertinent in extrapolation of potential RFEM hazards arising from chronic exposure.

Baranski (1971b) exposed a large number of guinea pigs and rabbits both to continuous and pulsed 3.0-GHz fields in an anechoic chamber at power densities of 3.5 mW/cm^2 daily for 3 h over a period of 3 months. These exposures resulted in a significant leukocytosis, due entirely to increases in lymphocyte concentrations, with no effect on granulocyte numbers. Bone-marrow examination revealed no significant changes in the myeloid/erythroid ratios, but there were marked depressions in both pronormoblast and basophilic normoblast populations, with a shift to more mature forms. The mitotic index of erythroid cells, as determined following colchicine administration, was severely depressed in RFEM-exposed animals. Pronounced structural changes were also noted in the nuclei of normoblasts, but no such effects were seen in granulocyte precursors. Examination of lymph-node and spleen-impression smears revealed a marked increase in lymphoblasts and reticular cells, and in abnormalities of nuclear structure similar to those observed in normoblasts. The overall impression by the author was that of stimulation of the lymphoid system, and the effects observed were more severe in those animals exposed to pulsed as compared with those exposed to CW fields. Miro *et al.* (1974) exposed mice for 150 h to pulsed 3.1-GHz fields at a power density of 20 mW/cm^2. He reported an apparent stimulatory effect of irradiation on the reticulohistiocytic system. This determination was made by assay of ^{35}S-methionine incorporation into liver, spleen and thymus proteins as well as by histologic evaluation. However, at the power density employed, it is probable that thermal effects were operative.

Czerski *et al.* (1974a) exposed guinea pigs 4 h daily for 14 d to 2.95-GHz pulsed fields at an average power density of 1 mW/cm^2. These daily exposures were started at either 0800 or 2000 h to study possible effects of diurnal rhythm on bone-marrow mitoses as determined following mitotic arrest by colchicine. No effects were seen on the granulocyte precursors, and only minimal effects were found on the erythroid series, but pronounced phase shifts were noted in the stem-cell pool. Included in this latter category, however, were cells that are not normally considered as part of the hematopoietic stem-cell compartment, i.e., in addition to unidentified blast cells, they included early normoblasts, myeloblasts, and lymphocytes. The study was re-

peated on a large group of Swiss albino mice that were exposed once for 4 h to pulsed 2.95-GHz fields at 0.5 mW/cm^2 (Czerski, 1975). Another group was used to determine body temperature immediately after comparable exposures. Although initial temperature excursions and subsequent adjustment during thermoregulation were not measured, no significant increases in body temperature were found after the 4-h exposure. The results of this study are similar to those observed in the experiment with guinea pigs, i.e., the diurnal proliferation rate of the stem-cell population of exposed animals was amplified, and the phase was shifted from that of the control animals. The animals used in this series of experiments were housed in groups, and the power density was determined in the absence of the animals from the field. Czerski was quick to point out the pitfalls in attempting to relate field measurements to *SAR*s, but did find that the power densities were low enough to preclude increases in rectal temperature.

Siekierzynski (1972) exposed 3 groups of rabbits to 2.95-GHz pulsed and CW fields at a power density of 3 mW/cm^2 for 2 h daily. The first group was exposed for a total of 74 h to the CW field, the second for 74 h to the pulsed field, and the third for 158 h total to the CW field. No significant changes were observed in red-cell counts, in hemoglobin concentrations, or in the volume of packed red cells. However, ferrokinetic studies revealed alterations in erythrocyte production. Serum-iron levels were reduced significantly in all exposed rabbits, the plasma clearance of ^{59}Fe was prolonged, and the quantity of ^{59}Fe incorporated into erythrocytes was markedly reduced. The effects were most dramatic and were similar after the 74-h pulsed and 158-h CW exposures.

Switzer and Mitchell (1977) exposed 15 female Sprague-Dawley rats to 2.45-GHz CW fields in a multimode cavity that resulted in an *SAR* of 2.3 W/kg. The rats were exposed simultaneously, but were restrained individually in polystyrene cylinders. The animals were exposed 5 h daily for a total of 550 hours. Littermate controls were sham-exposed under similar handling and housing conditions. Red-blood-cell counts of the exposed rats were significantly increased over those of the sham-exposed rats, but mean hemoglobin and volume of packed-red-cell values did not differ between groups. Mean white-blood-cell counts of the exposed rats were slightly greater than those of the sham-exposed group, but the difference was not statistically significant. Comparisons of leukocyte differential counts revealed no significant differences between the two exposure regimens, although lymphocyte concentrations were lower and monocyte counts were higher in the exposed rats. This finding of alterations in one hematologic parameter (red blood cells) without concomitant changes in

other dependent variables is characteristic of several reports in the RFEM literature.

Ferri and Hagan (1975, abstract) exposed 6 rabbits to 2.45-GHz CW fields at an incident power density of 10 mW/cm^2 for 8 h daily, 5 d/week for 8 to 17 weeks. Their studies included 6 littermate controls that were sham-exposed and handled in a manner otherwise identical to the exposed group. No differences were observed between the two groups when weekly red- and white-blood-cell counts were compared.

Smialowicz *et al.* (1977, abstract) exposed rats *in utero* and through 40 d of age for 4 h daily to CW fields in a transverse-electromagnetic-mode (TEM) transmission line. Power densities were 5 mW/cm^2 at 2.45 GHz and 10 mW/cm^2 at 0.43 GHz. Specific absorption rates, as determined by twin-well calorimetry, ranged from 1.5 W/kg at 2.45 GHz to 3 to 7 W/kg at 0.43 GHz depending on the stage of gestation and the age of the pups. Exposure of rats at 0.43 GHz resulted in an absolute neutropenia and a relative lymphocytosis in two of three experiments. However, at the higher frequency, no effects were observed on peripheral blood counts.

In another study, Smialowicz *et al.* (1979a) exposed female BALB/C mice, housed individually, to 2.45-GHz CW fields at incident power densities of 5, 15, or 30 mW/cm^2 (*SAR*/unit power density = 0.72 ± 0.16 W kg^{-1}/mW cm^{-2}). Exposures were for 30 min on each of 8 consecutive days and included appropriate sham-exposed control groups. No hematologic effects of exposure were found in mice killed immediately after the last exposure or 6 d later. In another experiment, they exposed mice at 30 mW/cm^2 for 22 consecutive days and found a decreased concentration of neutrophils in the exposed mice, but the difference, when compared with sham-exposed mice, was not statistically significant.

In a more recent study, Smialowicz *et al.* (1981) exposed rats to RFEM fields in circularly polarized waveguides (970-MHz) 22 h daily for 70 consecutive days at *SAR*s of 2.5 W/kg. They included an appropriate sham-exposed control group. They reported significantly elevated serum levels of triglycerides, albumin and total protein in the exposed rats and no significant differences in body weights, hematologic end points, numerous serum enzyme and chemical constituents or in *in-vitro* responses of lymphocytes to mitogens between the exposed and sham-exposed rats. They suggest that the increased triglyceride levels, following these long-term exposures to RFEM fields, are due to a non-specific stress response.

Galvin *et al.* (1982) conducted exposures of male rats to 2.45-GHz CW fields for 8 h at 0, 2 or 10 mW/cm^2 (*SAR*s of 0, 0.44 or 2.2 W/kg,

respectively) and evaluated the effects on several blood and serum chemistry variables. No significant alterations in hematologic or serum end points were observed in the RFEM-exposed rats when compared with results from the sham-exposed group. These workers also studied mast cells and basophils from rats exposed identically to those above and did not detect any impairment of function in the histamine-secreting cells (Ortner *et al.*, 1981).

Ragan *et al.* (1983) exposed female mice to horizontally polarized 2.88-GHz pulsed fields 3 to 7.5 h daily over a period of 60 to 360 h at power densities of 5 or 10 mW/cm^2. The mice were housed individually during exposures in Lucite containers and were exposed in groups of eight. Specific absorption rates were determined with the animal's long axis of the body oriented parallel to the electric, magnetic or propagation vectors. Mean *SAR*s were 2.25 W/kg at 5 mW/cm^2, and 4.5 W/kg at 10 mW/cm^2. During each treatment, littermate controls were sham-exposed. In 2 of 5 studies at 5 mW/cm^2 with pulsed fields, there was a significant increase in bone-marrow cellularity compared with the sham-exposed groups, but in the other 3 studies no significant effect was observed. Significant differences were occasionally seen in erythrocyte, leukocyte and platelet measurements from RFEM-exposed groups, but were not consistently observed. The only effect seen in mice exposed to 5-mW/cm^2 CW fields was a reduction in reticulocyte concentrations. In 1 of 4 exposures to pulsed fields at 10 mW/cm^2, mean bone-marrow cellularity was reduced in the RFEM-exposed mice, and in another group the concentration of circulating lymphocytes was increased. In only one exposure condition (10 mW/cm^2 for 360 h) was any effect noted on serum proteins: a significant reduction to 5.1 $\pm$ 0.29 g/dl in the exposed as compared with 5.6 $\pm$ 0.36 g/dl in the sham-exposed mice ($p < 0.01$). This reduction was due to a decrease in alpha and beta globulins, with no effect on albumin or gamma-globulin concentrations. However, when an appropriate multivariate statistical analysis, rather than Student's *t* test, was applied to these hematologic and serum-chemistry data, there were no consistently significant differences between the exposed and sham-exposed groups. No effect on bone-marrow hematopoietic colony-forming units was revealed by CFU-agar assay techniques following exposure of mice to pulsed RFEM fields at 5 mW/cm^2. In 1 of 4 exposures of mice to 10 mW/cm^2 pulsed microwaves there was a significant increase in CFU-agar colonies. No exposure-related histopathologic lesions were found when numerous tissues were examined from mice that had been exposed at 10 mW/cm^2 for 200 to 360 hours.

Chou *et al.* (1978, abstract) exposed rabbits to 2.45-GHz CW or

pulsed fields at a maximal power density of 1.5 mW/cm^2 for 2 h daily for 3 months. The mean *SAR* was 0.5 W/kg. An additional group of 6 rabbits was sham-exposed. No significant differences between groups were seen in hematologic profiles obtained monthly.

One study on the effect of RFEM exposure on blood coagulation has been reported by Richardson (1959). Anesthetized mongrel dogs weighing 11 to 18 kg were exposed to 2.45-GHz CW fields at average power densities of 158 and 197 mW/cm^2. The exposure horn was only 5 cm above the skin over the region of the liver. Nine dogs were subjected to a single 10-min exposure, and the whole-blood clotting time was determined immediately afterward. Pre-exposure clotting times were used as control values. Mean clotting time increased significantly (~27 percent) over control values. This peak increase occurred 17 min after exposure, and clotting time returned to the control level within 30 minutes. Another series of studies employed three exposure periods of 10 min each on 8 dogs, with a 5-min interval between the first and second exposures, and 2 h between the second and third exposures. After the first exposure, clotting time was again significantly increased over control values, and then significantly decreased after the second exposure as compared with pre-exposure values. These values had returned to control levels by ~60 minutes. Following the third exposure, there was again a decrease in clotting time below the control value. This latter study was repeated on another group of 8 dogs subjected to the same procedures but without exposure. In this control study, there was a slight, but statistically insignificant, decrease in clotting time.

There have been several studies on the effects of exposing blood cells *in vitro* to RFEM radiation. Baranski *et al.* (1974) exposed washed erythrocytes from rabbits to 3.0-GHz CW fields at power densities of 1, 5, or 10 mW/cm^2 for periods of 15 to 180 minutes. A dose-related hemolysis, increased osmotic fragility, and elevated potassium leakage were noted, indicating alterations in the red-cell membrane. Studies of isolated granulocytes, based on liberation of intracellular enzymes as markers, indicated similar alterations in granulocytic membranes (Szmigielski, 1975). In these studies, suspensions of control cells were kept at room temperature, but there were no conventionally heated controls. Peterson *et al.* (1978, abstract) exposed rabbit and human erythrocytes to 2.45-GHz CW fields, and monitored temperature continuously. The permeability of the red-cell membranes to potassium and the hemoglobin of the exposed cell suspensions were compared with those of thermal-control and room-temperature-control suspensions. Exposure at 10 mW/cm^2 caused no increase in potassium or

hemoglobin values above those found in the room-temperature controls. The authors concluded from their series of experiments that effects of RFEM fields on erythrocyte permeability could be ascribed to simple thermal influence.

Hamrick and Zinkl (1975) exposed washed erythrocytes from rabbits to 2.45-GHz CW fields at 4, 10 and 75 mW/cm^2 (*SAR*s, 3, 7.6 and 57 W/kg, respectively) or to 3.0 GHz at 5 mW/cm^2 (5.2 W/kg) for 1 to 3 h resulting in temperatures between 22 and 42 °C. Control erythrocyte suspensions were heated in a water bath. There were no significant differences in potassium efflux or osmotic resistance between the RFEM-exposed and thermal-exposed erythrocyte suspensions.

In contrast to the reports that increased permeability of erythrocytes to RFEM exposure is apparently only a thermal effect, there are others that implicate an athermal influence. Olcerst *et al.* (1980) exposed washed erythrocytes from rabbits for 1 h to 2.45-GHz CW fields in a waveguide system at *SAR*s of 100, 190 and 390 W/kg. They report the cation efflux at all three levels to be statistically greater than one would predict from a strictly thermal response. Fisher *et al.* (1982) exposed human erythrocytes, washed and loaded with ^{24}Na, to 2.45-GHz CW fields in a waveguide system at *SAR*s of 2 to 3 W/kg for 1 to 2 hours. They found increased passive ^{24}Na efflux and decreased ATP-mediated ^{24}Na efflux only when erythrocytes were exposed to low-level fields at 22 to 25 °C.

Liu *et al.* (1979) exposed suspensions of rabbit, canine and human erythrocytes, diluted 1:1 with saline, to S-band fields in a waveguide chamber and compared potassium and hemoglobin release to that of similar erythrocyte suspensions heated in a water bath. Three-hour exposures to 3.0 GHz (*SAR*, ~200 W/kg), 2.45 GHz (*SAR*, 80 W/kg) or 3.95 GHz (*SAR*, 100 W/kg) resulted in potassium and hemoglobin releases, but they were statistically equivalent to conventional heating at comparable temperatures ranging between 25 and 44 °C. More recently, these investigators (Cleary *et al.*, 1982) exposed whole-blood suspensions or 1:1-saline-diluted suspensions of rabbit erythrocytes to CW or pulsed 8.42-GHz fields in a waveguide for 2 h at *SAR*s of 22, 65, 87 or 90 W/kg. Statistically significant increases in potassium efflux relative to thermal controls were found in the RFEM-exposed whole-blood suspensions, whereas the 1:1-diluted erythrocyte suspensions exposed to the fields or to conventional heating had similar potassium release. There were no detectable differences in heating rates and in thermal gradients between the whole-blood and diluted-erythrocyte suspensions that would explain the increased potassium efflux of the undiluted blood.

Ismailov (1977) evaluated the ultrastructure of human red blood cells exposed to 1.0-GHz pulsed and CW fields. At 45 mW/cm^2, he found conformational changes in the erythrocyte membrane that were not manifested at 5 to 8 mW/cm^2. No differences were noted between pulsed- and CW-irradiated cells.

7.2 Effects on the Immune System

There have been numerous investigations, particularly more recently, of immune competence after exposure of animals or cells to RFEM radiation. However, much of the speculation regarding potential immunological effects has been based on reports that circulating populations of lymphocytes are increased or decreased following exposure of experimental animals to RFEM fields and on the *in-vitro* response of lymphocytes to mitogenic stimulation.

Stodolnik-Baranska (1967) exposed cultures of human lymphocytes daily for 3 to 5 d to 3.0-GHz fields at power densities of 7 mW/cm^2 over 4-h periods and at 20 mW/cm^2 over 15-min periods. After 3 d, there was a 2-fold increase of cells undergoing lymphoblastic transformation at both power densities as compared with control values, and a 5-fold increase after 5 days of culturing. Smialowicz (1976) cultured mouse spleen cells, maintained at 37 °C during exposure, to 2.45-GHz CW fields in the far field of an anechoic chamber. Exposures of these cell cultures were made for 1, 2, and 4 h at a power density of 10 mW/cm^2 and at a calculated *SAR* of 19 W/kg. Temperature and viability of the cells following RFEM exposure were comparable to those of control-cell cultures. Following irradiation, the ability of cultured lymphocytes to undergo blastic transformation was determined in response to different T- and B-lymphocyte mitogens. No consistent difference was found between the blastogenic response of RFEM-exposed and control splenic lymphocytes as stimulated by the mitogens phytohemagglutinin (PHA), pokeweed, concanavalin A, and bacterial lipopolysaccharide. Smialowicz *et al.* (1979a) repeated these lymphocyte function studies after exposing intact mice to 2.45-GHz CW fields for 30 min daily for as many as 22 consecutive days at incident power densities of 5 to 35 mW/cm^2 (*SAR*/unit power density $= 0.72 \pm 0.16$ W $kg^{-1}/mW\ cm^{-2}$). No consistently significant alterations were found in the immunologic parameters following RFEM exposures of these mice.

In a more recent study, Smialowicz *et al.* (1982a) exposed pregnant

mice to 2.45-GHz fields at 28 mW/cm^2 (*SAR*, 16.5 W/kg). Exposures were made for 100 min/d from day 6 to day 18 of gestation. These studies included an appropriate sham-irradiated group of mice. When the offspring were 3 and 6 weeks of age, they were assessed for development of the primary immune response to sheep red blood cells, *in-vitro*, mitogen-stimulated lymphocyte proliferation, and natural killer cell activity. They found no consistently significant differences in these end points between the RFEM-exposed and sham-exposed control mice.

Huang *et al.* (1977) exposed Chinese hamsters 15 min/d for 5 consecutive days to 2.45 GHz CW fields in the far field at incident power densities of 0, 5, 15, 30, or 45 mW/cm^2 (*SAR*/unit power density = 0.46 W kg^{-1}/ mW cm^{-2}). The hamsters were exposed in individual polycarbonate holders, and another group of hamsters was sham-exposed. One hour after RFEM or sham exposure, blood was collected for lymphocyte culture to determine spontaneous and PHA-induced blastic transformation. Unstimulated, but RFEM-exposed, lymphocytes showed a dose-related increase in the transformation index, which, at 30 mW/cm^2, was about 4-fold greater than in control cultures. At 45 mW/cm^2, blastic transformation fell to a level between those at 0 and 5 mW/cm^2. Repeated observations after irradiation indicated a progressive return of transformations to control levels over a 5- to 10-d period. When lymphocytes were stimulated into mitoses by PHA, there was a dose-dependent decrease in the mitotic index. Czerski (1975) exposed rabbits 2 h daily for 6 months to pulsed 2.95-GHz fields at 2 mW/cm^2 and found an approximate 20-fold increase in spontaneous blastic transformation of peripheral blood lymphocytes in culture as compared with that of control blood. The transformation and mitotic indices were also higher in PHA-stimulated cultures of lymphocytes from irradiated animals. This investigator also studied the immune responses of mice exposed to 2.95-GHz pulsed fields at a power density of 0.5 ± 0.2 mW/cm^2 in an anechoic chamber 2 h daily 6 d/week for total exposures of 72 or 144 hours. At the end of the exposure period, the mice were injected with sheep red blood cells, and then were euthanatized 4 to 20 d later to determine antibody-forming, lymph-node cells by the Jerne plaque-forming technique. Serum-hemagglutination titers were also evaluated. In addition, lymph-node cytology was evaluated from smears of cell suspensions. From these studies, it appears that the number of antibody-producing, lymph-node cells was increased in mice exposed for the period of 6 weeks, but not for the period of 12 weeks. The serum-hemagglutination titers against sheep red blood cells were also greater following either of the RFEM exposure regimens than in the control group. However, the

data presented do not include estimates of variances; therefore, it is not possible to establish the statistical significance of these tests.

Huang and Mold (1980) investigated the immunologic responsiveness of mice exposed to 2.45-GHz CW fields at power densities of 5 to 15 mW/cm^2 (*SAR* = 3.6 to 11 W/kg) for periods ranging from 1 to 17 days. Responsiveness of spleen lymphocytes to various mitogens (phytohemagglutinin, concanavalin A, and *E. coli* lypopolysaccharide) generally was reduced after 2 d of exposure, and then was enhanced after 4 to 9 d of exposure as compared with values from the sham-exposed controls. The cytotoxicity of lymphocytes, as assayed by tumor-killing activity, did not differ between RFEM exposed and sham-exposed mice.

Krupp (1977a, abstract) exposed mice to 2.6-GHz fields at power densities of 10, 15, and 20 mW/cm^2 for various periods and then sensitized them to sheep red blood cells. The spleens were collected and assayed for plaque-forming cells (B-lymphocytes). There was an increased count of these cells when the exposure resulted in increases of rectal temperature of ≥3.0 °C.

Szmigielski *et al.* (1975) exposed rabbits to 3.0-GHz CW fields at 3 mW/cm^2 5 h daily for 6 or 12 weeks (*SAR* not specified, estimated to lie between 0.12 and 60 W/kg). After irradiation, the animals were infected with a virulent organism (*Staphylococcus aureus*), and then several end points were evaluated. Following infection, both controls and animals exposed for 6 weeks developed a marked granulocytosis, whereas no granulocytic response was observed in animals exposed for 12 weeks. These outcomes were accompanied by a reduced, bone-marrow-granulocyte reserve in both groups, as well as a decrease in serum-lysozyme levels. Nitroblue tetrazolium reduction, a measure of granulocyte function, was not decreased by RFEM exposure. These results indicate that RFEM exposure may result in a decreased marrow reserve of granulocytes, but no alteration in the functional capacity of circulating granulocytes.

Szmigielski and coworkers (1976, abstract) also exposed mice to 3.0-GHz fields for 2 h daily at 40 mW/cm^2 over a period of 2 to 14 days. At various times before and after exposure, the mice were infected with *Herpes* or *Vaccinia* viruses to evaluate the course of the disease. Exposure after vaccinia infection markedly reduced the number of dermal lesions. In mice first infected with herpes and subsequently irradiated, the survival rate was much higher and the incidence of encephalitis much lower as compared with the control mice. However, the relatively high power density used could have resulted in thermal immunostimulation.

The effect of both local and systemic heating on transplanted tumors

has been studied by Szmigielski and Janiak (1977, abstract) and Szmigielski *et al.* (1982). In both Guerin's epithelioma-bearing rats and in mice with Sarcoma-180 transplants, field-induced hyperthermia, whether local or systemic, reduced the tumor mass as compared with that of sham-irradiated, tumor-bearing controls. The authors speculated that immunostimulation is important in the hyperthermic inhibition of tumor growth, although they admit that the mechanism of inhibition is poorly understood.

Shandala *et al.* (1977, abstract) exposed rats, guinea pigs, and rabbits for 30 d to 2.38-GHz fields at very low power densities of 10, 50, and 500 $\mu W/cm^2$. Lymphocyte blastic transformations, stimulated by mitogens, were studied at various times during the 30-d exposure period. Exposures at 500 $\mu W/cm^2$ resulted initially in stimulation of transformation, followed by suppression. The phagocytic ability of guinea-pig leukocytes was determined after RFEM exposure of the animals. At 10 $\mu W/cm^2$ the phagocytic index was elevated, and at 500 $\mu W/cm^2$ it was suppressed as compared with control values. Also, there was a reduced incidence of anaphylaxis in sensitized, irradiated guinea pigs that were subsequently challenged with equine serum. Of interest is the reported finding of anti-brain and anti-liver antibodies in the three species exposed at power densities $\geq$500 $\mu W/cm^2$. The authors conclude that exposure to these low power densities can result in a primary lesion of the immune system, and may also result in autoimmune disease. Unfortunately, there is no description in this abstract of methods used in these assays, or even whether appropriate sham-exposed groups were used.

Miro *et al.* (1974) exposed rabbits and guinea pigs at low power densities (1.2 ± 0.2 mW/cm^2) to 2.45-GHz fields and reported a significant increase in gamma-globulin levels after 8 d of exposure. In contrast, Ragan *et al.* (1983), after exposing mice at power densities of 5 and 10 mW/cm^2 for 60 to 360 h, found no effects on gamma-globulin levels when data on exposed mice were compared with those of sham-exposed, littermate controls.

Liburdy (1980) exposed mice to 2.6-GHz CW fields for 1 h at a power density of 25 mW/cm^2 ($SAR = 19$ W/kg) or at 5 mW/cm^2 ($SAR = 3.8$ W/kg), and then measured lymphocyte migration *in vivo* by following the activity of transplanted, syngeneic ^{51}Cr-labeled splenic lymphocytes. He employed appropriate sham-exposed, warm-air-treated, and steroid-treated control groups. Hyperthermic RFEM exposure caused a 1.6-fold reduction in lymphocytes, which left the lung and entered the spleen, but a 3-fold increase in spleen lymphocytes that entered the bone marrow. A similar migration was observed in

the steroid-treated mice. Irradiation at 5 mW/cm^2 and warm-air treatment did not result in altered lymphocyte migration.

With the use of similar exposure regimens in another study, Liburdy (1979) determined thymic weights, plasma corticosteroid levels, and *in-vivo* delayed hypersensitivity response to footpad injection of sheep red blood cells following thermogenic and non-thermogenic RFEM exposure, sham exposure, warm-air exposure or prednisolone injections. At acute and chronic thermogenic RFEM exposures, the mice developed a transient lymphopenia concurrent to increases in splenic T- and B-cell lymphocytes, suppressed delayed hypersensitivity responses, and plasma corticosteroid levels several times greater than warm-air- or sham-exposed mice. Similar results were evident following injection of glucocorticoids. From the results of his studies, a tenable hypothesis is presented that whole-body RFEM hyperthermia stimulates the hypophyseal-hypothalamus-adrenal axis directly through heating, which in turn triggers the release of adrenal steroids that act to alter lymphocyte distribution and functions.

Several studies of lymphocyte populations following irradiation have been conducted by Wiktor-Jedrzejczak and coworkers (1977a,b). Mice were exposed individually in a polystyrene holder to 2.45-GHz fields in a waveguide. Duration of exposures was 30 min and the *SAR* was 13.0 W/kg. A single 30-min exposure resulted in significant increases in the number of complement-positive B-lymphocytes in the spleen. Three 30-min exposures induced increases in the total number of spleen cells, in the number of complement-receptor-positive cells, and in the more mature immunoglobulin-positive B-lymphocytes. There were no changes detected in T-lymphocyte populations following single or multiple exposures.

More recent studies by these workers have investigated possible mechanistic actions to explain their observed effects of RFEM exposure on lymphocyte populations. They exposed adult male mice to 2.45-GHz CW fields in an environmentally controlled waveguide system at a forward power of 0.6 W (*SAR* ~ 12 W/kg) for one or three 30-min exposures (Wiktor-Jedrzejczak *et al.*, 1980). Following exposure, lymphocytes were isolated from spleen, bone marrow and peripheral blood, and the incorporation of nucleic acids was determined. RFEM exposure did not result in any detectable change in DNA, RNA or protein synthesis when compared to sham-exposed controls. The authors suggest that these data indicate that increases in the frequency of complement-receptor and surface-immunoglobulin-bearing cells observed following RFEM irradiation are not due to an increase in cell proliferation, but rather may be due to stimulating B-cell precursors

into a maturation phase. In a subsequent, rather elegant study, mice were exposed under the same conditions described above and then cells from RFEM- and sham-exposed controls were studied using diffusion-chamber techniques (Wiktor-Jedrzejczak *et al.*, 1981). The chambers, implanted in the peritoneal cavities of mice, are permeable to humoral factors but not to cells. Based on the results of these studies, the authors concluded that the increase in complement-receptor-positive cells reported following RFEM exposure are not the result of alterations of lymphocyte recirculation patterns, but may be mediated by a soluble humoral factor produced by cells within the spleen.

There is a limited literature on hematologic or immunologic effects of RFEM radiation at frequencies <1000 MHz.

Lin *et al.* (1979b) exposed mice to 148-MHz fields at 0.5 mW/cm^2 in a TEM chamber 1 h/d, 5 d/week over a period of 10 weeks starting near 1 week of age. The exposed and sham-exposed mice (88 mice/group) were contained individually in Styrofoam cups. Blood samples were obtained at 28 and 70 d of age and then at 5 time periods after exposure to 600 d of age. No effects of RFEM exposure were found in erythrocyte and leukocyte end points.

Smialowicz *et al.* (1979b, abstract) exposed 20 rats to 100-MHz fields in a TEM transmission line at 50 mW/cm^2 (averaged *SAR* = 2.8 W/kg) for 4 h daily, 7 d/week. Their studies included an appropriate sham-exposed group of rats. When examined at the 21st and 42nd days of exposure, there were no effects observed in hematologic or immunologic end points as compared with those from the sham-exposed rats, i.e., complete blood counts, mitogen responses of lymphocytes, frequency distribution of T- and B-lymphocytes, and antibody response to *Streptococcus-pneumoniae* capsular antigens.

In a later study, these workers (Smialowicz *et al.*, 1982b) exposed rats, pre- and postnatally to 425-MHz CW fields at a forward power of 20 W and found an increased responsiveness of their lymphocytes to mitogens. Subsequently, they exposed female mice to 425-MHz CW and pulse-modulated fields in a strip-transmission line at forward powers of 78, 17.7 or 5 W for CW and 17.7, 5 or 1.25 W for pulsed fields (Smialowicz *et al.*, 1982c). Mean *SAR* was 7.7 W/kg for forward power of 70 W. In contrast to the results from the rat exposures to 425 MHz, in the mice there were no differences observed in the responsiveness of mitogen-stimulated lymphocytes or in the primary immune response to sheep erythrocytes between the exposed and sham-exposed mice or between CW- or pulse-exposed mice.

Mitchell and Gass (1971) exposed 12 rhesus monkeys in the far field to 10.5-MHz pulsed fields at power densities of 200 mW/cm^2 (pulse

width 1.5 ms, repetition rate 111 pps) for 1 hour. These studies were repeated at 19.3 MHz and 115 mW/cm^2 4 h daily for 14 d, and at 26.6 MHz and 100 mW/cm^2 for 1 hour. Periodic blood samples were collected before and after exposure, and these data were compared with those from sham-exposed controls. There were no obvious effects of RFEM exposures on the hematologic parameters examined.

Krupp (1977b, abstract) exposed 18 monkeys to 15-, 20-, and 26-MHz fields at power densities of 500 or 1270 mW/cm^2 for 2 h on two occasions. When standard, clinical-pathology profiles were examined 1 and 2 y after exposure, no residual effects of exposure were observed.

Smialowicz *et al.* (1979c, abstract) evaluated the primary immune response of mice to sheep red blood cells after exposure to 425-MHz fields in a TEM transmission line for 1 h on each of 5 consecutive days. Exposures to CW fields were made at power densities of 39, 10 and 2.5 mW/cm^2 (SAR/unit power density = 0.11 W kg^{-1}/mW cm^{-2}) and to pulsed fields at 9, 2.5, and 0.63 mW/cm^2 (1-ms pulses at 250 pps). There were no differences in primary immune response between exposed and sham-exposed mice or between mice exposed to CW and pulsed fields.

Majde and Lin (1979, abstract) exposed C3H mice in a Crawford cell to 148-MHz fields at 0.5 mW/cm^2 (averaged SAR = 0.013 W/kg) or at 30 mW/cm^2 (averaged SAR = 0.75 W/kg) to evaluate hypersensitivity responses. The mice were immunized by a subcutaneous injection of human red blood cells and, 24 h later, were exposed 1 h daily for 3 days. They were subsequently challenged on day 14 with footpad injection of 10^9 human red blood cells. A mild but significant depression of anaphylactic response was seen in mice exposed at 30 mW/cm^2, but not at 0.5 mW/cm^2. There was no consistent effect of exposure on the Arthus (delayed-type) response. The degree of suppressed anaphylaxis was comparable to that of mice exposed to a cold environment (5 °C) for 1 hour.

An effect of RFEM irradiation on immunocompetence is implied also in the results of Liburdy (1977). He evaluated the inflammatory response of rats to footpad injection of sheep red blood cells, and in mice by tail-vein trauma from repeated bleedings. The animals were pretreated by exposure to a 26-MHz CW TEM field at a power density of 8600 mW/cm^2, which resulted in an elevation of rectal temperature of 2 to 4 °C, or by exposure to heated air, which resulted in a comparable elevation. The response of rats to the sheep red blood cell injection was evaluated 4 h after exposure. The response in field-exposed rats was 33 percent less than in hot-air-treated rats and 46 percent less than in sham-exposed controls. In mice, the heat- and

sham-exposed controls developed a leukocytosis following tail-trauma that was a result of increases in both neutrophils and lymphocytes. Irradiated mice had reduced lymphocyte concentrations at 3 h, followed by a progressive return to normal values over the ensuing 92 hours. Over the same period, neutrophil values increased and then progressively decreased.

Prince (1971) exposed rhesus monkeys (*M. mulatta*) to pulsed 10.5-, 19.2-, and 26.6-MHz fields each at a power density of 1300 mW/cm^2 for 30 min (estimated *SAR*s, 0.43, 1.3 and 2.6 W/kg, respectively). When examined ~70 h after exposure, the response of blood lymphocytes to PHA-induced blastic transformation was 9- to 15-fold greater than in similar studies based on lymphocytes obtained prior to exposure. These data reveal no evidence of a proposed depressive effect of RFEM exposure on cell-mediated immunocompetence and are consistent with the *in-vitro* studies of Stodolinik-Baranska (1967).

7.3 Summary and Conclusions

Irradiation at non-thermogenic levels, i.e. at *SAR*s below 1 W/kg and at frequencies between 300 kHz and 300 GHz, results in few, if any, unequivocal effects on the hematopoietic or immune systems of experimental animals. Under some exposure conditions, especially under exposure to pulsed fields, the most consistent effects seem to be associated with lymphocyte populations. There may be lymphocytosis, which appears to be associated with an increase in the B-lymphocyte population. This effect, reported by several investigators, is consistent with findings of enhanced hemagglutination titers in exposed mice. Because B-lymphocytes are associated primarily with the humoral immune response, one might predict such an enhancement. There have been few studies reporting potential effects on the cell-mediated immune responses after RFEM exposure, and those studies that have been conducted are based primarily on *in-vitro* assays. Probably the most pertinent *in-vivo* tests of immune competence are those in which Szmigielski found that exposure attenuated the severity of immune-virus infections. Appropriate and critical *in-vivo* assays of cell-mediated immune responses have not been reported, except for those by Ragan *et al.* (1983) who found no consistent effects at power densities below 10 mW/cm^2.

Additional appropriate *in-vivo* assays of immunocompetency associated with non-thermogenic RFEM exposures are critically needed

for risk-assessment evaluations. Szmigielski's work indicates that RFEM exposure did not impair granulocyte functions of rabbits, but at thermogenic levels attenuated the severity of the immune response to viral infections in mice. *In-vivo* tests of both cell- and humoral-mediated immune responses were not compromised in mice by non-thermogenic RFEM exposures in the studies by Smialowicz *et al.*, Liburdy, or Ragan *et al.* Of particular interest in regard to *in-vivo* immunocompetence are the studies of Liburdy in which he observed similar immune alterations and lymphocyte effects when he compared thermogenic RFEM exposures to those following injection of glucocorticosteroids.

The only evidence that very low-dose RFEM exposure may have a depressive effect on erythropoiesis was reported by Siekierzynski, who found a reduced plasma-iron clearance and a reduced iron incorporation into developing erythrocytes of rabbits.

In-depth evaluations of the hematopoietic and immune systems must be conducted with both pulsed and CW fields under very exacting experimental conditions and under well-defined *SAR*s that do not result in a systemic thermal burden (i.e., *SAR*s that are below the resting specific metabolic rate) and must include an appropriate sham-exposed group. Exposures to radiation should extend over a considerable portion of the life-span of the species. Even if effects are found under idealized experimental designs and are confirmed in several laboratories, it will be extremely difficult to extrapolate and interpret these effects into potential detrimental effects in man without a better understanding of the cellular mechanisms involved.

8. Effects on Endocrine System

8.1 Introduction

To maintain homeostasis, a mammal possesses two control mechanisms that react to changes in internal and external environments (adequate stimuli or physiological stresses). These two control mechanisms are the neural and endocrine systems. Separation of endocrine from neural control is not always possible as neural signals are integrated at the hypothalamus to react to deviations in the internal or external environments.

The neuroendocrine system (NES) is an exquisitely sensitive organ-and-chemical system intimately involved with and under the influence of the central nervous system (CNS). This system exhibits a profound influence on the body, often through effects on metabolism of various tissues. The NES, in coordination with higher nervous centers, is a major regulatory system in the body. The functional relationships among components of the NES follow a cybernetic pattern, with feedback mechanisms playing an essential role. These relationships are distinguished by a heirarchy of activities, which consist of three levels of organization (hypothalamus, hypophysis, endocrine gland) in which overall output function, the secretion of hormones by the endocrine gland, is controlled by the balances of signals. Hypothalamic-hypophysial-adrenocortical (HHA), hypothalamic-hypophysial-thyroidal (HHT), and hypothalamic-hypophysial-somatotrophic (HHS) components participate in homeostatic control through negative-feedback mechanisms.

Neuroendocrine activity is modified by direct neural inputs from higher brain centers and peripheral nerves. As an example, adrenergic neurons in the hypothalamus stimulate thyrotropin-releasing hormone (TRH), which acts on the anterior pituitary to increase thyrotropin (TSH), which in turn enters the general circulation to stimulate thyroid secretion of triiodothyronine (T_3) and thyroxine (T_4). The T_3 and T_4 then act by negative-feedback control to reduce hypophysial TSH secretion.

It appears that growth hormone (GH) is regulated by a specific releasing factor (GRF) and a specific inhibiting factor (GIF) that

originate in the hypothalamus, whereas adrenocorticotropic hormone (ACTH) and TSH are regulated by releasing factors. The absence of inhibiting factors for TSH and ACTH is probably best explained by their action on specific target tissues, which, in turn, produce hormones that provide negative feedback to the hypothalamus. Growth hormone, which possesses no specific target tissue, requires some mechanism to control its production. This control is achieved by the concentration of circulating metabolites that are integrated with higher center inputs and that affect hypothalamic GIF or GRF release when appropriate. It is interesting and significant to note that this area of the hypothalamus, located in the medial basal area, together with the lateral hypothalamus, also functions as a final integrative center for energy balance and food intake. Also, these areas are intimately associated with the region of the hypothalamus involved in temperature regulation (Schally *et al.*, 1973; Martin, 1973).

Physical stimuli, emotional arousal, or any interference with the body's ability to maintain homeostasis (heat, cold, infections, toxins, lack of oxygen, injury) can result in the liberation of corticotropin releasing factor (CRF), which in turn stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary (hypophysis). The ACTH then stimulates the secretion by the adrenal cortex of glucocorticoids, which are hormones related to the immune response.

Acting alone or in concert, the various components of the neuroendocrine system play a central role in the integrative activities that are required for homeostasis. Normal integrative functions of the body, or those activities that result from stimuli within the individual or from alterations in the physical environment, are integrated by the reciprocal relationships of the CNS and the endocrine system. The sensitivity of this system to perturbation is greatest at its highest level, the hypothalamus, where small chemical or electrical stimuli can produce significant alterations in the amount of hormones secreted by an endocrine gland. Thus, the neuroendocrine system provides a sensitive series of indicators for analyzing responses to the influence of environmental changes.

The pathophysiologic picture of stress has been characterized as the General Adaptation Syndrome, which develops in three stages: the alarm reaction, the stage of resistance, and the stage of exhaustion (Selye, 1950). The classic triad of alarm reaction (adrenocortical stimulation, thymicolymphatic hypotrophy and gastrointestinal ulcer) denotes the stereotypic response of the body to any demand that severely taxes the regulatory processes. The triad of reactions also

illustrates the involvement of the hypothalamic-hypophysial-adrenocortical system and autonomic control. Only recently has the secretory pattern of adenohypophysial hormones (other than adrenocorticotropin) been found to be involved in non-specific stress responses. It is now well established in rats that acute stress inhibits secretion of growth hormone (GH) and stimulates release of adrenocorticotropic hormone (ACTH) (Matsuyama *et al.*, 1971) and prolactin (Neill, 1970). In general, stress-induced hormonal changes are not related uniquely to the particular stressing agent but also to the intensity and duration of stress.

The hypothalamic-adrenocortical interaction displays a diurnal or circadian rhythmicity. The interaction is intensified during stress to the point of changing or obliterating the diurnal or circadian pattern of secretion. Among the strongest of stressful stimuli are surgery, anesthesia, cold, narcosis, burns, high environmental temperature, rough handling, electric shock, and physical restraint.

Great care must be exercised to ensure that changes in hormone levels are the response to the specific stressor under investigation, (i.e., an RFEM field) rather than to extraneous factors. Investigation of endocrine reactions must be carefully designed and conducted with animals properly adapted to the experimental environment with appropriate sham exposures. The adaptation period for rats should be at least 14 days (Grant *et al.*, 1971). An environmental or a manipulative technique that alters the animal's behavioral patterns results in anxiety, in aversive behavior, and in loss of body mass; these patterns can all be interpreted as responses to stress. Standard laboratory stresses are commonly found in the experimental procedures that are used in biomedical studies. Such commonplace procedures as handling, novelty of the experimental environment and procedures, extreme environmental temperatures, forced muscular exercise, immobilization, transportation, noise, electrical shock, and ether anesthesia can act as stressors under certain conditions (*cf*, e.g., Justesen *et al.*, 1974; Bermant *et al.*, 1979; Riley, 1975; Weiss, 1971).

Unless these factors are taken into consideration, it is not possible to eliminate stress reactions due to extraneous factors in experiments that are intended to investigate adrenal neuroendocrine function in relation to RFEM exposure (Mikolajczyk, 1977). Control of extraneous sources of stress is of paramount importance if one is interested in studying subtle responses to RFEM irradiation, especially at low intensities, if applied for either short or long periods of time.

Functional alterations in the neuroendocrine system of both experimental animals and human beings exposed to RFEM fields have been

reported by several investigators. The findings include changes in the secretions of the pituitary gland, of the adrenal cortex, of the thyroid gland, and of the gonads. Some investigators believe that such changes result from stimulation of the hypothalamic-hypophysial system by thermalization of the hypothalamus or the immediately adjacent hypophysis (pituitary), or of the particular endocrine gland or organ under study. According to other investigators, the observed changes might be the result of direct RFEM interactions with higher centers in the central nervous system. Regardless of the mechanisms involved, the highly integrated, extremely labile hormonal systems have a great potential for useful study. Shifts of a few millidegrees Celsius may alter firing rates of hypothalamic cells (Nakayama *et al.*, 1963). On the other hand, brain temperature changes in the range of 0.1 to 2.0 °C are possible with exercise or in response to certain environmental stresses (Baker and Chapman, 1977). It is reasonable, then, to expect that alterations in the levels of the secretory products of these organs will occur in response to RFEM irradiation. In any case, one cannot consider neuroendocrine alterations as necessarily pathologic, because the function of the neuroendocrine system is to maintain homeostasis, and hormone levels will fluctuate to maintain such organismic stability.

Several reviews (Michaelson, 1977a; Michaelson *et al.*, 1975; Baranski and Czerski, 1976; Cleary, 1977; Lu *et al.*, 1980a) have considered neuroendocrine responses in relation to RFEM exposure.

8.2 Neuroendocrine and Endocrine Effects

Responses of the endocrine system of rats to RFEM irradiation have been studied in recent years, but most of the reports are based on relatively short exposures at modest to high power densities (Lotz, 1978, abstract, 1979, abstract; Lotz and Michaelson, 1978, 1979; Guillet *et al.*, 1975; Guillet and Michaelson, 1977; Houk *et al.*, 1975; Travers and Vetter, 1977, abstract; Micolajczyk, 1972, 1974, 1977; Lu *et al.*, 1977a, b, 1979a, b, 1980a, b, 1981; Magin *et al.*, 1977a, b).

8.2.1 *Hypothalamic-Hypophysial-Adrenal Response*

Several investigators have reported biochemical and physiological changes as a result of exposure to RFEM fields, all of which indicate

an adrenal response. Dumansky and Shandala (1974) reported adrenocortical changes in rats and rabbits chronically exposed (10 to 12 h/d, 180 d) to 2.5 GHz at 2 or 10 $\mu W/cm^2$. According to Petrov and Syngayevskaya (1970), 3 and 24 h after dogs were irradiated by 3000-MHz fields at 10 mW/cm^2, the corticosteroid content in their blood had increased by 100 to 150 percent above the original level. Serum potassium was decreased by 5 to 10 percent and sodium was increased by the same amount. They also noted that the susceptibility of rats to irradiation was sharply increased one week after bilateral adrenalectomy. Kirchev (1959) reported that, under the influence of 3- to 300-MHz fields of unspecified strength, adrenal mass increased as a result of hyperplasia, indicating adrenal stimulation. Petrov and Syngayevskaya (1970) suggest that the enhancement of corticosteroid activity during and after irradiation could be an adaptive reaction.

Dumansky *et al.* (1972) reported that chronic (120 d) exposure of rats to 500-MHz and 2.5-GHz fields (CW or pulsed) at power densities of 1 to 10 $\mu W/cm^2$ was accompanied by reduced activity of blood cholinesterase, by an increase of 17-ketosteroids in urine, by a reduced amount of ascorbic acid in adrenal glands, and by reduced adrenal mass. The physiologic implications of these findings are unclear because blood cholinesterase activity is mostly "pseudocholinesterase", which has no correlation with acetylcholine activity as the authors imply. Detailed methods used in these studies were not given.

Schliephake (1960) observed an increase in 17-ketosteroids in the urine of human beings exposed to centimetric fields (50 mW/cm^2, 10 min); in rats, a marked increase in the ascorbic acid content of the adrenal cortex was observed. The results of Leytes and Skurikina (1961) also indicated increased adrenocortical hormone production 1 to 2 h after a 10-min exposure to 3 GHz at 100 mW/cm^2. It has been suggested that these results are an indirect indication of increased pituitary-adrenocorticotropic function.

According to Bereznitskaya (1968), the pituitary glands in female mice that were exposed to 3000-MHz fields (10 mW/cm^2) twice daily for 5 months retained their gonadotropic function, although their activities were reduced in comparison with those of nonexposed animals. Tolgskaya and Gordon (1964), in discussing the dynamics of changes in the neurosecretory function of the hypothalamus, noted the reversibility of the process after exposure was terminated.

Lenko *et al.* (1966) found that rabbits exposed to 3-GHz fields (50–60 mW/cm^2) 4 h daily for 20 d tend to show an initial decline in the amount of urinary 17-hydroxycorticosteroids (17-OHCS) followed by a gradual return to normal. No change was evident in the excretion of 17-ketosteroids in urine.

In rats exposed to 2.9-GHz fields at 100 mW/cm^2, no quantitative changes in corticosterone were found in the adrenals or blood plasma if they were properly acclimatized to their environment (Mikolajczyk, 1972). Prepubescent hypophysectomized rats displayed no differences in adrenal growth rate when treated with pituitary homogenates collected either from rats exposed to RFEM fields or from control rats.

Rats exposed to 2450-MHz CW fields at 10 mW/cm^2 for 4 h showed no change in adrenal mass, in phenylethanolamine-N-methyl transferase (PNMT) activity, or in epinephrine levels (Parker, 1973). After 16 h of exposure at 15 mW/cm^2 (0.4 °C increase in rectal temperature compared with that of controls), there was a significant decrease in adrenal epinephrine (32 percent) and PNMT activity was elevated (25 percent). There were no statistically significant differences in adrenal- or plasma-corticosterone levels between exposed and sham-exposed animals.

Michaelson *et al.* (1967) reported that exposure of dogs to 2880-MHz pulsed fields at power densities above 100 mW/cm^2 resulted in physiologic responses indicative of adrenocortical stimulation, which is consonant with the concept of non-specific stress. As a general conclusion, the authors suggested that irradiation at high power densities can elicit a "stress" response that could affect integrative physiologic regulation, resulting in an alteration in homeostatis.

Lotz and Michaelson (1978) reported that plasma corticosterone (CS) levels in rats exhibited a variable power-density threshold; the threshold for a 120-min exposure was different from those for 30- or 60-min exposures to 2540-MHz CW fields (Figure 8.1). For all these durations of exposure, a strong correlation was evident between the mean of colonic temperature and the mean plasma level of corticosterone (Figure 8.2). The threshold power density was 50 mW/cm^2 for a 30- or 60-min exposure and 20 mW/cm^2 for a 120-min exposure. These thresholds occurred at *SAR*s of 8.0 and 3.2 W/kg, respectively. An independent study confirmed 50 mW/cm^2 as a threshold power density for a 60-min exposure of 300-g rats (Lu *et al.*, 1980b). Plasma CS increased within 15 to 30 min of the start of exposure to 2450-MHz fields and fell sharply within 15 to 30 min after termination of exposure (Michaelson *et al.*, 1977) (Fig. 8.3). The CS response of the adrenal cortex was transient in all cases.

In contrast to the pronounced adrenocortical response observed in intact rats, plasma CS levels in acutely hypophysectomized rats exposed to 2450-MHz fields at 60 mW/cm^2 for 60 min were below control levels (Figure 8.4). The CS response to fields at 50 mW/cm^2 for 60 min was completely suppressed by 3.2 μg of dexamethasone per 100 g

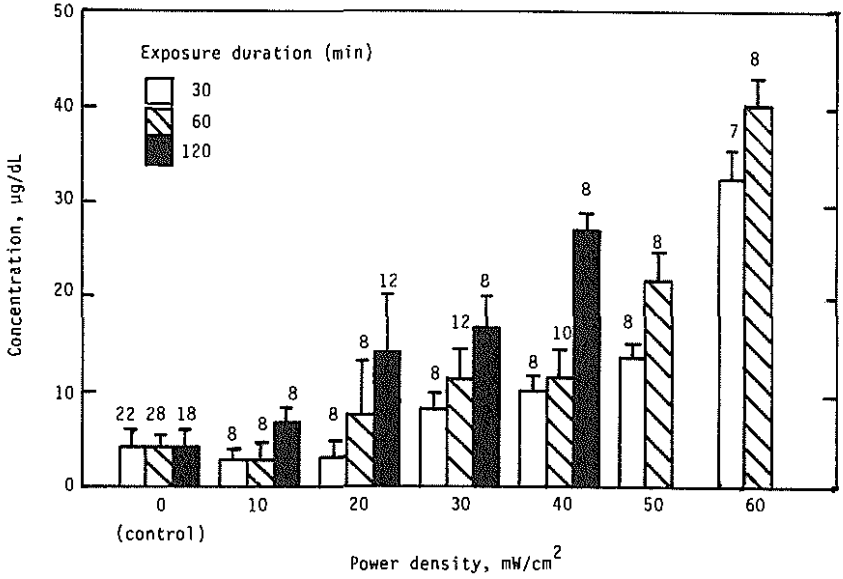


Fig. 8.1. Plasma corticosterone (CS) levels in relation to power-density and duration of exposure in rats exposed to 2.45-GHz fields. Concentration is expressed as the mean and its standard error. Values above the error bars are the number of animals. (After Lotz and Michaelson, 1978.)

body mass (Figure 8.5) (Lotz and Michaelson, 1979). These results are consistent with the hypothesis that stimulation of the adrenal axis in the exposed rats is a systemic, integrative process due to a general hyperthermia. The results indicate that the RFEM-induced CS response observed in rats depends on adrenocorticotropin secretion by the pituitary, i.e., the adrenal gland is not directly stimulated by RFEM exposure.

Novitskii *et al.* (1977) studied the corticotropin releasing factor (CRF) of the median eminence, the ACTH of the hypophysis and the 11-oxycorticosteroid (11-OCS) of the plasma in 180- to 230-g Wistar rats exposed at 0, 0.01, 0.1, 10 and 75 mW/cm^2 to 2.6-GHz horizontally polarized fields for 30 minutes. Results indicated that the threshold intensity was 0.1 mW/cm^2 for increases in CRF, ACTH and 11-OCS; maximal increases were observed at 1 mW/cm^2. The finding indicates that adrenocortical stimulation might be a process mediated by the central nervous system. In discussing their study, Novitskii *et al.* (1977) suggested that increased hypothalamic-hypophysial-adrenocortical (HHA) stimulation with increasing intensities from 0.01 to 1 mW/cm^2 (at 2.6 GHz) could be an indicator of an adaptive reaction of the organism to a harmful agent. The findings from repeated 30-min

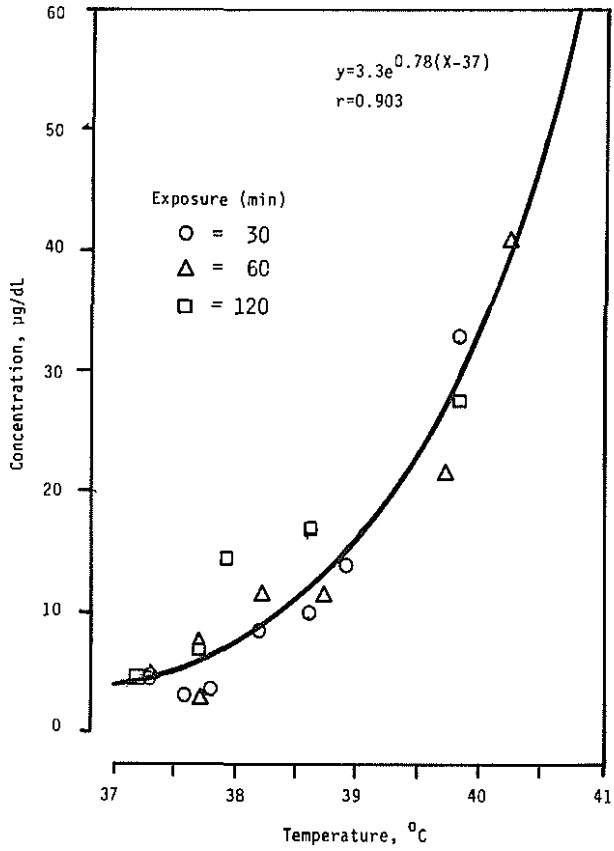


Fig. 8.2. Correlation between plasma corticosterone level and colonic temperature in rats exposed to 2.45-GHz fields. (After Lotz and Michaelson, 1978.)

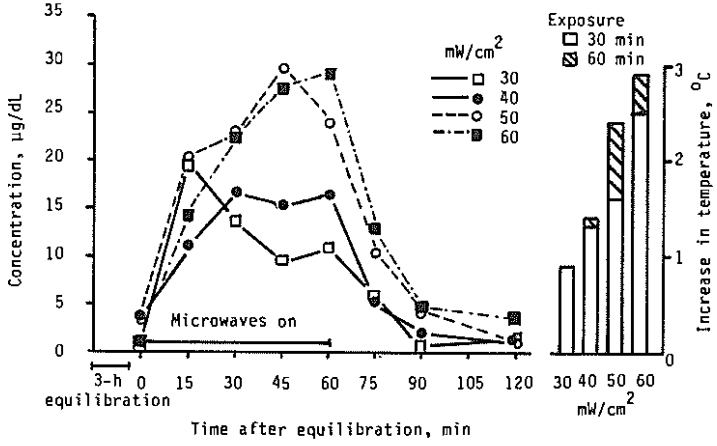


Fig. 8.3. Temporal response of plasma corticosterone and elevation of colonic temperature in rats exposed to 2.45-GHz fields. (After Michaelson *et al.*, 1977.)

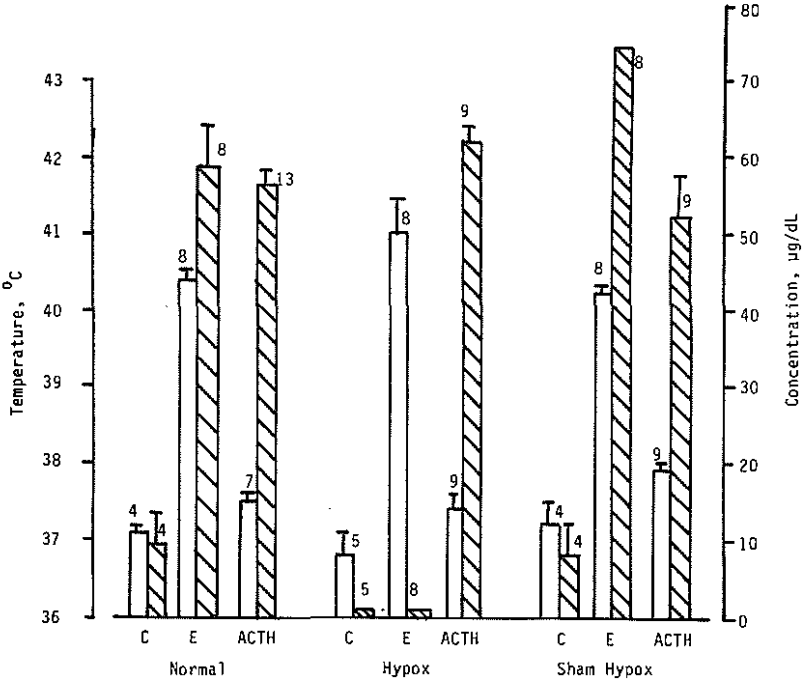


Fig. 8.4. Rectal temperature and plasma corticosterone levels in acutely hypophysectomized rats exposed to 2.45-GHz fields at 60 mW/cm^2 for 60 minutes. Concentration and temperature are expressed as the mean and its standard error. Values above the error bars are the number of animals. Open bars are temperature; cross-hatched bars are concentration. C = controls; E = exposed; ACTH = treatment with adrenocorticotropic hormone. (After Lotz and Michaelson, 1979.)

exposures of animals to 2.6-GHz fields at 1 mW/cm^2 were considered to be evidence of a "cumulative effect" by RFEM exposure. The pattern of this HHA reaction could very well fit into the picture of the general adaptation syndrome (Selye, 1946).

In a study by Lu *et al.* (1977b) to assess the neuroendocrine responses to protracted exposure, adult rats were exposed to 2450-MHz CW fields at 0, 1, 5, 10 or 20 mW/cm^2 for 1, 2, 4, or 8 hours. Exposure at power densities below 10 mW/cm^2 shifted the appearance of the peak colonic temperature to an earlier time of the day (Figure 8.6). In rats exposed at 20 mW/cm^2 for 8 hours, serum CS was significantly below the expected circadian elevation. This inhibition of CS elevation was also noted in rats (Figure 8.7) exposed at 0.1 and 1 mW/cm^2 for 4 h (Lu *et al.*, 1981). A significant correlation between colonic temperature and CS level was found in sham-exposed rats that were euthanatized

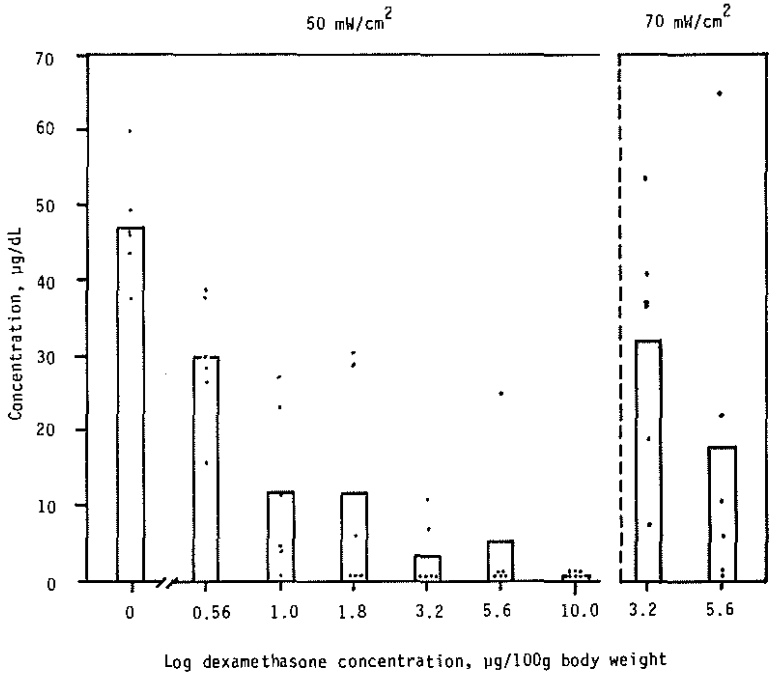


Fig. 8.5. Plasma corticosterone levels in rats pretreated with dexamethasone and exposed to 2.45-GHz fields at 50 and 70 mW/cm^2 for 60 minutes. (After Lotz and Michaelson, 1979.)

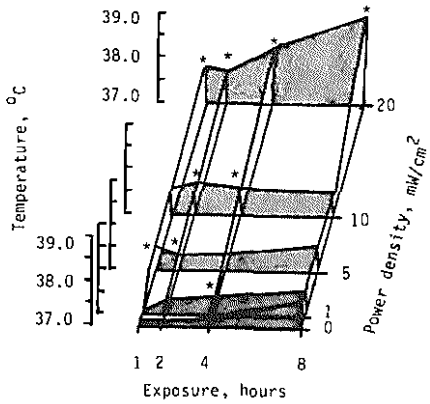


Fig. 8.6. The relation between colonic temperature, power density and duration of exposure in 20 groups of rats exposed to 2.45-GHz fields. The stars (★) over some of the points indicate the significance level for $p < 0.05$. (After Lu *et al.*, 1977.)

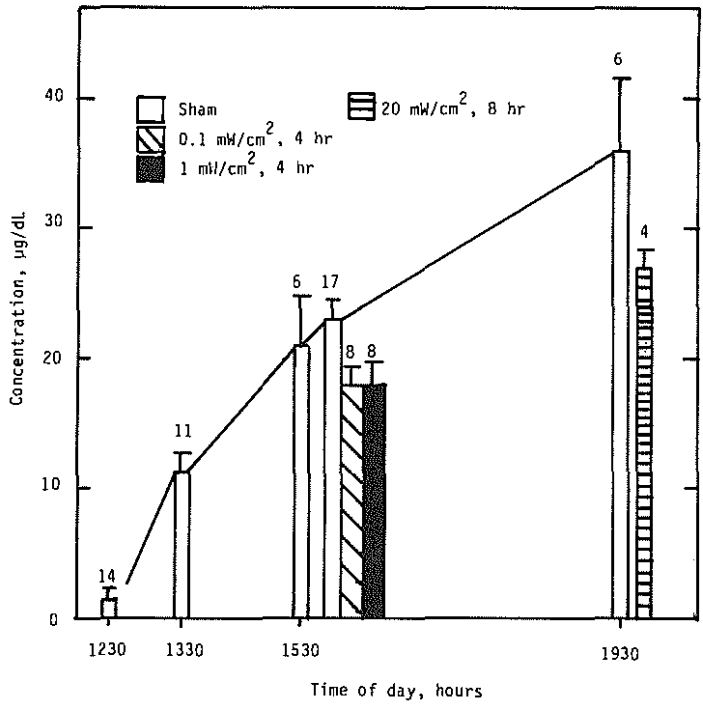


Fig. 8.7. Suppressed circadian, post-meridian plasma corticosterone increase in rats exposed to 2.45-GHz fields for 4 h at 0.1 and 1 mW/cm² and for 8 h at 20 mW/cm². Concentration is expressed as the mean and its standard error. Values above the error bars are the number of animals. (After Lu *et al.*, 1981.)

between 1230 and 1930 hours. A similar correlation was noted in rats exposed at 1 to 70 mW/cm² for 1 h and euthanatized at 1230 hours, as well as in rats exposed to 0.1 to 40 mW/cm² for 4 h and euthanatized at 1530 hours. The temperature coefficient decreased sequentially among sham-exposed, 1-h exposed and 4-h exposed rats, respectively. The temperature coefficient of CS was significantly lower in the 4-h exposed rats than in the sham-exposed rats.

To delineate acute neuroendocrine responses to RFEM exposure, Lu *et al.* (1980b) exposed "gentled" rats to the same frequency at power densities ranging from 1 to 70 mW/cm², 1 to 8 h at an environmental temperature maintained at 24 °C. For exposure of 1 h, colonic temperature increased with power density at 20 mW/cm² and higher, but consistent elevation of serum CS did not occur below 50 mW/cm². Lower serum TSH and GH levels also occurred at this and higher power densities. Significant serum T_4 elevations were noted at 40 and 70 mW/cm², but they were not consistently related to power density. For sham exposures and exposures at 1 to 20 mW/cm² for

longer durations (2 to 8 h), the results were rather equivocal, presumably because such exposures encompassed significant portions of the circadian cycle. Thus, a dual action of RFEM fields on the hypothalamic-hypophysial-adrenocortical axis was demonstrated in which low-intensity exposure of the rat (<10 mW/cm^2) inhibited CS levels during the peak period of the CS oscillation, while higher-intensity exposure (>20 mW/cm^2) stimulated CS secretion during all parts of the circadian periodicity.

Adrenocortical stimulation generally has been accepted as indicating a response to a stressful stimulus, i.e., a level of stimulation that requires bodily adjustment to counteract the insult. There is consistent evidence that exposure of rats above 25 mW/cm^2 (*SAR*, 5 W/kg) stimulates the HHA axis, and that this stimulation is modulated by the central nervous system. The response to exposure below 25 mW/cm^2 was variable, indicating stimulation or inhibition in some cases, or no change in others. It may be that alterations in adrenocortical function at low-intensity irradiation are smaller than the magnitude of the daily oscillation of this system and are modified by their timing with respect to the normal biological periodicities (Lu *et al.*, 1980a).

It has been shown that increased adrenal function due to RFEM exposure is correlated with increase of colonic temperature in rats (Lotz and Michaelson, 1978). Plasma corticosterone levels in hypophysectomized rats exposed at 60 mW/cm^2 (*SAR*, 12 W/kg) for 60 min were below control levels. When rats were pretreated with dexamethasone before being exposed at 50 mW/cm^2 (*SAR*, 10 W/kg) for 60 min, the corticosterone response was suppressed. These results suggest that the RFEM-induced corticosterone response observed in intact rats is dependent on adrenocorticotropic hormone secretion by the pituitary, i.e., the adrenal gland is not the primary endocrine gland stimulated by RFEM radiation. The evidence obtained in these experiments is consistent with the hypothesis that the stimulation of the adrenal axis in RFEM-exposed rats is a systemic, integrative process due to a general hyperthermia (Lotz and Michaelson, 1978).

8.2.2 *Hypothalamic-Hypophysial-Thyroid Response*

One of the major functions of thyroid hormones is control of basal and resting metabolic rates. Pituitary secretion of thyrotropin (TSH) has been shown to respond in a specific metabolic pattern to extreme environmental temperature, and it appears to respond in a nonspecific manner to other stressful stimuli. Thyrotropin secretion is under the

control of the central nervous system, as are the secretions of the other adenohypophysial hormones.

The thyroid gland plays an essential role in regulating basal metabolism in the organism as well as in generation of metabolic energy in tissues. The functional and structural integrity of the thyroid gland is essential for normal homeokinesis of the organism. Not only do the thyroid hormones act on metabolism at the cellular level by regulating cellular processes to maintain homeostasis, but the thyroid is also an integral component of the neuroendocrine system and its activity is interdependent with the functional aspects of other members of the system.

The release of thyrotropin (TSH) by the anterior pituitary gland is regulated by an interaction between hypothalamic thyrotropin-releasing hormone (TRH), which stimulates release of TSH and of the calorigenic (metabolically active) thyroid hormones [thyroxine (T_4) and triiodothyronine (T_3)], which suppress TRH. Of interest, also, is the indication that somatostatin (GH-RIH), the growth hormone-release inhibiting hormone, may regulate TSH secretion by its inhibitory action on TSH release. Interest in this endocrine axis is, therefore, appropriate when considering the possible physiologic perturbations of the thyroid as a consequence of RFEM exposure.

Alterations in thyroid physiology (increased radioiodide uptake) and pathology (enlarged thyroid) have been included by Soviet clinical investigators (Smirnova and Sadchikova, 1960) as a component of "microwave sickness" in persons occupationally exposed to microwaves. In these reports, increased thyroid function was rarely accompanied by other symptoms related to hyperthyroidism. Usually, pathology and pathophysiology were included as a prevalence in a symptom-complex within the exposed population; they were studied in a rather selected subpopulation of "sick" persons. Other investigators, however, have not found thyroid disorders among persons occupationally exposed to RFEM (Czerski *et al.*, 1974b; Djordjevic *et al.*, 1979; Robinette *et al.*, 1980) in systematic examinations. These factors preclude any serious attempt at risk analysis other than a causal relationship between thyroid changes and a past history of RFEM exposure. Epidemiological study and animal experimentation are needed to resolve the issue.

The literature offers comparatively few experimental studies of the effect of RFEM fields on the thyroid. Both stimulatory and inhibitory actions of RFEM exposure on thyroid function have been noted in animals (Lu *et al.*, 1980b, 1981; Michaelson, 1974). In a study by Milroy and Michaelson (1972), rats exposed to RFEM radiation under

various regimens (2450-MHz CW fields at 1 mW/cm^2 continuously for 8 weeks or at 10 mW/cm^2, 8 h/d for 8 weeks) were evaluated in terms of their thyroid and thyrotropic activity. No alterations in structure or function were noted. On the other hand, Baranski *et al.* (1972) reported a stimulatory influence of 3-GHz fields (5 mW/cm^2, 3 h/d, 48d) on the trapping and secretory function of the thyroid gland of rabbits.

In rats exposed for 16 hours to 2450-MHz CW fields at 10 to 25 mW/cm^2, tests of thyroid function in general showed no statistically significant deviations from the norm except that in animals with a 1.0- to 1.7-°C increase in colonic temperature there was a reduction in the ability of the thyroid to concentrate iodide after 60 h at 15 mW/cm^2 (Parker, 1973).

Indirect evidence has been obtained of some protective influence of lowered, general and tissue metabolic rate following hypophysectomy on the time-related lethal exposure of rats to RFEM fields. Mikolajczyk (1974) found that the survival time of exposed normal rats (2860 to 2880 MHz, CW, 120 mW/cm^2) is essentially inversely proportional to body mass; in contrast, survival time per unit of body mass is significantly longer in hypophysectomized rats than in normal ones.

Shutenko and Shvayko (1972) found an increase in thyroid activity in animals subjected to a prolonged exposure to low-intensity centimeter waves. Michaelson *et al.* (1967) reported transiently increased radioactive iodide uptake (RAIU) in dogs exposed to 1280- or 2880-MHz pulsed fields at 100 to 165 mW/cm^2.

It has been reported that RFEM-exposed workers developed enlargement of the thyroid gland as well as increased RAIU, but in some cases without clinical symptoms of hyperfunction (Smirnova and Sadchikova, 1960). None of the reported alterations in thyroid function was irreversible or resulted in morbidity. D'Yachenko (1970) described the results of a study of thyroid function in 38 men who operated microwave equipment (centimeter band) for 3 to 15 years. Enhanced ^{131}I uptake by the thyroid was found, which was attributed to secondary effects resulting from radiation-induced disturbances of the sympathetic nervous system involving the hypothalamus. Denisiewicz *et al.* (1970) did not find significant disturbances in thyroid function among 142 men that were exposed at power densities of 10 $\mu W/cm^2$ to 1 mW/cm^2 while servicing microwave equipment.

Lu *et al.* (1977a) reported that serum thyroxine levels were transiently elevated in rats after exposure to 2.45-GHz fields at 1 mW/cm^2 (*SAR*, 2 W/kg) for 4 hours. This transient increase was not

accompanied by changes in serum TSH (Lu *et al.*, 1977b). Magin *et al.* (1977a, b) demonstrated that localized exposure of the dog thyroid (2.45 GHz, CW, 72 to 236 mW/cm^2, 58 to 190 W/kg, 120 min) resulted in thyroidal temperature elevation of 2 to 8 °C and increased thyroid secretion in the absence of pituitary irradiation.

Levels of thyroid hormone were found by Vetter (1975) to decrease as the power density of a 2.45-GHz field increased from 5 to 25 mW/cm^2. Lu *et al.* (1977a) also noted decreased thyroxine levels in rats exposed to a 2.45-GHz field at 20 mW/cm^2 (*SAR*, 4 W/kg) for 4 to 8 hours.

Depression of the thyroid apparently reflects inhibition of hypophysial TSH secretion as evidenced by decreased TSH prior to and accompanied by decreases in serum thyroxine in rats exposed to 2.45-GHz CW fields at 10 mW/cm^2 for 1 and 2 h, and at 20 mW/cm^2 for 2 h and 8 h (Lu *et al.*, 1977b). Lotz (1982a) investigated TSH levels in rats exposed to 2.45-GHz fields at 13 to 60 mW/cm^2 for 30, 60 and 120 minutes. His results indicated that a 30-min exposure did not affect the TSH levels. Depressed TSH levels were noted in rats exposed at 30 mW/cm^2 (*SAR*, 4.8 W/kg) or more for 60 min and at 13 mW/cm^2 (*SAR*, 2.1 W/kg) or more for 120 minutes. Plasma thyroid hormone levels were not studied. Decreased TSH concentration was persistent during exposure of rats to 2.45 GHz at 20 mW/cm^2 (*SAR*, 4 W/kg) for 8 h (Lu *et al.*, 1980b). The threshold power density for decreased serum concentration in the rat is 30 mW/cm^2 (*SAR*, 6 W/kg) for 2-h and 50 mW/cm^2 (*SAR*, 10 W/kg) for 1-h exposures. A high correlation between decreases in serum thyroxine and TSH was also reported in rats exposed to 2.45-GHz fields at 8 mW/cm^2, for 8 h daily and for periods to 20 days (Travers and Vetter, 1977, abstract).

Stimulation of thyroid function, apparently to counteract the influence of decreased TSH, could be revealed in rats exposed to a field at relatively high power density (2.45 GHz, 70 mW/cm^2, *SAR*, 4 W/kg) for 1 h or in rats with TSH suppressed by triiodothyronine at the time of exposure to 2.45-GHz fields at 40 mW/cm^2 (*SAR*, 8 W/kg) for 2 h (Lu *et al.*, 1980b).

Perturbation of the thyroid gland may be the result of an indirect effect; e.g., thermal stress may produce a hypothalamic-hypophysial response. This possibility is consistent with RFEM-induced thermal stimulation of hypothalamic-hypophysial-thyroid (HHT) activity (Michaelson *et al.*, 1961). These changes in thyroid activity could be the result of increased TSH and/or increased metabolic activity of the thyroid gland due to heating. McLees and Finch (1971), after reviewing the experimental animal data that indicate an increased uptake of radioiodine by the thyroid following RFEM exposure, pointed out that

temperature elevation and heat stress have been associated with alterations in turnover rate of radioactive iodine. The HHT axis has been shown to be sensitive to environmental temperature (Collins and Weiner, 1968). Differences in rate of temperature change or alteration in thermal gradients in the body would also result in qualitative differences in endocrine response.

Thus, there appear to be two types of action of RFEM exposure on the HHT axis, i.e., local thyroid stimulation and axial inhibition. The local thyroid stimulation is, in contrast to the ACTH-dependent, adrenocortical stimulation, caused by high-intensity RFEM exposure. The inhibition of the HHT axis by thermogenic RFEM exposure probably is a homeostatic reaction to an increased thermal burden. Inhibition of metabolism can be viewed as a specific stress response.

8.2.3 *Growth Hormone*

The polypeptide growth hormone (GH), also known as somatotropin (STH), is a secretory product of the pituitary gland. Fasting, various forms of physical and psychologic stress, onset of sleep, arginine infusion, alterations of protein intake, changes in plasma-glucose levels, and administration of L-dopa, glucagon, or vasopressin—all affect plasma GH levels and pituitary production (Martin, 1973).

Growth hormone circulates in the plasma in an unbound form and has ubiquitous sites of action, unlike its adenohypophysial counterparts, TSH and ACTH, which rely on their target-gland secretory products. Among its actions, GH antagonizes the effects of insulin in that it inhibits cellular uptake of glucose (glucose-sparing or diabetogenic effect), and it causes the release of free fatty acids from tissue storage depots.

In man and in some other primates, a variety of stresses can produce an acute release of GH. Such stress in the rat is known to effect reduction of plasma GH levels (Brown and Reichlin, 1972). Pulsatile bursts of GH secretion occur for apparently inexplicable reasons that are not associated with any changes in plasma metabolites (glucose, free fatty acids, or circulating amino acids) that affect or are affected by GH secretion.

In the rat exposed to 2.45-GHz fields at 13 mW/cm^2 (*SAR*, 2.6 W/kg), there is an increase in GH, whereas at 36 mW/cm^2 (*SAR*, 7.2 W/kg) rat serum GH drops significantly after 60 min of exposure (Michaelson *et al.*, 1975). Lotz *et al.* (1977) noted that the threshold intensity for GH inhibition is 50 mW/cm^2 (*SAR*, 8.0 W/kg) for rats exposed to 2.45-GHz CW fields for 30 and 60 minutes. For a 2-h

exposure, at 13 mW/cm^2 (*SAR*, 2.1 W/kg) or higher, GH levels were lower than control levels of sham-exposed animals, and GH was progressively lower at each successively higher power density. Part of this sensitivity may be attributed to the higher GH levels in the 2-h sham-exposed rats than in the 30- or 60-min sham-exposed rats, which indicates a possible stress effect of routine confinement of small experimental animals. The significance of this report (Lotz *et al.*, 1977) is that the GH levels were determined in the same rats as those used in the CS study (Lotz and Michaelson, 1978).

8.2.4 *Conclusion*

Responses of the endocrine system of the rat exposed to 2.45-GHz fields at a power density higher than 40 or 50 mW/cm^2 (8–10 W/kg) exhibit a pattern of increased serum corticosterone (CS) concentration, decreased serum thyrotropin (TSH) concentration and decreased growth hormone (GH) concentration which resemble "stressor"-induced responses in this species of animal (Lu *et al.*, 1980b, 1981). At the same time, decreased TSH concentration may occur in rats exposed at a lower power density than that required to induce an increased CS concentration in rats (Lu *et al.*, 1981). Lotz and Podgorski (1982) noted that cortisol concentration in the monkey was increased during RFEM exposure while thyroxine and growth hormone remained unchanged. Thus, dissociation of endocrine response to irradiation is anticipated in experimental animals exposed at different strengths of RFEM fields. These observations emphasize the need to evaluate analytically the function of endocrine organs individually as well as collectively in order to characterize the extent of involvement or "severity" of biological reactions to the RFEM exposure.

8.3 Metabolic and Biochemical Effects

Various types of metabolic and biochemical alterations have been reported to result from exposure of experimental animals and human beings to RFEM fields. Such effects generally appear to be reversible, and no well-defined characteristic response pattern has been determined, nor is it known whether the changes are direct or indirect effects of exposure.

Dumansky and Rudichenko (1976) reported a decrease in liver-

glycogen content with increased lactic-acid levels and phosphorylase activity in the liver of rats chronically exposed to 2.45- or 10-GHz fields at intensities of 5 to 20 $\mu W/cm^2$. Malyshev and Tkachenko (1972) found that *in-vitro* exposure to 2.45- or 10-GHz fields at intensities of 25 to 1000 $\mu W/cm^2$ decreased the proteolytic activity of the mucous membrane of the small intestines of experimental animals, whereas the invertase and adenosine triphosphatase activity increased. Reduced synthesis of macroglobulin and macroglobulin antibodies resulted from exposure of experimental animals at 50 $\mu W/cm^2$.

Transient, dose-dependent elevations were found in serum glucose following exposure of rabbits to 2.45-GHz fields for 2 h at intensities of 5, 10, and 25 mW/cm^2, in uric acid (at 10 and 25 mW/cm^2) and in blood urea nitrogen (only at 25 mW/cm^2) with no detectable differences between CW and pulsed exposures at equivalent average power densities (Wangemann and Cleary, 1976). There were increases in the means of colonic temperature of 1.7 °C at 25 mW/cm^2 (pulsed) and of 3 °C at 25 mW/cm^2 (CW).

Exposure of rats for 15 min to pulsed 2.86-GHz fields at 5, 10, 20, 50, or 100 mW/cm^2 resulted in statistically significant changes in serum albumin and phosphorous levels only at 100 mW/cm^2 (Fulk and Finch, 1972). The same investigators did not detect any change in serum-glucose levels in rats exposed to 0.43- and 2.86-GHz pulsed fields at 5 mW/cm^2. Single or repeated exposures of rabbits to 3- or 10-GHz fields at intensities of 5 to 25 mW/cm^2 resulted in alterations in the serum albumin/globulin ratio (Swiecicki and Edelwejn, 1963a, b).

Baranski (1972) found inconsistent changes in cholinesterase activity in rabbit and guinea-pig brains following 3 months of exposure, 1 h/d, by pulsed 2.45-GHz fields at 25 mW/cm^2. He also found a decrease in cholinesterase activity in the brains of guinea pigs after a single 3-h exposure at a power density of 3.5 mW/cm^2 and a further decrease in activity at 25 mW/cm^2. Pulsed fields were found to have a more severe effect than CW fields of the same root-mean-square power density, indicating that these effects are due in part to peak strength of fields. Nikogosyan (1960) found increased blood cholinesterase activity in rabbits after a single 90-min exposure to 3-GHz fields at 40 mW/cm^2. He also found decreased cholinesterase activity in the brainstems, livers and hearts of rats at 10 mW/cm^2 for 13 to 23 weeks. Revutsky and Edelman (1964) also reported an increase in specific cholinesterase activity in rabbit blood exposed *in vitro* to 12.6-cm fields. As indicated earlier, there is no correlation between blood- and neural-cholinesterase activity. Olcerst and Rabinowitz (1978) found

no effect of 2450-MHz CW fields on cholinesterase exposed in aqueous solution at power densities to 125 mW/cm^2 for 0.5 h, or at 25 mW/cm^2 for 3 hours. No effect was found on cholinesterase activity in defibrinated rabbit blood exposed for 3 h at 21, 35, or 64 mW/cm^2 to 2450-MHz CW or pulsed fields. Under similar exposure conditions there was no effect on release of bound calcium or magnesium from rabbit red blood cells. The only significant changes in enzyme activity were seen when the quantity of absorbed energy was sufficiently large to cause thermal denaturation of protein.

8.3.1 *Neuroendocrine and Metabolic Correlations*

Although hypothalamic-hypophysial-adrenocortical (HHA) activation and hypothalamic-hypophysial-growth-hormone (HHS) inhibition can be viewed as reactions to non-specific stress, hypothalamic-hypophysial-thyroid (HHT) depression may be considered as a specific reaction. The acute reaction of the HHT to highly thermalizing radiation is the inhibition of a hormone that controls the resting metabolic rate. Phillips *et al.* (1975a) have shown that decreases in the resting metabolic rate of male rats depended on the rate of absorption of RFEM energy. The threshold *SAR* of 6.5 W/kg observed by Phillips *et al.* is approximately double the rat's resting specific metabolic rate (SMR). Ho and Edwards (1977) studied oxygen consumption in mice exposed to 2.45 GHz at various *SARs* in a waveguide exposure system and found that the animals compensated homeostatically to *SAR* of 10.4 W/kg or greater by a decrease in metabolic rate to compensate for thermal loading. Normal metabolic activity was resumed following cessation of exposure. The decreased SMR in a moderately thermalizing field probably reflects an autonomically mediated reduction of energy production involved in thermoregulation (Justesen, 1983a).

The foregoing discussion indicates that investigators need to be aware of the effects of increased body temperature on secretion of pituitary hormones so that precise biological effects can be allocated specifically to irradiation. Threshold intensities can vary in relation to what is considered to be the normal range in sham-exposed or unexposed populations of animals. As an example, pituitary, nonspecific, stereotyped reactions could occur in rats exposed to 2.45-GHz fields at 50 mW/cm^2 (*SAR*, 8.0 W/kg) for 1 hour. Adjustments in TSH levels of rats to an increased thermal load could occur at 10 mW/cm^2 (*SAR*, 1.6 W/kg) (Lu *et al.*, 1981).

Gandhi (1975a) has shown theoretically that RFEM fields near the scaled half-wave resonant frequency of man (~68 MHz) can produce hot spots in the lower neck of human models with a peak *SAR* of ~31 W/kg in a vertically polarized, 10-mW/cm^2 field. Likewise, the model presented by Magin *et al.* (1977a, b) can predict the biologic effects of RFEM radiation when hot spots occur in the neck region.

de Lorge (1979a) plotted the relation between body mass and power density at which disruption of ongoing operant behavior occurred in rats, squirrel monkeys and rhesus monkeys as a basis for interspecies comparison. Although comparable comparisons for neuroendocrine parameters have not been made, Lotz (1979, abstract) found that rats responded to 1.29-GHz fields (2-μs pulses, 1000 pps) by increased corticosterone levels at 15 mW/cm^2 for 30 min or longer. Irradiation in the same field was without effect on adrenocortical and GH secretions of male adult rhesus monkeys when exposed 3 times at 20 and 28 mW/cm^2 for 8 h (Lotz and Podgorski, 1982). The increases in rectal temperature averaged 0.6 and 1.5 °C, respectively, but no changes were observed in plasma growth hormone, in cortisol or in thyroxine concentrations. These differences indicate that neuroendocrine function in the rhesus monkey is more stable than in the rat during thermogenic RFEM exposure. This finding illustrates the differences in the response of a given species of animal to irradiation at various frequencies resulting from differences in energy deposition and distribution.

8.4 Summary and Conclusions

The effects of exposure to RFEM fields on endocrine function are generally consistent with both immediate and long-term responses to thermal input and to non-specific stress, which can also arise from thermal loading. The acute effects of RFEM fields on endocrine function are generally increased adrenocorticotropic secretion, decreased thyrotropic secretion, and decreased GH secretion. These stereotyped changes can be observed simultaneously in rats acutely exposed to 2.45-GHz fields at 50, 60 or 70 mW/cm^2 (*SAR*, 10 to 14 W/kg) for 1 h (Lu *et al.*, 1981). The characteristics of these changes in hypothalamic hormones constitute stress reactions. Because of their physiologic significance, these biological end points of RFEM exposure can serve as meaningful criteria for hazard evaluation if sufficient care has been incorporated into the design of chronic or repeated-exposure experiments.

Some investigators believe endocrine-related changes are caused by stimulation of the hypothalamic-hypophysial system in consequence of thermal interactions at the hypothalamus, or at the particular endocrine gland or end-organ under study. Other workers interpret the observed changes as effects of direct RFEM interactions with the central nervous system.

In the present state of the art, endocrine activity cannot be separated from the functional state of the neural network. The influence of endocrine function on body metabolism is also longer lasting than that due to neural disturbances. In spite of the obvious importance of this subject, only sparse and sometimes insufficiently documented data are available. Non-specific stress reactions to irradiation must be isolated from extraneous factors that are usually associated with experimental procedures. Furthermore, evaluation of a given endocrine end point involves not only its perturbation, but also its recovery—or its delayed manifestation, if such should occur. It should be noted that existing studies generally agree that RFEM-induced neuroendocrine changes are reversible.

The neuroendocrine data are consistent with the hypothesis that the adenohypophysial responses are the integral results of CNS processing of multiple signals from many body locations, such that no single localization of absorbed energy is pivotal to the onset of a response. Factors such as circadian rhythmicity, stimulus intensity, and interspecies differences are important in determining the pattern of these responses. Thus, in addition to further studies to characterize the basic neuroendocrine response to irradiation by RFEM fields, studies are needed to determine the physiological mechanism or mechanisms by which this regulatory system is affected during RFEM exposure.

Evidence indicates that the neuroendocrine effects induced by RFEM fields require a definite threshold intensity for the onset of the response. The exact levels of these thresholds are yet unclear because of conflicting reports. The endocrine response appears to be a non-specific stress reaction in the case of the field-induced adrenocortical and GH changes, but it is apparently a metabolically specific response to increased energy input in the case of the pituitary-thyroid changes. The long-term response of animals to whole-body RFEM exposure at thermally significant levels is a decrease in the level of pituitary thyrotropic hormone in the blood plasma, followed by a decrease in the level of thyroxine.

Changes found in plasma levels of corticosterone and growth hormone are typical reactions of animals to non-specific stress. Such

results emphasize the great care that is required in performing experiments to ensure that changes in hormone levels do not result from stress caused by handling of the animals or by the novelty of the experimental milieu.

Although some studies indicate that exposure to RFEM fields can be manifested by endocrinopathy or hormonal changes, the nature of the interaction between RFEM fields and endocrine organs is not known. Evidence indicates that RFEM energy can act as a stressor in that it may affect the integrative and regulatory mechanisms of the body, which would result in altered homeokinesis. Studies indicate that hypothalamic-hypophysial-adrenal and hypothalamic-hypophysial-thyroid effects are induced at relatively high field strengths in a particular animal species.

The hypothalamus exerts a central influence on thermoregulatory processes, and, when temperature is increased, it assumes control over integration of food and water intake, metabolic rate, osmoregulation, growth, and reproduction. Because neuroendocrine function is an integration of numerous underlying chemical and biologic processes (Shizume and Okinaka, 1964), caution is required in interpreting the significance of changes in the endocrine system induced by exposure to RFEM fields.

Several components of the neuroendocrine system have been shown to be critically sensitive to environmental temperature (Collins and Weiner, 1968; Brown-Grant *et al.*, 1954; Dempsey and Astwood, 1943; Johnson *et al.*, 1966). Thus, neuroendocrine perturbations induced by weak fields could be a manifestation of sensitivity to small changes in peripheral temperature, or a selective stimulation of any component of the neuroendocrine system through alteration of thermal gradients in the body.

Because moderate conditioning of thermal tolerance raises the functional activity of the adrenal cortex (Stefanovskaya and Klochkova, 1969), the reported enhancement of corticosteroid activity during and after RFEM exposure could be an adaptive reaction (Petrov and Syngeyevskaya, 1970).

In regard to stress and adaptation, it should be emphasized that a new environment or a new manipulation can alter animal behavioral patterns, namely, by inducing anxiety, avoidance behavior, and loss of body mass, which, by themselves, could be interpreted as being stressful. Therefore, investigations of neuroendocrine response to RFEM exposure must be carefully designed and controlled and should be conducted in animals properly adapted to environmental conditions.

Careful review and analysis of available information on effects of

RFEM exposure indicate a consistency with a pattern of neuroendocrine involvement in the many physiologic adjustments of the organism relative to increased body temperature or to alterations in thermal gradients within the body that could affect any individual component or combination of components in the neuroendocrine hierarchy. Much more refined and sophisticated studies are required at various exposure levels to determine energy-distribution patterns and their relation to subtle responses before more conclusive statements can be made about RFEM-induced effects on the neuroendocrine system.

There is no reliable evidence, nevertheless, that endocrine disturbance of a pathophysiologic nature occurs in rats at *SAR*s less than 4 W/kg. Assuming a similar sensitivity of the human being, endocrine disturbance should not occur below an average *SAR* of 0.4 W/kg.

9. Effects on Cardiovascular Function

9.1 Experimental Findings

Several investigators have reported changes in cardiovascular function of experimental preparations exposed to RFEM fields. Some have used *in-vitro* preparations to investigate the possibility of a direct action of such fields on the heart. Others have examined cardiovascular function in response to direct exposure of the heart *in situ* or in response to exposure of various regions of the body. Lastly, there is a body of data that has come from studies in which the entire animal was irradiated.

Paff *et al.* (1963) exposed isolated hearts of 72-h embryonic chicks to 24 GHz CW fields at 74, 167, 297, or 478 mW/cm^2 for a period of a few seconds to 3 minutes. At the two highest exposure levels, there was marked thermal damage, with injury to the atrium more marked than that to the ventricle; the P wave of the electrocardiogram disappeared. At 74 mW/cm^2, an exposure level that was not associated with thermal damage, there was an immediate and consistent effect on the electrocardiogram. The T wave was deformed, the P wave was inverted, and the QT interval was shortened.

Several investigators have reported a chronotropic effect of RFEM exposure on isolated heart preparations (Levitina, 1966; Lords *et al.*, 1973; Olsen *et al.*, 1975, 1977; Tinney *et al.*, 1976; Reed *et al.*, 1977). Isolated turtle hearts, (Levitina, 1966; Lords *et al.*, 1973; Tinney *et al.*, 1976) and rat hearts (Olsen *et al.*, 1975, 1977; Reed *et al.*, 1977) exposed at 960 MHz (1.5 to 10 W/kg) exhibited bradycardia. Results from studies based on treatments with pharmacological agents indicate that the chronotropic effect of RFEM exposure on *in-vitro* heart preparations may be due to neurotransmitter release. Olsen *et al.* (1977) observed bradycardia in isolated, perfused rat hearts exposed at 960 MHz for 5 min (1.3 or 2.1 W/kg). When a parasympathetic blocking agent, atropine, was added to the perfusate, a marked tachycardia occurred during irradiation. When a sympathetic, beta-site blocking agent, propranolol, was added to the perfusate, a more marked brady-

cardia occurred during irradiation than that seen without the drug. The authors hypothesized that the RFEM energy interacted with residual segments of the autonomic nervous system within the heart to produce the observed chronotropic effect. After probing the turtle heart with pharmacological agents, Tinney *et al.* (1976) suggested that the field-induced, rate-change effect might be due to neurotransmitter release from the cut nerve endings in the isolated preparation. Reed *et al.* (1977) found that the 5- to 10-percent reduction in the heart rate of rats exposed at 960 MHz (2 W/kg for 10 min) was eliminated by adding both atropine and propranolol to the perfusate.

In contrast to the chronotropic effect of RFEM fields on isolated turtle, frog, and rat hearts, similar results have not been observed in the quail embryo, or in the isolated, spontaneously beating rat atrium. Hamrick and McRee (1980) exposed 9- to 13-day-old quail embryos to 2450-MHz fields at 0.3 to 30 W/kg. No effect of the exposure on heart rate was found. Galvin *et al.* (1982) investigated the chronotropic and inotropic effects of 2450-MHz fields in the isolated, spontaneously beating rat atrium. Atria were irradiated (2 or 10 W/kg) for 30 min at 22 or 37 °C in a temperature-controlled exposure system. Contractile force and beating rate were the same before, during, and after irradiation. Contractile force and rate were not affected at either exposure level or at either temperature. Also, no inotropic effect was noted at either exposure level. In comparing the results of this study with those of Reed *et al.* (1977) and Olsen *et al.* (1977), the authors noted that the rate of contraction of their isolated atrial preparation was 100/min, whereas the rate of contraction in the preparations of Reed *et al.* and Olsen *et al.* was 18/minute. The authors suggested that the bradycardia observed by the other investigators may have been due, in part, to differences in the basal condition of the rat-heart preparations. They suggest that irradiation may have had direct cardiac effects in pathophysiological conditions. However, based on the results of the rat-atrium study, irradiation does not appear to have an effect on the myocardium or on neural components (i.e., on the pacemaker cells of the atria).

Experimental studies in which *in-vitro* preparations were exposed to pulsed RFEM fields has produced conflicting results. Frey and Seifert (1968) exposed isolated hearts of frogs to 10-μs pulses at 1425 MHz. The peak power density was 60 mW/cm^2, the average power density, 0.6 μW/cm^2. Hearts were exposed at the peak of the P wave, and at 100 or 200 ms after the P-wave peak. The authors found that heart rate was increased by the 10-μs pulses delivered 200 ms after the P wave, about the time the QRS complex occurred. Arrhythmias

occurred in about 50 percent of the cases and were associated with exposure to the field.

In a later study, Eichert and Frey (1977) reported on effects of 1200-MHz fields on the *in-vivo* heart rate of frogs at an average power density of 5 $\mu W/cm^2$ and a peak power density of 50 mW/cm^2 (5-ms pulses). Tachycardia was produced when the incident pulse was synchronized with the rise of the R wave. In a similar but not identical study, Liu *et al.* (1976) found no significant change in the contractile rates of frog hearts irradiated *in situ* by pulsed (100-μs pulses) 1420-MHz and 1-GHz fields that were synchronized with the R wave. They also exposed isolated frog hearts to 100-μs pulses of 1420-MHz fields at 3.3 mW/cm^2 and found no effects. Similar negative findings have been reported by Chapman and Cain (1975). They exposed isolated frog hearts to pulsed 3000-MHz fields (2 or 10 μs, 5 W/cm^2 peak) at specific times in the contractile cycle, but they observed no change in heart rate. The authors suggested that the positive findings by Frey and Seifert (1968) may have been due to an induced-current artifact produced by metal electrodes in contact with the myocardia. However, in the Chapman and Cain (1975) study, an effect may not have been seen because the pulse widths and exposure durations of the RFEM fields were shorter than those used by Frey and Seifert.

The chronotropic effect of RFEM irradiation of *in-vitro* preparations of frog, turtle, and rat hearts may or may not occur when hearts are exposed *in situ* or when the whole animal is exposed. Cardiovascular function is clearly affected by intense fields when moderate-to-intense heating occurs. At intensities not resulting in significant body heating, cardiovascular responses to RFEM exposure are equivocal.

Early research based on the use of diathermy applicators demonstrated that heating of tissue can result in marked cardiovascular responses. Marks *et al.* (1961) exposed the anterior mediastinum of the dog to 2450-MHz fields at a sufficiently high level to produce significant volume heating. Heart rate increased about 15 to 30 percent and there was a transient T-wave change related to elevated cardiac temperature. These authors also noted a marked increase in cardiac output and coronary blood flow during exposure. These changes were noted at power levels that did not produce morphologically discernible damage to the myocardium.

In a recent study, Galvin and McRee (1981) examined the effects of RFEM irradiation of the intact, but extirpated hearts of cats with and without surgically induced myocardial ischemia. The hearts were irradiated by 2450-MHz fields for 5 h at an *SAR* of 30 W/kg. No increase in aortic blood temperature occurred during irradiation. No

effects of exposure were observed in terms of blood pressure, cardiac output, heart rate, plasma or creatinine phosphokinase or in the ST segment of the electrocardiogram. The authors concluded that cardiovascular effects observed by others in whole-animal exposures are possibly secondary to effects of irradiation on other parts of the body.

Michaelson (1977b) and Lu *et al.* (1975) reported that exposure of a dog's head to 2450-MHz fields at 80 mW/cm^2 resulted in an increased heart rate. Sinus arrhythmias developed with an increased depth of respiration, followed by bradycardia. Ventricular conduction time increased as respiratory rate increased. This cardiorespiratory response was interpreted as an early increase in sympathetic activity, followed by a supervening parasympathetic response.

Presman and Levitina (1962a, b) exposed various regions of rabbit bodies to 2400- or 3000-MHz CW or pulsed fields and then examined heart rate. Exposure of the ventral parts of the body to 3000-MHz fields at 7 to 12 mW/cm^2, or to pulsed fields at an average 3 to 5 mW/cm^2 (1-ms pulses at 700 pps) produced bradycardia. Exposure of the rabbit's head or dorsal surface resulted in tachycardia after the termination of exposure. With exposure of the ventral surface, bradycardia occurred during exposure. The observed changes in heart rate were more pronounced on exposure to pulsed fields than to CW fields. In another series of experiments, rabbits were exposed to two types of pulsed radiation: 0.1-s pulses at 2 pps for 20 min at peak power densities of 700 to 1200 mW/cm^2, or 1-ms pulses at 700 pps for 20 min at a peak power density of 350 to 380 mW/cm^2. Bradycardia occurred during exposure of any region of the body and could be abolished by treating the skin of the exposed region with the analgesic mesocain. The authors concluded that the bradycardia was a centrally mediated response as a result of skin-receptor excitation.

Kaplan *et al.* (1971) repeated part of the Presman and Levitina experiments using similar equipment and methodologies (2400-MHz fields at 10 mW/cm^2), but were unable to confirm the earlier findings. A later experiment by Birenbaum *et al.* (1975) also failed to confirm the results of the Presman and Levitina studies. They found no detectable changes in heart rate until power density was increased to 80 mW/cm^2, at which level tachycardia was observed.

In a recent study by Chou *et al.* (1980), rabbits were exposed dorsally and ventrally to 2450-MHz fields for 20 min/d under several field conditions: (1) CW fields at 5 mW/cm^2; (2) pulsed fields (1-μs pulses at 700 pps) at 5 mW/cm^2 average and 7.1 W/cm^2 peak; (3) pulsed fields (10-μs pulses) at 13.7 W/cm^2 peak at the P-, QRS- and T-wave components of the electrocardiogram; and (4) CW fields at 80

mW/cm^2. Electrocardiograms were made before, during, and after irradiation. Heart rate was elevated in the rabbits exposed to CW waves at 80 mW/cm^2, but no changes in heart rate were detected at lower power densities. Also, no cumulative effects were observed over four months of repeated exposures.

Sparks *et al.* (1976) exposed rabbits to 2450-MHz fields at power densities of 20 to 30 mW/cm^2 for 4 h/d over 8 to 10 weeks. No differences from controls were noted in concentration of serum cholesterol or of cholesterol in the aortic wall, or in severity of experimentally induced atherosclerotic lesions.

The cardiovascular changes that occur in dogs and rats exposed to high power densities appear to be the result of hyperthermia. Exposure of dogs to 2450-MHz fields at 170 mW/cm^2 produced tachycardia (Lambert *et al.*, 1972). Whole-body exposure of rats to 2450-MHz fields at 80 mW/cm^2 has been shown to increase cardiac output, heart rate, and blood pressure, and to decrease peripheral resistance (Cooper *et al.*, 1961 abstract, 1962a, b, 1965; Pinakatt *et al.*, 1963). Vagotomy and administration of hexamethonium bromide (ganglionic blocker) reduced the circulatory response to RFEM-induced hyperthermia (Cooper *et al.*, 1962a). Administration of reserpine also reduced the cardiovascular response to hyperthermia (Cooper *et al.*, 1962b). Bilateral adrenalectomy completely abolished the circulatory response to irradiation (Cooper *et al.*, 1962a), demonstrating the importance of the endocrine system in its role as a compensatory mechanism in RFEM-induced hyperthermia. Ouabain (Pinakatt *et al.*, 1963) had no effect on blood pressure or heart rate of control animals, but abolished the cardiovascular response of irradiated animals. It is difficult to interpret the significance of such a response. Similarly, the response to pyridoxine and pyridoxal (Cooper *et al.*, 1965) is difficult to interpret. These two vitamins did not affect the heart rate or blood-pressure increases to microwave exposure, but did eliminate the increased stroke volume.

Phillips *et al.* (1973a, abstract, 1975a) examined the cardiovascular response of rats exposed to pulsed (120 pps) 2450-MHz fields for 30 min at *SAR*s of 4.5, 6.5 and 11.1 W/kg. Exposure at 4.5 W/kg (an energy-absorption rate equivalent to the resting metabolic rate of the rats used in the study) had no detectable effect on the electrocardiogram or on the heart rate of rats during a 5-h period after irradiation. In rats exposed at 6.5 W/kg, a mild bradycardia developed immediately after irradiation and persisted for about 2 hours. About 20 percent of the rats exhibited irregular rhythms for about 1 h after irradiation. In the group of rats exposed at 11.1 W/kg, a marked bradycardia was evident at the end of exposure. Recovery to the level of controls

occurred withn 2 h, at which time the exposed rats exhibited tachycardia for the remaining 3 h of the measurement session. All rats exposed at 11.1 W/kg exhibited irregular heart rates after irradiation. Incomplete heart block occurred in 70 percent of the animals within 7 to 30 min after exposure. Complete recovery from the heart block was evident within 1 h after exposure.

The bradycardia observed by Phillips *et al.* is consistent with results of several Soviet investigators (Kevork'yan, 1948; Sadchikova and Orlova, 1958; Tyagin, 1959). The irregular heart rhythm that occurred after exposure, apart from that attributable to incomplete heart block, was probably the result of field-induced heating of the central nervous system. Johnson and Guy (1972) demonstrated that energy absorbed from 2450-MHz fields is not uniform, and that high *SAR*s could occur in the brain of small animals such as the rat. It is likely that the distribution of energy absorption was such that some areas of the brain had marked elevations in temperature, and the observed physiological responses might have resulted from such localized absorption and thermalization of energy. The incomplete heart block among rats exposed at 11.1 W/kg was probably a consequence of excessive heating, and was caused either by the action of toxic metabolites (Heilbrunn *et al.*, 1946), of elevated serum potassium (Frankel, 1959), or of myocardial ischemia (Michaelson, 1967).

The cardiovascular response of rats to RFEM irradiation is modified somewhat by repeated, daily exposure. Exposure of rats to 2450-MHz fields at 11.1 W/kg for 30 min/d over 10 days resulted in a lower incidence of incomplete heart block, no irregular heart rhythm, and a prolonged duration of bradycardia (Phillips *et al.*, 1973b). The modified responses with repeated, daily exposures appears to be related to acclimation of the rats to repeated bouts of hyperthermia.

Numerous studies have been conducted by Soviet scientists on the effects of repeated and prolonged exposures to RFEM radiation on cardiovascular function. The results of these studies have been reviewed by Subbota (1970) and Gordon *et al.* (1974). According to Subbota, the cardiovascular responses to field-induced hyperthermia do not differ from responses to a hot environment or to infrared radiation.

Soviet investigators have noted that workers exposed to RFEM fields exhibit bradycardia, delayed atrial and ventricular conduction, decreased blood pressure and electrocardiographic changes (Gordon, 1976). These changes do not diminish work capacity and are reversible (Osipov, 1965). No serious cardiovascular disturbances have been observed in people as a result of exposure to low levels of RFEM radiation (Edelwejn, 1974).

9.2 Summary and Conclusions

The chronotropic effect of RFEM irradiation on isolated heart preparations appears to be a result of neurotransmitter release at the cut nerve endings and is not an effect on the myocardium or pacemaker cells *per se*. No effects were seen during irradiation of hearts *in situ*. Exposure of the whole body or segments of the body at levels that produce significant heating causes cardiovascular reactions akin to those arising from conventional body heating, albeit with differing distributions of energy. Based on available data, exposure to fields at low levels (<10 mW/cm^2 or <2 W/kg) for short periods of time does not appear to produce cardiovascular effects. Data on long-term exposure are scanty and contradictory.

10. Interactions with the Blood-Brain Barrier

10.1 Introduction

The blood-brain barrier (BBB) is an anatomically verified system involving specialized blood vessels that invest most areas of the brain. Although the anatomical makeup of the BBB and its subordinate system, the cerebrospinal-fluid (CSF) barrier, are well characterized, their functional role is far from fully understood (*cf.* Davson, 1967; Karnovsky, 1967; Oldendorf, 1975, 1977; Rapoport, 1976; and Rapoport *et al.*, 1979).

The discovery of the BBB has been attributed to Paul Ehrlich, who reported before the turn of the century that an intravenously administered dye extensively stained various organs but not the brain of a mammal; however, anatomists of antiquity doubtless observed a similar sparing in brains of the jaundiced cadaver (Oldendorf, 1975). Goldmann (1912) is credited with performing the first systematic studies that led to the concept of the blood-brain barrier, but his use of a vital dye as a tracer raised doubts about the barrier as a normal physiological process. Only after Wallace and Brodie (1939, 1940) compared distributions of small ions in plasma and brain, and after Bakay (1956) introduced radioisotopic assays of various ions, was there confirmation of the barrier's existence in the normal animal.

10.2 Current Concepts of Anatomy and Function

The current anatomical conception of the barrier is that of a highly differentiated organelle, a specialized capillary (Figure 10.1). The cells of these capillaries form *tight junctions* (Reese and Karnovsky, 1967; Oldendorf, 1975; Rapoport, 1976). In contrast to most capillaries that lie outside the brain and spinal cord, most capillaries within the cranial vault are generally lacking the intracellular fenestrae and intercellular clefts that would allow ready passage of small molecules from blood to

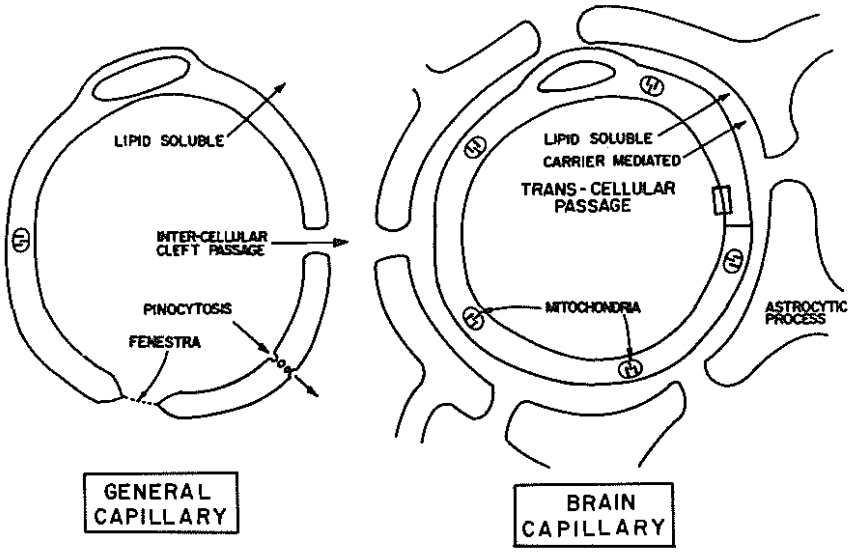


Fig. 10.1. Schematic showing the major structural differences between extracranial and brain capillaries. Intercellular clefts, fenestrae, and pinocytotic activity (i.e., formation of vesicles by which fluids are drawn into cells) are almost non-existent in brain capillaries. As a result, transcellular exchange of fluids must take place between capillary and brain-cell membranes, often by active transport. In most extracranial capillaries, transcellular exchange is subordinate to other routes. (From Oldendorf, 1977.)

the interstitial fluid (Table 10.1). The presence of tight junctions and the absence of fenestrae in most brain capillaries are not the only distinguishing morphological features; the pinocytotic vesicles that transport larger molecules across the capillaries of peripheral organs are much diminished in the brain (Karnovsky, 1967; Oldendorf, 1975, 1977). In addition, cells of brain capillaries possess more mitochondria—Oldendorf (1975) estimates five times the number found in cells of peripheral capillaries—which presumably correspond to the greater expenditures of metabolic energy required for active transport of metabolites from the vascular system to the brain's intercellular space.

Functionally, the blood-brain barrier is a selectively permeable, hydrophobic membrane (Oldendorf, 1975; Rapoport, 1976). Small, lipid-soluble molecules readily cross the membrane. Certain lipid-insoluble molecules such as glucose also readily cross the membrane via carrier proteins that have a high affinity with specific molecules. These carriers increase the intercellular flux of transported molecules well above the rate afforded by simple diffusion. In all, eight carrier

TABLE 10.1—*Nomenclature and characteristics of three major types of cell junctions*[a]

Junction type	Other name	Major function	Ultrastructural characteristics
Desmosome	Macula adherens	Cell adhesion	a. 15- to 35-nm-wide interspace between apposed plasma membranes b. Intercellular matrix contains proteinaceous material c. Cytoplasmic surface of membranes is condensed with tonofibrils d. Occurs as spots between cells
Gap junction	Nexus	Cell-to-cell communication	a. 2- to 4-nm-wide gap between apposed plasma membranes b. Hexagonally arrayed subunits contain channels for cell-to-cell exchange c. Occurs as spots and as discontinuous regions between cells
Tight junction	Zonula occludens	Restriction of intercellular diffusion	a. Width less than two plasma membranes on thin-section electron microscopy b. Fibrillar network links plasma membranes c. Surrounds cell as continuous belt

[a] After Oldendorf (1977).

systems have been demonstrated for the blood-brain barrier: for D-glucose and some other hexose sugars; for short-chain monocarboxylic acids; for several large, neutral amino acids; for some basic and for some acidic amino acids; for certain purines; for choline; and for certain nucleosides (Oldendorf, 1977). The carriers are stereospecific; while the ratio of L to D transport is variable, the L form is always preferred (Oldendorf, 1973).

Unless the barrier fails to function, polar molecules without specific carriers diffuse only slowly from the blood into the brain's intercellular compartment. This selective resistance to flow of molecules functionally defines the barrier. As for the rapid diffusional permeation of the barrier by non-polar, lipid-soluble molecules, one notes that these are rarely present in the blood of most mammals in the natural state. From an evolutional perspective, the phylogenetic drive to erect a barrier to lipid-insoluble molecules is largely absent. The legacy for the human being is a marked sensitivity to non-polar, psychoactive molecules that readily pass from bloodstream to brain: ethyl alcohol, heroin, amphetamine, nicotine, caffeine, and cannabis.

Although knowledge of the barrier's adaptive role is far from complete, there is a gathering consensus that it serves not only to restrict entry of toxic polar molecules into the brain but also as a regulatory system that stabilizes and optimizes the fluid environment of the brain's intercellular compartment (*cf.* Oldendorf, 1977, with Rapoport, 1976).

10.3 Pathophysiological Considerations

10.3.1 *General*

Bakay's early pronouncements (1956) that the integrity of the barrier is threatened only by severe insult, but that loss of integrity leads to certain death, are seemingly at odds with clinical and experimental observations. The barrier is not fully formed either in the fetus or in the neonate of the mammal (Davson, 1967; Adinolfi *et al.*, 1976). The placental barrier does provide some protection of the fetus, but the neonate nonetheless survives a period during which its blood-brain barrier is not fully functional. Clinical diagnostic maneuvers such as the intravenous infusion of urea-like compounds or of contrast materials that are used in radio-angiographic scans of the head result in a reversible breaching of the barrier without apparent adverse consequence. Moreover, a host of agents and treatments has been reported to increase transiently the permeability of the barrier: hypnotics and anesthetics such as barbiturates, chloral hydrate, halothane, and diethyl ether (Angel and Lafferty, 1969; Angel *et al.*, 1972); bilateral adrenalectomy and inhibitors of protein synthesis (Angel and Burkett, 1971); anti-depressant drugs (Angel and Roberts, 1966); electroconvulsive shock (Angel and Roberts, 1966; Lee and Olszewski, 1961; Hartman and Angel, 1964); food deprivation (Angel, 1969); swimming in a water maze (Angel and Burkett, 1971; Hartman and Angel, 1964; Angel, 1969); behavioral avoidance training involving a single, brief electrical shock to the feet (Angel *et al.*, 1972); sensory deprivation (Bondy and Purdy, 1974); cold stress (Sabbot and Costin, 1974); focal concussion of parietal cortex (Rinder and Olsson, 1968); and, finally, x irradiation (Nair and Roth, 1964; Miguel and Haymaker, 1965).

On the basis of the available data, one might be tempted to challenge Bakay's prediction of dire consequences of a failed barrier. However, two factors have constrained such a challenge. First has been the absence of a *quantitative* index of failure; indeed, until the late 1970s

(Bradbury, 1979), all widely used assays were either qualitative in nature or were potentially confounded by the possibility that an agent alters, not the barrier's permeability, but the brain's circulatory flux (cf. Rapoport, 1976; Rapoport *et al.*, 1979; Oscar *et al.*, 1981; Gruenau *et al.*, 1982). Second is the factor of duration. Simply put, one does not know how much of a breach or how long a breaching of the barrier must occur to produce irreversible injury and lethality. One can argue in principle only that complete functional loss of the tight junctions for some finite period would permit a rapid influx of normally excluded hydrophilic molecules into the intercellular compartment, which would result in cerebral edema, in increased intracranial pressure, and in irreversible damage to the brain.

10.3.2 *RFEM Fields and the Blood-Brain Barrier*

As revealed in the preceding paragraphs, the blood-brain barrier is reportedly altered by stresses that embrace physical, chemical, and psychophysiological categories of perturbation. That thermal stress would alter indices of barrier permeability is a likely argument that finds support in the work of Sutton and Carroll (1979). These investigators employed horseradish peroxidase as a tracer in studies in which heads of rats were exposed to an intense 2450-MHz CW field for various periods during which their brains were elevated to temperatures that peaked at values from 40 to 45 °C. Uptakes of peroxidase were strongly correlated with the product of time and intensity. At a temperature of 40 °C, irradiation for 60 minutes was required before a reliable uptake of the tracer was observed; at 45 °C, reliable increases were observed after 10 minutes of irradiation. Rats first rendered hypothermic (30 °C rectal temperature) not only exhibited longer latencies to increased uptake than did normothermic rats (Figure 10.2) but they exhibited a lower incidence of febrile lethality. Brain temperatures of 45 °C were frequently fatal for normothermic animals, but not for pre-cooled animals. Because of the influx of cooled blood from the lower body, it is highly likely that vital brain-stem centers in the pre-cooled animals were considerably cooler than the more superficial areas of the cerebrum in which temperatures were measured. This supposition agrees with the observation of increased latencies of peroxidase uptake in initially hypothermic animals.

Contrasting with the highly intense fields of Sutton and Carroll are the relatively weak fields employed by Frey *et al.* (1975), who investigated uptakes of Na-fluorescein in brains of rats after the animals

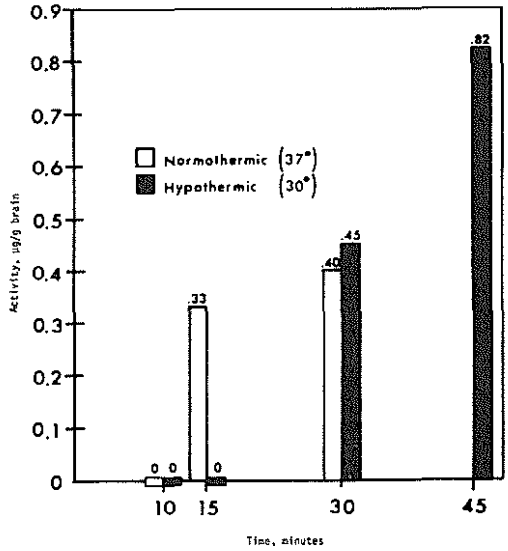


Fig. 10.2. Residual peroxidase activity, an index of blood-brain-barrier permeability, for rats the heads of which were selectively heated in a RFEM field. The temperature of the superficial neocortex was monitored via an indwelling thermistor sensor. The temperature at this site was elevated to, then maintained at, 42 °C in a 2450-MHz, CW field. Because irradiation took place in the near field, power densities were indeterminate, but the field was intense, i.e., elevations of cortical temperature to 42 °C required less than 5 minutes. Before irradiation, one set of rats was subjected to whole-body hypothermia (core temperature, 30 °C). Sixteen pre-cooled rats and as many normothermic counterparts (core temperature 37 °C) constituted two groups, each of which was subdivided into subgroups of four animals. Then the rats were irradiated for a period of 10, 15, 30, or 45 minutes. The hypothermia had a short-term inhibiting effect on brain uptakes of peroxidase. For example, after 15 min of irradiation, there was a marked increase of peroxidase tracer in brains of the non-cooled rats, but not in those of the previously cooled animals. The hypothermia also protected against lethality: none of 4 non-cooled rats survived 45 min of irradiation; all pre-cooled rats survived. Circulatory convection of cooler blood to the brain as a whole was cited by the authors as responsible for the protective effect of pre-irradiation hypothermia. (After Sutton and Carroll, 1979.)

were anesthetized and exposed for 30 min to 1200-MHz CW fields at a power density of 2.4 mW/cm^2, or to pulsed fields (0.5 ms pulse width, 1000 pps) at a peak power density of 2.1 mW/cm^2. Frey *et al.* observed brain slices from control and irradiated rats under UV light and reported that fluorescence was markedly greater in slices from exposed rats. Even though the averaged (rms) power density of the CW radiation was an order of magnitude higher than the rms value of the pulsed radiation, the latter was two to three times more effective in

promoting fluorescence (Table 10.2). These findings are consistent with behavioral data reported by Frey and Feld (1975), who found during four exposures of rats to sham or RFEM radiation, under the same field conditions as those of the fluorescein study, that pulsing was associated with a tendency of the animals to escape from the field; in contrast, the CW field did not promote a tendency to escape.

The apparent linkage of radiation-induced changes of brain and behavior could be taken as evidence that pulsed fields at low rms

TABLE 10.2—*Effect of RFEM radiation on entry of fluorescein tracer into brains of rats*[a,b]

Head positions[c]	Intensity of fluorescence[d] (mean)		
	Pulsed (A)	CW (B)	Sham (C)[e]
I	1.5	0.8	0.2
II	1.8	0.7	0
III	2.0	1.0	0.2
IV	2.2	0.7	0
V	0.2	0	0
A vs B vs C: $p < 0.001$[f]			A vs B: $p < 0.001$[f]
A vs C: $p < 0.001$			A (I, II, III, IV) vs (V): $p < 0.001$
B vs C: $p < 0.005$			B (I, II, III, IV) vs (V): $p < 0.005$
Head positions	Number of sections that fluoresced (median)		
	Pulsed (D)	CW (E)	Sham (F)
I	2.5	0.5	0
II	9.5	1.5	0
III	7.5	3.5	0
IV	1.5	0.5	0
V	0	0	0
D vs E vs F: $p < 0.001$[f]			D vs E: $p < 0.005$[f]
D vs F: $p < 0.001$			D (I, II, III, IV) vs (V): $p < 0.001$
E vs F: $p < 0.005$			E (I, II, III, IV) vs (V): $p < 0.005$

[a] From Frey *et al.*, 1975.

[b] Animals exposed at an average power density of 2 mW/cm^2 for CW and 0.2 mW/cm^2 for pulsed 1200-MHz fields.

[c] Orientation of direction of propagation of field with respect to head of animal: I, perpendicular to ventral surface of head; II, perpendicular to top of head; III, perpendicular to left side of head; IV, perpendicular to right side of head; V, perpendicular to left side of head with head tucked down toward front legs.

[d] Fluorescence determined by human observers visually under ultraviolet light using arbitrary 10-point scale.

[e] Although the median number of sections that fluoresced was zero, some sections did fluoresce slightly. This is reflected by the non-zero means in column C.

[f] p values determined by Kruskal-Wallis analysis of variance.

power densities might have potentially non-trivial consequences. It could also be argued that fluorescence of the irradiated brain is less remarkable than absence of fluorescence in control brains. Zero levels of fluorescence were reported by Frey *et al.* in all brain slices of most of their sham-irradiated rats, which is difficult to explain, because tight junctions are missing in several regions of the brain, e.g., the walls of the cerebral ventricles and aquaducts, the pineal and posterior pituitary bodies, the *area postrema*, the preoptic area of the hypothalamus, the *tuber cinereum*, and the olfactory tubercles (Oldendorf, 1975; Rapoport, 1976; Albert and De Santis, 1975). Questioned about the near absence of fluorescence in control brains, Frey (1977) indicated that only differential uptakes were observed, i.e., normally fluorescing areas of the brain were not included in visual analysis of irradiated and control sections. As for the tendency of the rats of Frey and Feld (1975) to escape from the pulsed field, the well-confirmed stimulation of auditory receptors by RFEM pulses (see Section 12) may have produced sounds that annoyed the animals, much as tinnitus is annoying to the human being.

Oscar and Hawkins (1977) exposed rats to pulsed or CW, 1300-MHz radiations for 20 minutes. In initial pilot studies in their laboratories, assays based on UV activation of Na-fluorescein were used, but excessive fluorescence in brain materials from control animals led the authors to use a different assay, the dual-indicator technique of Oldendorf (1970, 1975). Brain uptakes of radiolabeled polar isotopes of differing molecular weight were compared with uptakes of tritiated water, which served as a standard. In one set of experiments on anesthetized rats, uptake of ^{14}C-labeled D-mannitol by the hypothalamus, by the hippocampus, and by the neocortex was slightly but significantly greater in irradiated brains than in those of sham-irradiated animals, larger relative uptakes were found in the cerebellum, and larger still, in the medulla (Figure 10.3). Paradoxically, 10-μs pulses at 50 pps, which yielded an average power density of 0.3 mW/cm^2, were consistently more effective in increasing uptakes than were 10-μs pulses at 1000 pps, which yielded an average power density of 2 mW/cm^2.

In a second study of anesthetized rats, Oscar and Hawkins (1977) observed uptakes of ^{14}C-labeled-mannitol, -inulin, or -dextran after 20 min of sham irradiation or after a 20-min exposure to 0.5-μs pulses at 1000 pps (peak power density, ~600 mW/cm^2; averaged power density, ~0.3 mW/cm^2). Essentially the same regional pattern of increased uptakes of mannitol and inulin was observed as in the first study, but little differential uptake of dextran was noted (Figure 10.4). Mannitol

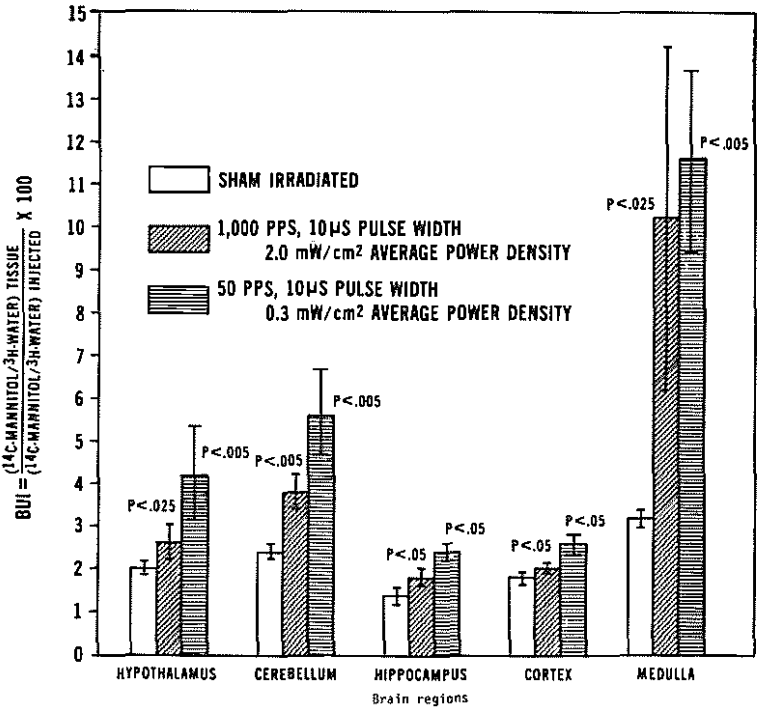


Fig. 10.3. Brain uptakes of ^{14}C-labeled mannitol in sham- and RFEM-irradiated rats as expressed by the Brain Uptake Index (BUI), which reflects the ratio of the quantity of tracer in the brain's intercellular space to that in the vascular space. A total of 15 rats underwent sham irradiation (n = 5), irradiation in a pulse (50 pps, 10-μs pulse width) 1300-MHz field at an average power density of 0.3 mW/cm^2 (n = 5), irradiation in the same field at 1000 pps (10-μs pulse width) at an average power density of 2 mW/cm^2 (n = 5), all treatments of 20 min duration. Each rat yielded BUI data (means and standard deviations) on five brain regions, as shown. The largest BUIs were observed for the medulla; note, too, that standard deviations also increased in association with irradiation. (After Oscar and Hawkins, 1977.)

and inulin have relatively small hydrodynamic diameters when compared with that of dextran. From the standpoint of passive transfer of a molecule across the barrier, hydrodynamic diameter inversely determines rate of permeation.

A third study by the same authors under the same field conditions was performed on rats that were not anesthetized until exposures to pulsed, CW, or sham radiation were completed. A period of 8 min, 4 h, or 24 h intervened between termination of irradiation and time of anesthetization. Then the animals were injected with a labeled compound and decapitated. Uptakes of mannitol in the hypothalamus,

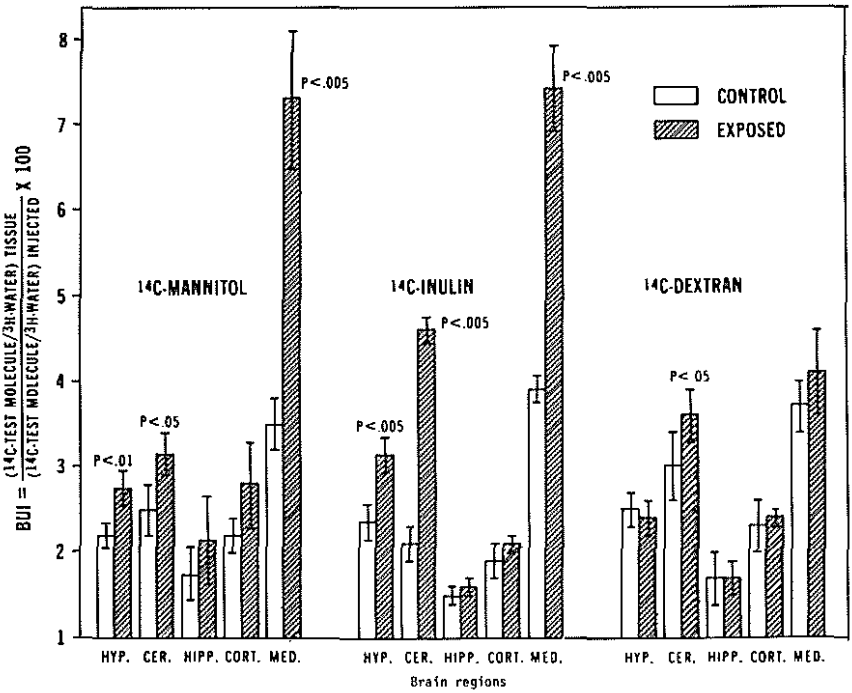


Fig. 10.4. Brain uptake index (BUI) for ^{14}C-labeled-mannitol, -inulin, and -dextran tracers as assayed in 5 regions of the rat's brain. In each tracer condition, 5 control rats were sham irradiated, and 5 rats were exposed for 20 min to a pulsed 1300-MHz field (1000 pps, 0.5-μs pulse width, average power density 0.3 mW/cm^2). The largest increases (means and standard deviations) of the BUI were associated with mannitol and inulin in the medulla (see Figure 10.3). Dextran has the largest hydrodynamic diameter of the three tracers, and would encounter the greatest resistance in entering the intercellular space. (After Oscar and Hawkins, 1977.)

cerebellum, and medulla were significantly elevated by 50 to 100 percent or more in brains from irradiated animals of the 8-min and 4-h groups, but only the medulla exhibited a significant increase (20 percent) in brains from animals of the 24-h group (Figure 10.5).

In a final study, Oscar and Hawkins determined uptakes of mannitol in the medulla as a function of pulsed and CW waves. Curvilinear functions were observed under both modes of irradiation. Peak uptakes in the brain after CW irradiation occurred at power densities near 1 mW/cm^2; the Brain Uptake Index (BUI), which reflects the ratio of labeled tracer to labeled standard, exhibited a maximal 9-fold increase. Peak uptakes under pulsed irradiation (0.5 μs pulse width, 1000 pps) occurred near 0.5 mW/cm^2 (rms) and were associated with a 7.5-fold

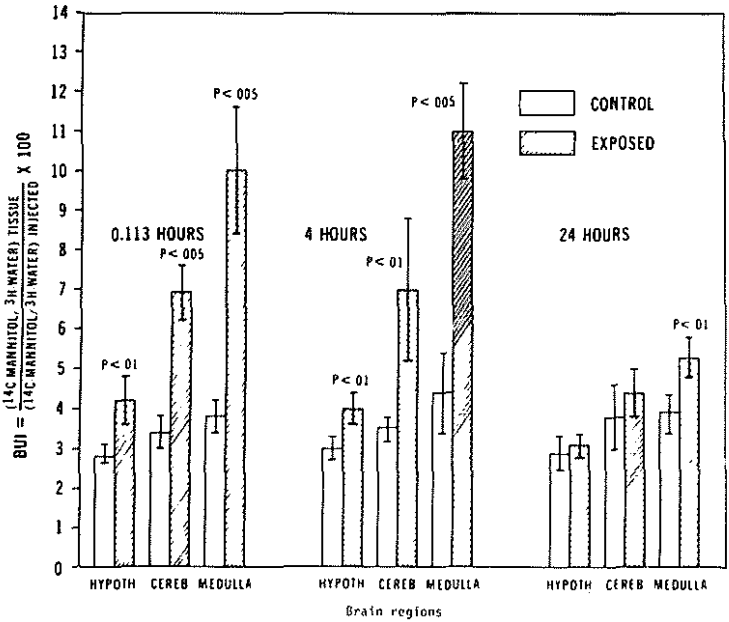


Fig. 10.5. Brain-uptake index for ^{14}C-labeled-mannitol tracer for three brain regions (hypothalamus, cerebellum, and medulla) of sham-irradiated rats and rats exposed to a pulsed 1300-MHz field (1000 pps, 0.5-μs pulse width, average power density 0.3 mW/cm^2) for 20 minutes. Five controls and 5 rats in each of 3 groups were assayed respectively for BUIs at 8, 240, and 1440 min after exposure. The data (means and standard deviations) indicate that the radiation-induced increase of blood-brain-barrier permeability is reversible, although one region of the brain, the medulla, still exhibited a small but statistically significant increase in the BUI 24 h after exposure. (After Oscar and Hawkins, 1977.)

enhancement of the BUI. The greatest sensitivity observed by Oscar and Hawkins was associated with a 7-fold enhancement of medullary BUI in brains of rats that had been exposed for 20 min to 10-μs pulses that recurred at the very low rate of 5 pulses per second. The corresponding averaged power density was only 30 μW/cm^2 (Figure 10.6).

Ultrastructural studies of the barrier have been reported for RFEM-irradiated rats and hamsters after longer exposures at relatively high power densities (Albert and De Santis, 1975; Albert, 1977, 1979; Albert and Kerns, 1981). In one study (Albert, 1977), awake Chinese hamsters were sham exposed or exposed for 2 to 8 h in the far field to 2450-MHz CW radiation at an averaged power density of 10 mW/cm^2; they were then anesthetized and infused intravascularly with peroxidase tracer 5 min before decapitation. The brains were then prepared for examination under light- and electron-microscopy.

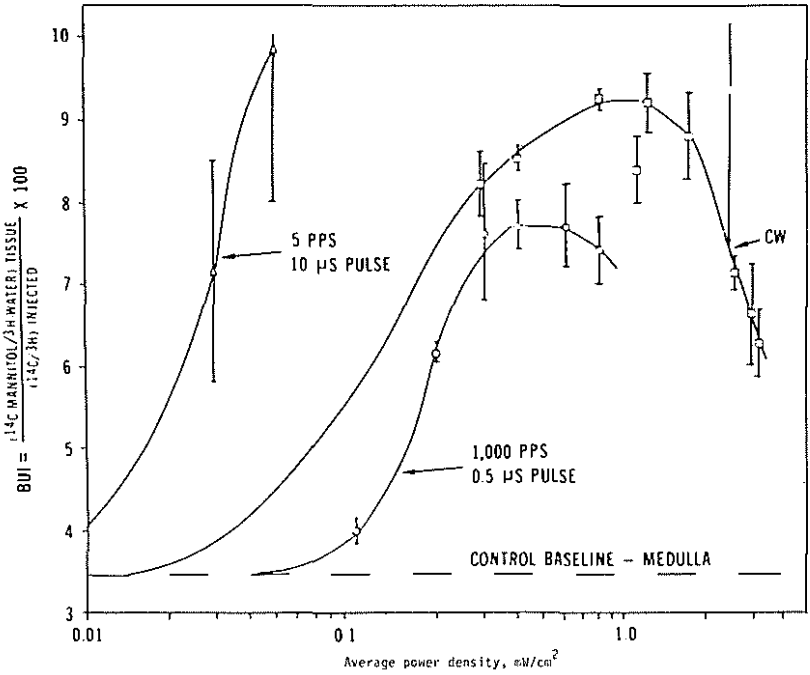


Fig. 10.6. Brain-uptake index as a function of power density of incident radiation for rats exposed for 20 min to a CW 1300-MHz field or a pulsed 1300-MHz field (5 or 1000 pps, 10-μs and 0.5-μs pulse widths, respectively). The control baseline reflects the medullary BUI of sham-irradiated rats. The sample size of each data point ranges from 3 to 13. The data (means and standard deviations) indicate that pulsed irradiation had a stronger influence on the BUI than did a CW field, that pulse-repetition rate was a strongly controlling factor, and that a curvilinear ("windowed") relation may exist between intensity of irradiation and the blood-brain-barrier's permeability. These conclusions are tempered by the authors' qualification that altered flow of cerebral blood, not the barrier as such, may have been the affected end point (see text). (After Oscar and Hawkins, 1977.)

Some evidence of limited, highly focal infiltration of the tracer into the neuropil was observed in irradiated animals, but examination of tight junctions revealed that their integrity had not been compromised. Albert concluded that vesicular transport of the tracer was a more probable route of RFEM-induced infiltration than was a structural failure of the barrier.

In a second study, Albert (1979) exposed anesthetized hamsters and rats in the near zone of a CW 2800-MHz field for 2 h at a nominal power density of 10 mW/cm^2. Some of the animals and their sham-irradiated controls were infused with a peroxidase tracer and then

were euthanatized shortly after termination of irradiation; preparation of other animals for histological analysis was delayed by 1 or 2 hours. Once again, Albert observed evidence of vesicular transport of tracer into the neuropil. Compared with the minimal-delay group, focal signs of infiltration were much less evident in animals of the 1-h delay group and were virtually absent in animals of the 2-h delay group (Fig. 10.7).

10.3.3 *RFEM Fields and the CSF Barrier*

Although functionally a part of the blood-brain barrier, the cerebrospinal-fluid (CSF) barrier is identified anatomically with the choroid plexus of the lateral, third and fourth ventricles (Figure 10.8). The plexus is formed of specialized epithelial cells and is the primary source of the CSF, which is drawn from plasma constituents of the bloodstream and flows from the ventricles into the subarachnoid space,

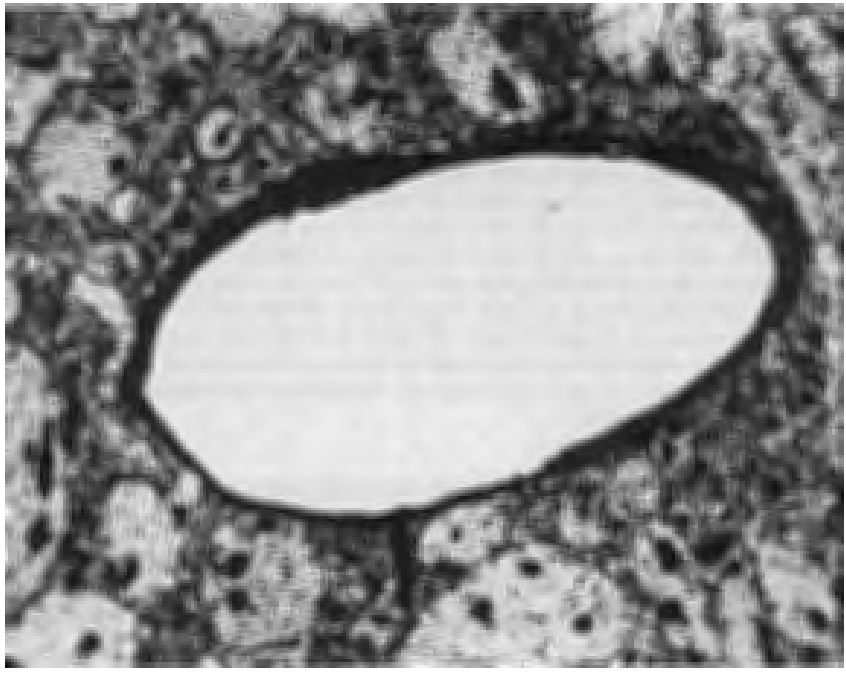


Fig. 10.7. Photomicrograph of a brain-capillary cross section from the hippocampus of a RFEM-irradiated rat. The capillary presents morphological evidence that the tracer substance (horseradish peroxidase), which heavily invested the interior capillary wall (dark stain), did not enter the intercellular space. (From Albert, 1977.)

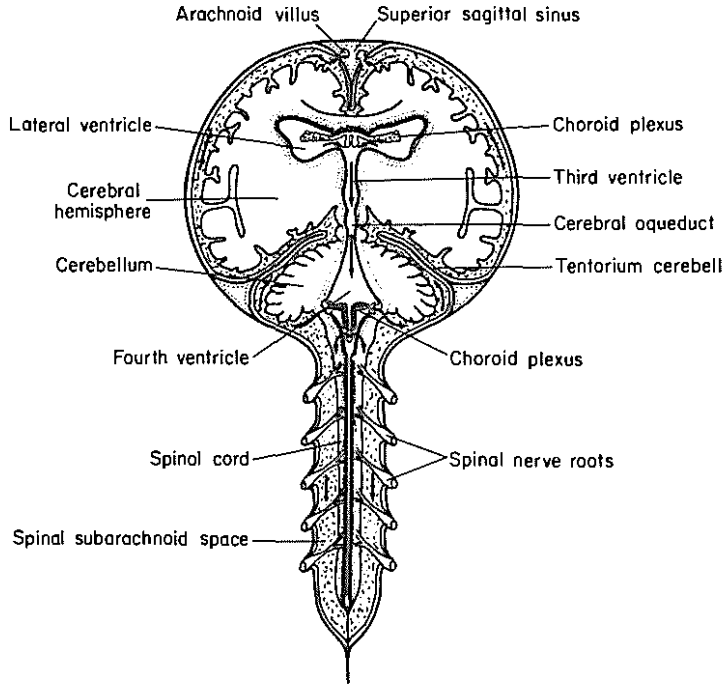


Fig. 10.8. Pictorial representation of the origin (choroid plexus of the lateral third and fourth ventricles) of mammalian cerebrospinal fluid and its routes of flow in the subarachnoid spaces. (From Rapoport, 1976.)

then into the spinal canal. The tight junctions of the plexal epithelia restrict transfer of lipid-insoluble molecules from the bloodstream into the CSF, but their failure would result in invasion of the intraventricular space of normally excluded molecules.

To ascertain whether hyperthermia from 918-MHz irradiation would result in passage of IgM antibody into the CSF, Hodges *et al.* (1979, abstract) first drew blood samples from and then immunized 18 rats with Type-III pneumococcal polysaccharide vaccine. Seven days later, each of 9 animals was subjected to a 30-min period of irradiation in a multi-mode cavity at a variable *SAR* (20 to 70 W/kg) that was adjusted to maintain colonic temperature at 42.5 °C. The animals were anesthetized during sham or RFEM irradiation (Na-pentobarbital, 40 mg/kg, i.p.). Immediately after irradiation, 6 experimental animals and 6 controls were randomly sampled and then euthanatized to permit collection of CSF and blood. Levels of circulating IgM antibody (specific to the antigen) were zero before immunization but had reached high levels 7 d later in all 12 rats. In contrast,

antibody was absent in the CSF of the same 12 animals on the 7th day post immunization. The remainder of control (n = 3) and experimental animals (n = 3) yielded CSF and blood 14 d after immunization. Circulating antibody was still present, although at lower titers than that observed on the 7th day (Figure 10.9), and, once again, the antibody was absent in the CSF of control and irradiated rats.

IgM is a large molecule (m.w. 900,000, hydrodynamic diameter ~10 nm) and might encounter difficulty in traversing even a loosened junction. A more sensitive test of the hyperthermal response of the CSF barrier to immune globulins would be afforded by assays of IgC and IgA, which are relatively small molecules and which are normally found in small quantities (0.2 to 0.4 percent relative to those in plasma) in the CSF (Rapoport, 1976).

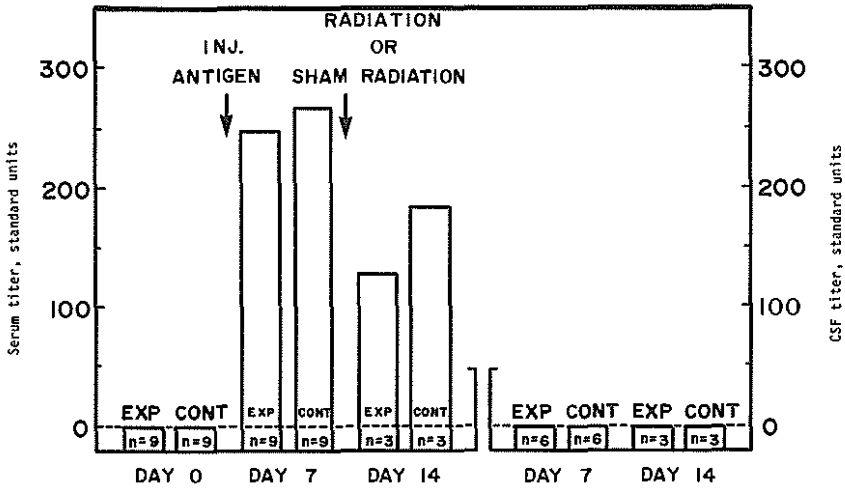


Fig. 10.9. Serum and cerebrospinal-fluid titers (geometric means in standard units) of IgM antibody for 18 rats, 9 of which served as sham-irradiated controls and 9 of which were irradiated in a 2450-MHz field in a multimode cavity for a period of 30 min 7 d after immunization by pneumococcal antigen. The *SARs* ranged variably downward from 70 to 20 W/kg as colonic temperature was quickly elevated to and maintained at 42.5 °C. Blood was taken from a random sample of 3 control and 3 irradiated rats on the 14th day post-immunization; assays for IgM antibody, which is specific to the antigen, revealed that circulating antibody was present but lower in titer than that measured 7 d after immunization. Cerebrospinal fluid (CSF) from 12 of the rats on the 7th day and from the remaining 6 on the 14th day post-immunization yielded no evidence of IgM antibody in control or irradiated rats. Although the IgM antibody has the largest hydrodynamic diameter of the immunoglobulins, it is notable that a near-lethal elevation of body temperature was not associated with entry of antibody into the CSF. (After Hodges *et al.*, 1979.)

10.4 Attempted Replications and Extensions of Previous Studies

Merritt *et al.* (1978) attempted to repeat the irradiation and fluorescein-uptake procedures of Frey *et al.* (1975), but reported no differential fluorescence between brain slices of irradiated and control rats under UV light. The authors also performed another study in which they employed a quantitative assay of fluorescein uptake—in rats anesthetized as in the UV study—which revealed several findings of interest (Table 10.3, Figure 10.10). First, mean uptakes of tracer were slightly (19%) but invariably *higher* in sham-irradiated rats than in rats irradiated at an averaged power density of 1 mW/cm^2. Second, not only did means of uptakes correlate highly and positively with averaged power densities of irradiation that ranged from 1 to 37.5 mW/cm^2, but variances—scatter of individual uptake scores—also increased as a function of power density. Third, brain and rectal temperatures above those of sham-irradiated controls were observed in irradiated rats at averaged power densities as low as 1 mW/cm^2 and were also highly correlated with power density. And finally, animals of a control group were subjected to infrared radiation in a hot box. After elevation of core temperature to 43 °C for 30 min the rats exhibited peaks of brain temperature that paralleled those of rats exposed at 37.5 mW/cm^2 for the same period of time. Compared with the sham-irradiated controls, the mean percentages of differential (larger) uptakes of fluorescein in brains of irradiated rats were modest, even at 37.5 mW/cm^2 (~29 percent), and were less than that of hot-box controls (~48 percent). Further, BUIs of controls were lower by at least an order of magnitude than those of active-control animals that had received an intravascular infusion of urea, which demonstrably loosens tight junctions (Rapoport, 1976).

Although the irradiation-associated increases in measures of blood-brain-barrier permeability are readily discerned in the quantitative data of Merritt *et al.* (1978), the authors reported that none of the increases met a two-tailed probability of 0.01 in tests for statistical reliability. Later, after recognizing that reliance on multiple *t* tests to evaluate pairs of (control and experimental) means resulted in an insensitive assay of field-induced changes of BUIs, Merritt re-evaluated his uptake data for each region of the brain by analysis of variance. As noted by Justesen and Baird (1979) and Justesen (1980), following personal communications with Merritt, these analyses revealed that increased permeation of the barrier by tracer was significantly increased in several regions of the brain as the intensity of irradiation increased from 1 to 37.5 mW/cm^2.

TABLE 10.3—*Effects of RFEM radiation on fluorescein concentration in brains of rats*[a]

Exposure conditions[b]	Fluorescein concentrations in brain tissue						
	Hypothalamus	Striatum	Midbrain	Hippocampus	Cerebellum	Medulla	Cortex
	ng/g	ng/g	ng/g	ng/g	ng/g	ng/g	ng/g
Sham	260 ± 111 (20)[c]	194 ± 103 (20)	239 ± 82 (20)	198 ± 72 (20)	299 ± 100 (20)	301 ± 82 (20)	221 ± 86 (20)
2 mW/cm^2	255 ± 86 (11)	142 ± 62 (12)	197 ± 37 (11)	167 ± 50 (12)	261 ± 88 (12)	257 ± 61 (12)	181 ± 35 (12)
15 mW/cm^2	298 ± 66 (6)	166 ± 46 (6)	251 ± 68 (6)	157 ± 39 (6)	307 ± 36 (6)	315 ± 67 (6)	227 ± 30 (6)
25 mW/cm^2	406 ± 162 (6)	185 ± 73 (6)	238 ± 86 (6)	202 ± 99 (6)	346 ± 142 (6)	294 ± 115 (6)	228 ± 88 (6)
75 mW/cm^2	421 ± 233 (9)	235 ± 72 (9)	264 ± 102 (9)	246 ± 78 (9)	379 ± 115 (9)	375 ± 136 (9)	294 ± 102 (9)
Heated (in a hot box)	490 ± 164[d] (6)	252 ± 93 (6)	310 ± 75 (6)	291 ± 118 (6)	441 ± 94[d] (6)	457 ± 99[d] (6)	321 ± 113 (6)

[a] After Merritt *et al.*, 1978.

[b] Animals were exposed for 30 min to pulsed 1.2 GHz radiation (1000 pps, 0.5 ms pulse width) at the power densities indicated. Duty cycle was 50 percent; hence, time-averaged power density is half the values indicated.

[c] Numbers in parenthesis are the number of animals.

[d] Difference between heated and sham: $p < 0.01$ by Student's t test.

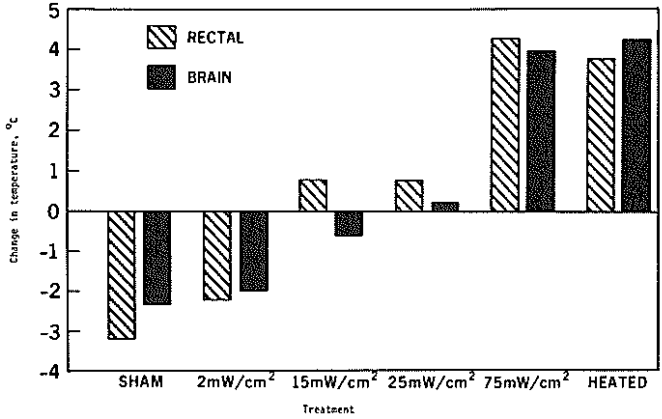


Fig. 10.10. Brain and rectal temperatures (differences of means between post- and pre-treatment) for pentobarbital-anesthetized rats as a function of sham-irradiation, conventional heating, and 20 min of a pulsed 1300-MHz field (1000 pps, 10-μs pulse width, power densities ranging from 2 to 75 mW/cm^2). Because a 50-percent duty cycle was used during irradiation, the average power densities of the RFEM field were half those shown in the figure. Note the hypothermal response to anesthesia, and the evidence that a weak 1300-MHz field (i.e., at an average power density of 1 mW/cm^2) can evoke a small elevation of temperature in the anesthetized rat. (After Merritt *et al.*, 1978.)

To date, the authors have not published quantitative details of the reanalysis, but their finding of significant differences resolved an anomalous conclusion in the published report: That conventional heating of active-control rats resulted in significant elevations of tracer in the brain's intercellular space, while comparable heating by microwaves did not.

Merritt *et al.* also attempted to confirm the findings of Oscar and Hawkins (1977), as did Preston (1982), Preston and Prefontaine (1980), Preston *et al.* (1979), and Oscar and Gruenau (1978; *cf.* Oscar *et al.*, 1981). None of these attempts was successful, but all were based on irradiation parameters, experimental procedures, and/or strains of rats that differed from those of Oscar and Hawkins. There is evidence, moreover, in many of the failed attempts to confirm, that anesthetization of the animals may have masked an irradiation-associated increase of barrier permeability by induction of pentobarbital hypothermia. In the study of Merritt *et al.*, for example, BUIs in some regions of the brain were considerably higher for sham-irradiated controls than those for rats exposed at low power densities (Figure 10.11). Similarly, BUIs of the medulla in the study by Preston *et al.* exhibited an inverted-U-shaped function as power density of 2450-

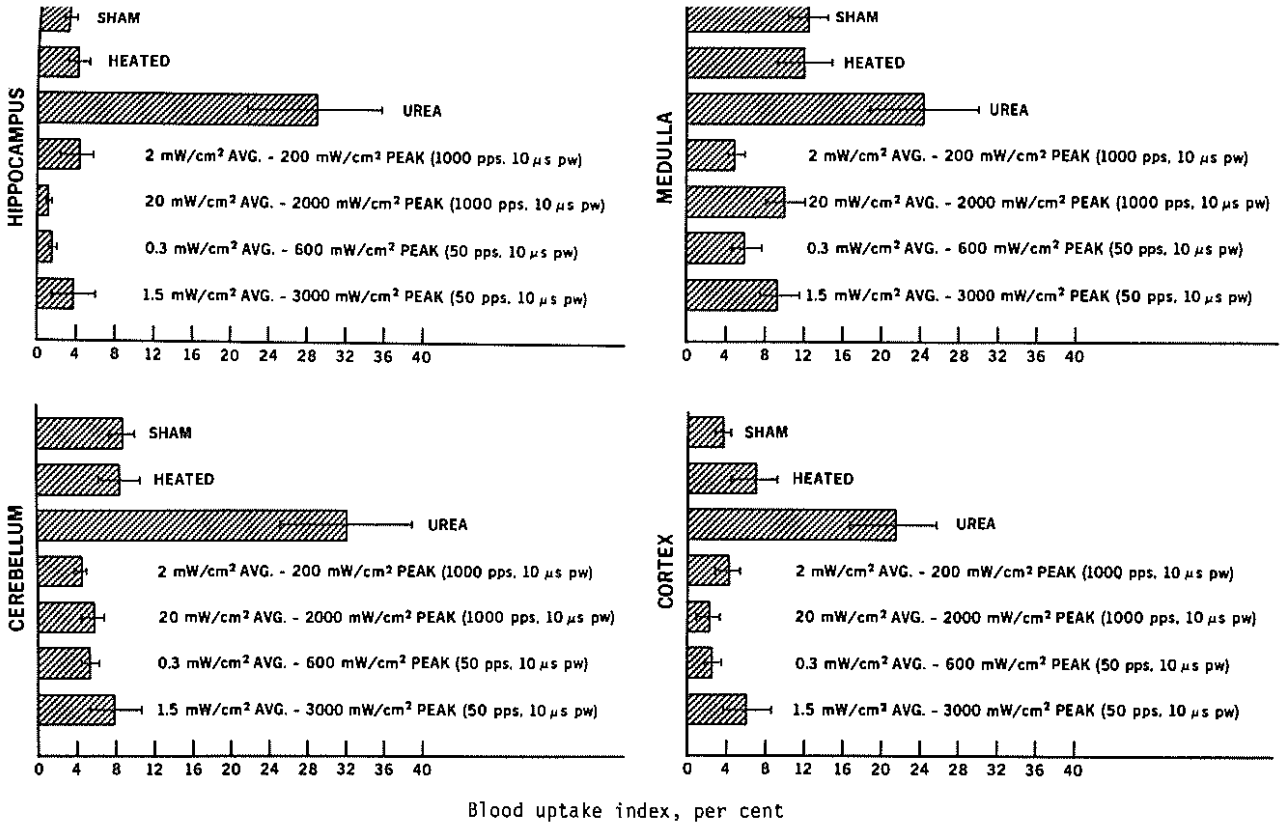


Fig. 10.11. Brain-uptake index (BUI) for four regions in the brains of rats after sham irradiation, heating in a hot box, or irradiation in a pulsed 1300-MHz field at the indicated average power densities. An active control treatment, infusion of urea, which demonstrably breaches the blood-brain barrier, was also used. Although there is little evidence that the irradiation produced a rise in BUIs relative to those of sham-irradiated rats, comparisons within conditions (e.g., the medullary BUIs) may be indicative of intensity-dependent increases. The data (means) in this figure should be compared with those presented in Table 10.3, in which a greater range of power densities is ostensibly associated with monotonic increases of the BUI in some regions of the brain, especially in the medulla. (After Merritt *et al.*, 1978.)

MHz CW fields increased from 0.3 to 30 mW/cm^2. Preston *et al.* reported that irradiation at 10 mW/cm^2 noticeably mitigated the fall in body temperature normally engendered by the barbiturate anesthesia.

The findings of Gruenau *et al.* (1982) were reported by Oscar and Gruenau (1978) at a special workshop on the blood-brain barrier, which was sponsored by the Department of the Navy and convened in Annapolis, Maryland on October 30 and 31, 1978 (see Benedick, 1979). The authors indicated that their inability to confirm the findings of Oscar and Hawkins (1977) was based on exposures of a different strain of rat to radiation at a higher carrier frequency (2.8 GHz); in addition, the dual-compartment technique of Rapoport *et al.* (1979) was used instead of Oldendorf's dual-indicator technique to assess changes of barrier permeability. The authors noted also that the dual-compartment technique controls for and permits assessment of changes in rate of flow of cerebral blood—which must remain constant or otherwise it will contaminate the BUI when the Oldendorf technique is used. They obtained evidence that 2.8-GHz fields at power densities between 1 and 15 mW/cm^2 do influence cerebral circulation.

Other papers based on RFEM irradiation were presented at the workshop in Annapolis (see Benedick, 1979), but most were based on studies that have already been reviewed here. Exceptions are a paper presented by Frey (1.2-GHz fields at unspecified parameters resulted in altered uptake of fluorescein in the vitreous humor of the rat's eye), a paper presented by Merritt (unpublished studies by him and Chamness revealed that brain uptakes in rats of L-phenylalanine, a water-soluble essential amino acid, were not influenced by pulsed 1260-MHz fields at averaged power densities that ranged from 0.1 to 10 mW/cm^2), and a paper by Barbara Chang. Chang subsequently published this work, which was performed in collaboration with Huang, Joines, and Kramer at Duke University (see Chang *et al.*, 1982).

The head of each of 21 mongrel dogs was irradiated for 20 min in the near field by 1000-MHz CW fields at nominal power densities of 2, 4, 10, 30, 50, or 200 mW/cm^2. Eleven dogs served as sham-irradiated controls. The animals were anesthetized with pentobarbital and were artificially ventilated during a 5-h, post-irradiation period after a bolus of radiolabeled albumin had been introduced intravascularly. Cerebrospinal fluid from the *cisterna magna* was aspirated every 20 min and assayed against venous blood for presence of the albumin.

With the exception of 4 of 11 dogs irradiated at 30 mW/cm^2, none of the irradiated dogs exhibited increases over controls in levels of albumin in the cerebrospinal fluid. Four of the dogs that were irradi-

ated at 30 mW/cm^2 exhibited 2- to 5-fold increases of cisternal albumin above the control mean. Although the small sample sizes (groups of n = 2) of animals observed at other power densities limit a strong conclusion, as does the absence of thermometric or dosimetric data, the possibility of marked individual differences in the barrier's response to RFEM irradiation, which was evident in the quantitative studies of fluorescein uptake by Merritt *et al.*, is raised anew. The absence of increased uptake at a power density of 200 mW/cm^2 may seem anomalous except for the restriction of the radiation to the dogs' heads; the whole-body-averaged *SAR* would have been considerably greater if the animals had been uniformly exposed at 200 mW/cm^2 to a plane wave in the far field.

Data from a potentially highly significant study were also presented at the Navy-sponsored special workshop (Spackman, Riley, Guy, and Chou, unpublished). In addition to Na-fluorescein, the authors employed several small amino acids as tracers, which were of species both permeant and non-permeant to the murine brain. Animals were exposed for 30-min to pulsed or CW 918-MHz fields that resulted in a range of low (0.52 W/kg) to highly thermalizing (27.7 W/kg) *SARs*. Other animals were sham irradiated or were subjected to severe hyperthermia in a hot box. No significant evidence of augmented uptakes of any tracer substance was found, even after treatments that resulted in marked hyperthermia. A limitation of the experiments based on intense fields and hot-box hyperthermia is the small number of animals per treatment condition—generally two and sometimes only one subject yielded data.

The invariably negative findings are of interest in view of the highly sensitive quantitative assays used by Spackman *et al.* (fluorimetric and amino-acid analyses) and of three major departures from protocols of most previous experiments based on murine subjects: (1) mice of a pigmented (as opposed to rats of an albinic) strain were used; (2) tracer substances were introduced intraperitoneally and not via an intravascular route; and (3) anesthesia was never used during irradiation of the animals. From these departures, four questions arise that have a bearing on the robustness of the cerebrovascular response to weak and intense fields: (1) Is the rat an anomalous reactor? (2) Is albinism associated with increased susceptibility to alteration of the BBB? (3) Does intravascular introduction of a tracer produce an artifactual reaction? (or contrarily, does intraperitoneal administration result in overdilution of the tracer?); and finally, (4) Does the anesthetic agent trigger susceptibility to or otherwise complex with irradiation?

10.5 Discussion

Although the reports of blood-brain-barrier changes by relatively weak fields (Frey *et al.*, 1975; Oscar and Hawkins, 1977; Merritt *et al.*, 1978) are provocative, the findings are limited in generality as evidenced by a preponderance of negative findings. Granted that even the most studious attempt to repeat a study involves some differences in environmental and procedural variables, one must accept the verdict that the alterations of the barrier reported by Frey *et al.*, Oscar and Hawkins, and Merritt *et al.* are not robust even while one scrutinizes the positive and negative studies for clues to the discrepant findings. It is likely that several factors, alone or in combination, are responsible for the discrepancies. An obvious candidate has been the near-ubiquitous practice of inducing barbiturate anesthesia before irradiating animals. Anesthesia can beget hypothermia, and both have been implicated as agents that affect measures of brain-barrier permeability (Angel and Lafferty, 1969; Angel *et al.*, 1972; Sabbot and Costin, 1974). Moreover, hypothermia resulting from electroconvulsive shock (Oke *et al.*, 1974) is associated with increased permeability of the barrier (Lee and Olszewski, 1961). If hypothermia resulting from heavy doses of barbiturates does increase permeability of the barrier (or artifactually confounds measures of permeability by altering cerebral blood flow), then values of brain uptakes of tracers in anesthetized controls are spuriously high. Similarly, because gross heating by RFEM radiation can mitigate hypothermia (*cf.* Merritt *et al.*, 1978, with Preston *et al.*, 1978), the differences between reported brain uptakes in anesthetized, sham-irradiated controls and irradiated animals might be spuriously narrow.

Another candidate to explain the discrepancy between positive and negative findings is resonant absorption. The positive findings of Frey *et al.*, Oscar and Hawkins, and Merritt *et al.* are based on exposures of rats to fields (1200 and 1300 MHz) that can promote rates of energy absorption well above those associated with fields of much higher or lower frequencies (Gandhi *et al.*, 1977; Durney *et al.*, 1978). The thermal measurements reported by Merritt *et al.* for rats exposed at 1200 MHz and by Preston *et al.* for rats exposed at 2450 MHz are instructive because the former authors reported measureable elevations of body temperature at 1 mW/cm^2, while the latter authors only at 10 mW/cm^2 or higher. It is unfortunate that dosimetric measurements, which are needed quantitatively to confirm the occurrence of resonant absorption, were not reported by these authors and, indeed, were not reported in any archival study of the barrier's response to

irradiation before more recent studies were reported by Lin and Lin (1980, 1982).

Lin and Lin coupled pulsed (10 μs pulse width, 500 pps) 2450-MHz fields to the brains of rats via an attached, direct-contact applicator. Focal *SAR*s in one cerebral hemisphere ranged from 0.04 to 240 W/kg during 20- to 30-min exposures. Uptake of Evans-Blue dye by brain materials was not observed at *SAR*s of 0.04 to 200 W/kg, but was observed unilaterally in neocortex, hippocampus, and brainstem at an *SAR* of 240 W/kg. Brain temperatures, at sites where the BBB failed, exceeded 43 °C as measured by an indwelling, field-non-perturbing probe. Because the volumes of the brain irradiated by the fields were not specified and because averaged *SAR*s in the brain were not reported, neither the whole-brain, whole-head, nor whole-body averaged *SAR*s can be determined from the authors' reports. This hiatus of information notwithstanding, it is clear that peak *SAR*s of focally introduced radiation must be very high to alter permeation of the rat's BBB to the tracer dye.

Other candidates to explain the discrepant findings relate to the variety of stresses that have been implicated in altered permeability of the blood-brain barrier. Elevation of body temperature, which does influence measures of permeability (*cf.* Merritt *et al.*, 1978, with Sutton and Carroll, 1979), occurs during handling and other sources of novel stimulation (Justesen *et al.*, 1974; Bermant *et al.*, 1979), and during physical restraint (Justesen *et al.*, 1971). Ambient temperatures in vivaria and laboratories, if excessively low or high, will obviously condition a rodent's metabolism and/or basal temperature. It follows that any of several maneuvers or environmental conditions that alter body temperature could have a confounding influence on measures of barrier permeability.

Other potential sources of confounding should be mentioned: differences in susceptibility that might arise in individuals, strains, or species. As an example, the extensive use of the albino rat invites an anomalous response of the barrier because of albinically linked enzymatic deficiencies that limit the animal's metabolic inactivation of barbiturates (*cf.* Creel *et al.*, 1976, with Shearer *et al.*, 1973).

When known or suspected sources of variation among reported studies are considered, some of the discrepant findings appear to be resolvable. Consider, for example, Oscar and Hawkins' finding that medullary Brain Uptake Indices increased 7-fold over control BUIs in rats that had been exposed to pulsed radiation (5 pps) at an averaged power density of only 30 $\mu W/cm^2$. Irradiation at a frequency of 1300 MHz can result in relatively high *SAR*s in the rat because of resonant

absorption. The rats were not anesthetized during the radiation treatment—one of the few cases of apparent barrier alteration in the RFEM-radiation literature that is not confounded by barbiturate-induced hypothermia. And finally, other studies have revealed that pulsed fields at the electrical parameters used by Oscar and Hawkins are acoustically perceptible (Guy *et al.*, 1975a; Frey and Messenger, 1973) and are sufficiently annoying to promote escape behaviors (Frey *et al.*, 1975; Hjeresen *et al.*, 1979).

One can make a case, therefore, that an unanesthetized animal at near resonance in a field of high peak power density will receive acoustic stimulation and, in undergoing generalized arousal (in both the physiological and hyperthermal sense), might exhibit an alteration of blood-brain-barrier permeability or an alteration of cerebral circulation that is misconstrued as altered barrier permeability. Either explanation is plausible, but should not preempt consideration of an alternate possibility. The finding of an effect at 30 $\mu W/cm^2$, even with the strongest resonant absorption, constitutes, for a continuous train of RFEM pulses, the lowest averaged power density associated with biological change that has been reported in the North American literature. Perhaps it is coincidental, but the repetition rate of five pulses per second falls within the spectrum of intrinsic electrical rhythms of the brain.

Adey and colleagues have been studying these rhythms in consequence of applying to brain materials RFEM fields that undulate or are modulated at the brain's intrinsic (EEG) frequencies (Bawin *et al.*, 1975, 1978a). When, for example, 6- or 16-Hz sinusoidally modulated VHF fields at ~1 mW/cm^2 were impressed on isolated chick brains for 20 minutes, a reliable increase in efflux of Ca^{2+} was observed, a finding later confirmed by Blackman *et al.* (1979). At modulation frequencies near 0.5 or 20 Hz, irradiation of chick brains at the same averaged power density produced a minimal efflux of Ca^{2+} (see Section 11 for more details). Paralleling these observations are others by Oscar and Hawkins, who found that increasing the repetition rate of 10-μs pulses from 5 to 1000 pps resulted in *decreased* medullary BUIs in spite of the 200-fold increase in averaged power density.

If a relation exists between the modulation-frequency-dependent findings of Ca^{2+} efflux and altered BUIs—a hypothetically appealing but by no means demonstrated connection—another connection may be attempted that has little *a priori* warrant. This is speculation that either phenomenon might be a potential "weak-field" hazard. The evidence cited earlier indicates that a multitude of moderate stresses—many not unlike those visited on everyone in the mundane affairs of

living—have effects on measures of brain-barrier permeability that are as great or greater than those produced experimentally by RFEM fields in the studies reported by Oscar and Hawkins and by Frey *et al.* Only one caveat precludes a conclusion that undulating or pulsed fields on the order of 1 mW/cm^2 have no health significance as concerns the blood-brain barrier and other cerebrovascular events. This caveat stems from the realization that all published experimental findings are based on acute studies and brief exposures. Most investigators that have reported positive findings have irradiated their animals only once for 20 to 30 min; the longest reported duration of exposure is less than 10 hours. Unless or until effects of long-term exposures over days, weeks, and months are assessed, concerns will persist, as will the gloomy speculations of those who confuse absence of evidence with presumption of peril (Justesen, 1977).

10.6 Summary and Conclusions

If the BBB is viewed as a structural entity, i.e., as an assembly of tight junctions that guard against access to much of the brain by many plasma constituents, there is virtually no warrant for the proposition that the barrier is affected adversely by weak RFEM fields, at least at the RFEM frequencies that have been studied to date. Viewed as a functional entity in which a multitude of specialized carriers is joined by vesicles, the whole of which is subject to physical and physiological laws that dictate responsiveness to changes of pressure and temperature, the BBB should be sensitive to RFEM fields. At least, the BBB should be sensitive to those fields of sufficient intensity to measurably thermalize the brain and/or to provoke, locally or peripherally, changes of blood pressure and flow.

Histological studies of RFEM-irradiated animals by Albert (e.g., 1979) have revealed no evidence of anatomical disruption of tight junctions despite his selection of durations of exposure and intensities of radiation that exceeded those of studies in which evidence of functional changes has been observed. It is possible that Albert was on the high side of a power-density "window." It is possible also that the biochemical techniques of BBB measurement have been insensitive or otherwise inappropriate, as Rapoport *et al.* (1979) and Blasberg (1979) have argued. Problems of measurement aside, there is the more fundamental issue of the substrate being measured. More hypothesis than datum is the presumed regulatory role of the barrier. If a passive

role is assumed by the tight junctions, then facilitation and inhibition of diffusion and of active transport of metabolites and other plasma constituents are likely the bases of the regulatory process. Given this premise, there is a need to determine threshold changes in rates of normally infiltrating molecules as a function of strength and frequency of the incident fields. Of especial interest is whether calorically equivalent fields, pulsed and CW, are equally effective in altering uptakes of normally permeant molecules, especially when fields are sinusoidally modulated or are pulsed at frequencies that fall within the EEG spectrum.

If the brain is actively involved in the regulatory process in the sense of neurologically controlling transfer of normal plasma constituents beyond the capillary space, it follows that characteristic differences in transfer rates should be correlated with differing stages of the EEG. Correspondingly, experimental induction of a stage by imposition of a modulated field may drive, not only the EEG, but also the BBB activity. The scientific promise of elucidating whether the brain does play an autoregulatory role via the BBB should encourage experimentation in these directions.

The histological evidence that moderately strong RFEM fields do not impair the integrity of the BBB's tight junctions—and the increasing indications that cerebral circulation and not barrier function is influenced by weaker RFEM fields (*cf.* Rapoport *et al.*, 1979, with Oscar *et al.* 1981)—might mitigate but do not, by themselves, abolish health concerns that relatively weak RFEM fields are capable of altering function of the central nervous system. Altered circulation would represent a mediating response by the nervous system to the field, which should invite concern. But concern should not be translated to alarm. Arguments doubtless will be offered that alteration of cerebral circulation by fields at power densities below 10 mW/cm^2 constitutes presumptive evidence of insult. Two counter arguments are offered. First, the extant data on the blood-brain barrier, even if they are confounded by circulatory changes, nonetheless reveal that alterations induced by fields that range upward to 35 mW/cm^2 are not greater than those produced in an animal by the stresses associated with swimming, moderate fasting, learning to escape from an annoying stimulus, or being gentled in the hands of a human being. Second, there is the larger, often dissociated, lesson that brief exposures of animals to nearly lethal fields that almost certainly disrupt the anatomical barrier have not left lasting signs of neurological or behavioral disorder in the surviving animal. One can conclude, therefore, that none of the investigations that has revealed altered measures of the

barrier by brief exposures to weak-to-moderate fields has generated evidence of irreversible physical insult.

It should be emphasized that effects of fully controlled, truly long-term irradiation on neurocirculatory and related events have never been performed, and that the data on a single, 20- or 30-min exposure that results in a reversible alteration of, say, cerebral circulation, cannot be generalized to the proposition that weeks or months of long daily bouts of irradiation (or of continuous irradiation) in the same field will be of no health consequence. That question remains to be answered.

There is the need for studies that repair the hiatuses of the experimental literature, i.e., acute and long-term experiments that:

1. Combine histological and functional approaches—for example, the electronmicroscopic techniques of Albert (1979) should be paired with dynamic methods akin to that of Rapoport *et al.* (1979), which would assure concomitant leverage on morphological and circulatory events;
2. Control for potentially confounding effects of anesthesia;
3. Provide accurate and comprehensive thermometric and dosimetric data;
4. Utilize non-albinic strains of animals and larger species, including primates;
5. Assess the extent and implications of individual and species differences;
6. Permit evaluation of possible carrier- and modulation-frequency dependencies, such as, respectively, part- and whole-body resonance, and interactions of external fields with intrinsic neuroelectric rhythms; and
7. Control environmental and procedural sources of stress that may confound or complex with the effects of irradiation.

11. Interactions with the Nervous System

11.1 Central Nervous System

11.1.1 *Introduction*

Absorption of RFEM energy is often associated with elevations of temperature in the absorbing material. For most mammalian tissues, this added thermal burden may amount to 70 percent or more of the metabolic heat production (1 to 3 W/kg) before a significant rise in tissue temperature occurs (>0.1 °C), due to efficient heat removal by adaptive physiological mechanisms that characterize endothermic species (see Section 15). Secondary effects of RFEM fields attributable to elevated temperature have been well categorized and in general differ little from effects of hyperthermia induced by other means (Presman, 1968; Michaelson *et al.*, 1975). However, it is now clear that some tissue interactions with RFEM fields that produce temperature increments orders of magnitude less than 0.1 °C result in major physiological changes that cannot be attributed to elevated temperature *per se*. The need for quite different models of transductive coupling of these weak fields relates to "windows" in frequency and incident energy, which characterize these interactions in brain and some other tissues, and to the very weak oscillating electric gradients in tissue shown to be effective in modifying cell functions by mechanisms that appear to "amplify" the triggering field. These amplification mechanisms may be based on nonequilibrium processes, with long-range, resonant, molecular interactions. They are in the class of "cooperative" processes and have been widely recognized as important in immunological and endocrine reactions, as well as in neurobiological excitation. A strong presumptive site for their occurrence is at the surface of the cell membrane.

11.1.2 *Observed Biological Sensitivities to Weak Environmental RFEM Fields*

Biological effects of environmental oscillating electric fields are related to the electric gradient they induce in the tissue. This gradient

will be determined by the degree of coupling between the field and the tissues. At frequencies below 300 Hz, electrical gradients at the surface of a body in air will be determined by the capacitance to free space (Barnes *et al.*, 1967), which is a function of the body's mass and shape. This capacitance, C, far from ground, is:

$$C = 4\pi\epsilon_0 r, \tag{11.1}$$

where ϵ_0 is the dielectric permittivity of free space and r is the distance to the point of interest. For a spheroidal model, this equation gives a capacitance of 50 pf for $r = 0.5$ meters. A typical value of specific impedance of brain tissue at ELF is 300 Ω cm (Freygang and Landau, 1955). If the induced electric gradient were uniform throughout a body having the electrical characteristics of brain tissue (a reasonable assumption for order-of-magnitude calculations), the expected tissue gradient for a 10-Hz environmental field of 10 V/m would be only 10^{-6} V/cm. This value agrees well with a total current measurement induced by such a field in a model of a monkey head (Valentino, 1972).

However, to appreciate fully the relation of these weak tissue components of ELF fields to possible excitatory effects in brain tissue, it must be remembered that nerve cells are enclosed in an extracellular fluid with a conductivity ~1000 times higher than that of the cell membrane. This fluid, thus, effectively shunts the cells it surrounds, providing a preferred pathway for field-induced currents. Extracellular fluid typically accounts for about 20 percent of the tissue volume and has a specific resistance from 4 to 20 Ω cm. Membrane resistance per unit area for different types of cells (Coombs *et al.*, 1959) ranges from 1000 to 5000 Ω/cm^2. Thus, only ~1/1000 of the induced extracellular current would be expected to flow through the cell membrane and, hence, to contribute directly to excitation of the nerve cell. For the 10-Hz, 10-V/m field cited above, the total tissue current is of the order of 10^{-8} A/cm^2. The expected transmembrane component entering the cell would be a mere 10^{-11} A/cm^2 for production of an impulse. Even though membranes of some nerve cells (in contrast to fibers) have been found two or three orders of magnitude more sensitive, there is a gap of about 10^5 between the magnitude of tissue components of these environmental fields and the usually accepted thresholds for excitation of nerve fibers. Nevertheless, evidence to be cited has shown that these weak-field gradients produce a variety of behavioral, physiological and chemical responses when they are within certain frequency and amplitude bounds.

A second class of windowed interactions with clear effects in brain tissue occurs in RFEM fields that are amplitude or pulse modulated at frequencies below 1000 Hz and particularly in the range between 1

to 20 Hz. Unmodulated fields do not produce these effects. Here, the field coupling to tissue is much stronger, and, for body dimensions from 0.05 wavelength to lengths that approach resonance, energy absorption is proportional to the square of the frequency (f^2) (Johnson *et al.*, 1977). For carrier frequencies between 150 and 450 MHz, behavioral and physiological effects have been observed under induced brain gradients in the range 10 to 100 mV/cm (Bassen *et al.*, 1977). For this band of carrier frequencies, gradients at these levels are induced in the brain of most mammals, including man, by incident fields at 0.1 and 1.0 mW/cm^2 (electric gradients in air approximately 19 and 60 V/m). These gradients have the same range of amplitudes as the intrinsic, low-frequency oscillations of the electroencephalogram (EEG) in brain extracellular fluid, when measured over the dimensions of a single neuron.

The search for "windowed" biological effects has centered on these two types of interactions; one involving direct interaction with low-frequency fields, and the other induced by RFEM fields amplitude modulated at low frequencies. Two "windows" have been detected, one involving ELF gradients of 10^{-5} to 10^{-8} V/cm, the other in ELF- or LF-modulated RF and microwave fields at 10^{-1} to 10^{-2} V/cm. A 50-V/m, 16-Hz field in air induces a tissue gradient of about 10^{-5} V/cm, and tissue gradients of 10^{-1} V/cm as induced by a 16-Hz field would require a gradient in air of 500 kV/m. It would thus be very difficult to achieve EEG-level gradients in tissue exposed to simple low-frequency fields (Bawin *et al.*, 1978b).

A wide range of effects has been reported in tissue components under environmental ELF fields between 10^{-7} and 10^{-8} V/cm. They include navigation and prey detection by sharks and rays, bird navigation, altered daily biological rhythms in man and birds, and subjective estimates of time by monkeys (Table 11.1). These sensitivities contrast sharply with the membrane potential of nerve cells. The "resting" potential is about 10^5 V/cm across the 4-nm dimension of the lipid bilayer or plasma membrane that forms the "backbone" of cell membranes. Excitation of nerve-fiber terminations (synapse) on the membrane's surface may depolarize it by about 10^3 V/cm. Thus, electric gradients in the fluid around brain cells (10^{-1} V/cm), with amplitudes approximately equal to those of the EEG, have usually been considered to have no role in excitation of brain neurons, and have been regarded merely as "the noise of the brain's motor." Recent evidence now strongly indicates a modulatory role for these fields, based on behavioral, neurophysiological and neurochemical evidence cited below. However, even these EEG-level tissue gradients are approximately six orders of magnitude greater than those associated with the behavioral effects listed in Table 11.1.

TABLE 11.1—*Bioelectric sensitivities*

Species	Function	Tissue gradient	Imposed field
		V/cm	
Sharks and Rays	Navigation/Predation	10^{-8}	DC to 10 Hz
Birds	Navigation	10^{-7}	0.3 Gauss[a]
Birds	Circadian Rhythms	10^{-7}	10 Hz, 2.5 V/m
Monkeys	Subjective Time Estimation	10^{-7}	7 Hz, 10 V/m
Man	Circadian Rhythms	10^{-7}	10 Hz, 2.5 V/m
	Cell and Tissue Neuroelectric Gradients		
	Membrane Potential	10^{5}	
	Synaptic Potential	10^{3}	
	Electroencephalogram	10^{-1}	

[a] Equal to 30 microtesla (μT) in the international system (SI) of units.

11.1.2.1 *Behavioral Effects of ELF Fields.* There is strong evidence that sharks and rays navigate and detect prey by environmental electric gradients as weak as 10^{-8} V/cm in the spectrum below 10 Hz (Kalmijn, 1974). Parker and van Heusen (1917) noted that nibbling responses in the catfish are elicited by a total current of approximately 1.0 μA between two electrodes about 2.0 cm apart. Rays can be trained to seek a food reward in a circular tank in which the earth's magnetic field is an essential cue (Kalmijn, 1978). Calculated electric gradients in tissue based on the rate of the animal's movement through the natural magnetic field are 0.5 μV/cm. These responses to movement faded out in magnetic fields weaker than the natural levels and were not observed in fields two orders of magnitude greater, indicating a magnetic-intensity "window." These low-frequency electric and magnetic perturbations are sensed by tubular electroreceptors that open on the skin of the head and are filled with a jelly-like substance. The walls of this ampullary canal have an extremely high resistance per unit area (6 MΩ/cm^2) and the core of the canal has a low specific resistance (31 Ω cm). The canal, therefore, exhibits ideal cable properties for DC potentials and for low-frequency electric oscillations. The low-pass frequency characteristics of the ampullary system give it an effective upper-frequency limit of about 10 Hz.

Human and avian circadian rhythms are lengthened in shielded environments that exclude natural and artificial electric fields. These rhythms return toward a 24-h periodicity in the presence of a 10-Hz, 2.5-V/m, square-wave field (Wever, 1968, 1977). Monkeys exposed to

7-Hz, 10- or 56-V/m fields shorten subjective estimates of a 5-s interval by about 10 percent (Gavalas *et al.*, 1970; Gavalas-Medici and Day-Magdaleno, 1976). There was an apparent threshold for 7-Hz fields at strengths between 1 and 10 V/m, but similar fields at 100 V/m were without effect, again indicative of a windowed interaction. Similar trends were noted in independent studies at 45 Hz and were statistically significant in the first series of exposures, but not in the second (de Lorge, 1973, 1974). Measurements of induced currents in models were in general agreement with calculated tissue gradients of the order of 10^{-7} V/cm in both circadian-rhythm and time-estimation experiments.

Although these data suffer from some difficulties in replication or in a lack of duplicate studies at this time, they show a general consistency in evidence of a tissue threshold between 10^{-7} and 10^{-8} V/cm for a variety of biological effects of ELF fields in fish, birds and mammals. There is also evidence to support some windowed interactions, with a decline in some responses for fields two orders of magnitude larger, a finding consistent with the electrochemical observations cited below.

11.1.2.2 *Neurophysiological Effects of Modulated RFEM Fields.* VHF or UHF fields at ~1.0 mW/cm^2 (61 V/m) induce an EEG-level gradient in brain tissue and may be tested for effects on brain function, with and without ELF amplitude modulation at frequencies in the EEG spectrum.

A persistent component in EEG spectral analyses at the pulse repetition frequency (PRF) of a RFEM field following irradiation has been reported by Servantie *et al.* (1975). Under a 3.0-GHz field pulsed at 500 to 600 pps (1.0-μs pulse width, average power density 5.0 mW/cm^2), rats exposed for 10 d showed a distinct spectral peak in the EEG at the PRF, which waxed and waned in cycles lasting several minutes. Persistent EEG changes occurred for several days in rabbits after exposure for 2 h daily for 4 to 8 weeks to a 5.0-MHz field amplitude modulated at 14 to 16 Hz (Takashima *et al.*, 1979). Fields at amplitudes of 90–150 V/m enhanced EEG activity at 10 to 15 Hz, and 500 V/m fields augmented 4- to 5-Hz waves. Amplitude modulation at 60 Hz was without effect. No detectable heating of the brain occurred during these exposures.

Bursts of EEG waves occurring in various brain nuclei of the cat as conditional responses to a flash of light (and thus constituting a learned response) were more frequent in the presence of a 147-MHz, 0.8-mW/cm^2 field that was amplitude modulated at the same ELF frequency as the EEG burst (Bawin *et al.*, 1973). Moreover, in the presence of the modulated RFEM field, but in the absence of punish-

ment for failure to make a correct response (so-called "extinction trials"), the decline of performance to pretraining levels occurred slowly over 45 to 60 days. Without the RFEM field, extinction occurred in 5 to 7 days. Even though this study was performed with metal electrodes that contacted the brain, spectral analysis of EEG records between wave "bursts" disclosed no artifactual rectification of imposed fields at the brain-electrode interface.

11.1.2.3 *Windowed Responses of Calcium-Ion Binding in Brain Tissue to ELF, VHF and UHF Fields.* As discussed below, calcium ions are essential in transductive coupling of a wide range of immunological, endocrinological and neurobiological events at cell-membrane surfaces. The fluid surrounding cells contains 2.0 mM calcium, whereas typical concentrations in the general cytoplasm within cells are far lower, around 10^{-4} mM. Effects of RFEM fields on calcium binding in cerebral tissue are believed to occur at cell membrane surfaces (Bawin *et al.*, 1978a). Calcium ions trigger their own release from intact cerebral cortex of cats in a highly nonlinear fashion, strongly indicative of a cooperative process (Kaczmarek and Adey, 1974). Weak oscillating electric gradients no larger than those of the EEG (50–100 mV/cm) increase efflux of calcium and the amino acid transmitter, gamma-aminobutyric acid (GABA), from cat cerebral cortex by almost 20 percent (Kaczmarek and Adey, 1973). These two findings have challenged accepted views that oscillating extracellular electric gradients as weak as the EEG play no part in neuronal excitability. This view is further challenged by the following evidence on RFEM-field sensitivity of brain tissue.

11.1.2.3.1 *Effects of Sub-ELF and ELF Fields.* Freshly isolated chick and cat cerebral tissues exposed to sinusoidal electric fields at 1, 6, 16 and 32 or 75 Hz (electric gradients in air of 5, 10, 56 and 100 V/m) exhibit a general trend toward a reduction in release of preincubated $^{45}Ca^{2+}$ (Bawin and Adey, 1976). Both frequency and amplitude sensitivities were observed. Maximal decreases of 12 to 15 percent occurred at 6 and 16 Hz. Thresholds were ~10 and ~56 V/m for chick and cat tissues, respectively. Similar, but nonsignificant trends, occurred during other exposures at 5 and 100 V/m. Tissue gradients were not measured, but estimates are of the order of 0.1 μV/cm. All results were statistically compared with matched samples of controls. Thus, the efflux was clearly windowed in both frequency and amplitude.

11.1.2.3.2 *Effects of Weak VHF and UHF Fields Modulated with ELF.* Similar frequency and amplitude windows have been observed in chick cerebral tissue exposed to VHF and UHF fields amplitude modulated with sub-ELF. Cerebral hemispheres of neonatal chicks

first incubated in a physiological medium containing $^{45}Ca^{2+}$ were then washed in a non-radioactive solution. They were then irradiated in a 147-MHz, 0.8-mW/cm^2 field, sinusoidally amplitude modulated at a depth of 80 to 90 percent at frequencies from 0.5 to 35 Hz. Unmodulated fields and modulation frequencies at 0.5 and 3 Hz did not induce a significant change in $^{45}Ca^{2+}$ efflux. In contrast, there was a progressive and statistically significant increase in $^{45}Ca^{2+}$ efflux at frequencies from 6 to 16 Hz. The response decreased progressively at higher frequencies from 20 to 35 Hz. Brains treated with 10^{-4} M sodium cyanide prior to $^{45}Ca^{2+}$ incubation and irradiation responded identically to unpoisoned tissue, indicating that the response was not dependent on integrity of cytochrome respiratory enzyme systems (Bawin *et al.*, 1975). These experiments were confirmed independently by Blackman *et al.* (1979), who also observed the modulation frequency "window" between 9 and 16 Hz. They also observed that these effects were only statistically significant at incident power densities of ~1.0 mW/cm^2. This power-density window has been confirmed for chick cerebral tissue exposed to a 450-MHz field, sinusoidally modulated at 16 Hz (Bawin *et al.*, 1978a). In the latter experiments, a statistically significant increase in $^{45}Ca^{2+}$ efflux occurred only at 0.1 and 1.0 mW/cm^2 and not at 0.05 and 5.0 mW/cm^2. Measurements showed tissue gradients of the order of 100 mV/cm at incident fields of 1.0 mW/cm^2.

11.1.2.3.3 *Evidence on the Site and Mechanisms of Transductive Coupling of Fields in Brain Tissue.* Attempts to evaluate the role of H^+ and HCO_3^- ions in controlling $^{45}Ca^{2+}$ movement in cerebral tissue and to identify more accurately the probable site of tissue coupling of the RFEM field have been reported by Bawin *et al.* (1978b). Addition of H^+ ions sharply enhanced $^{45}Ca^{2+}$ efflux in the presence of the UHF field, but was without effect on the non-stimulated efflux, indicating a role for H^+-ion binding in these field effects, perhaps in accordance with the model of competitive H^+-Ca^{2+} binding on membrane-surface macromolecules originally proposed in Pauling's laboratory (Bass and Moore, 1968), or perhaps in terms of proton tunneling across phase boundaries at the margins of cell-surface, fixed-charge domains (Adey, 1981a). The $^{45}Ca^{2+}$ efflux was sharply decreased following omission of HCO_3^- ions. This decrease is unlikely to be due to inhibition of movement of Ca^{2+} ions into mitochondria and other cell organelles because the bicarbonate concentration was only 2.4 mM in the control medium. Nor can the reduced efflux be explained by increased calcium entry into the cell, because the effect persisted in the presence of 0.5 mM La^{3+} and was enhanced at a higher concentration of this ion. On the other hand, inhibition of inward Ca^{2+} currents in the absence of

HCO_3^- ions could result in decreased transmembrane calcium exchange, followed by reduced intracellular Ca^{2+} efflux. This model would not explain evidence from the same study that response to the UHF field occurred in lanthanum-treated tissue, with the response probably mediated in the extracellular compartment.

Treatment of cerebral tissue with lanthanum prior to testing the effects of the UHF field on $^{45}Ca^{2+}$ efflux has proved a powerful tool in localizing at least one major class of these field interactions at the cell surface and in the intracellular space (Bawin *et al.*, 1978a). La^{3+} ions block the movement of Ca^{2+} ions either inward or outward across the cell membrane. Therefore, changes in $^{45}Ca^{2+}$ efflux that persist after La^{3+} treatment may be presumed to occur at sites located in the fluid surrounding cerebral cells. Addition of La^{3+} to the bicarbonate-free solution described above restored electrical responsiveness, but this response to the 16-Hz-modulated, 450-MHz field decreased (instead of increasing) $^{45}Ca^{2+}$ efflux. This response exhibited the same windowed specificity to field intensity observed previously in tissues in normal physiological solution (Bawin and Adey, 1976; Bawin *et al.*, 1975), with a stimulated decrease occurring only around 0.75 mW/cm^2 but vanishing at higher and lower field intensities. Together, these findings support the hypothesis that a limited number of extracellular cationic binding sites is involved in the transduction of weak, extracellular electrical events. Low-frequency, weak, extracellular electric gradients may be transduced in a specific class of extracellular negative binding sites that are normally occupied by calcium ions and are susceptible to competitive hydrogen-ion binding.

Studies of cerebral synaptosome fractions exposed to a 450-MHz field (0.75 mW/cm^2, 16-Hz sinusoidal modulation) lend strong support to this concept. Synaptosomes are the endings of nerve fibers that form synaptic junctions on the surface of nerve cells. They mediate the transmission of signals from one nerve cell to the next and have a mean diameter of 0.7 micrometers. They can be isolated from other elements in cerebral tissue by ultracentrifugation, and their membranes can be resealed, allowing the centrifuged fraction to be used as a model cerebral system. Exposure to the 16-Hz-modulated, 450-MHz field increased calcium efflux by 38 percent, but 60-Hz modulation was without effect. Manipulation of calcium levels in the bathing fluid in these experiments indicated that the increased calcium efflux came from sites on membrane surfaces, rather than from pools of intracellular calcium (Lin-Liu and Adey, 1982).

In non-nervous tissue, studies of hormone binding and cell-mediated immunity now provide categorical evidence for cell-membrane sites as the focus of major interactions with low-level fields. Cultured bone

cells and cultured embryonic bones exposed to a 72-Hz pulsed magnetic field (pulse duration 325 μs, peak intensity 20 gauss, typical induced current in culture medium 1 $\mu A/cm^2$, induced electric gradient 1.1 mV/cm) showed a response to parathyroid hormone (PTH) diminished by 90 percent. This peptide hormone binds to receptor sites in membrane-surface glycoproteins and stimulates the activation of the enzyme adenylate cyclase, which is attached to the inner surface of the membrane. In contrast, these fields exerted no influence on the activation of adenyl cyclase by 1,25-dihydroxy vitamin D_3, a substance that acts intracellularly, probably at the cell nucleus (Luben *et al.*, 1983).

Destruction of target cells by rupture of cell membranes (cytolysis) is a cell-mediated immune response of T-lymphocytes made allogeneic against these target cells and requiring actual contact between lymphocytes and target cells. This interaction was reduced by 20 percent when lymphocytes were exposed to a 450-MHz, 1.5-mW/cm^2 field sinusoidally modulated at 60 Hz (Lyle *et al.*, 1982). This response showed a windowed relation to the modulation frequency, with maximal effects at 60 Hz and progressively smaller responses at higher frequencies to 100 Hz and at lower frequencies to 3 Hertz. Unmodulated fields had no effect. Recovery of killing capacity occurred after 12 hours.

11.1.3 *Physiological Models of Weak RFEM-Field Interactions in Tissue*

No comprehensive models are yet available that adequately explain all transductive coupling phenomena involving weak fields in tissue. However, it has become clear that many of these biological effects in weak fields can only be understood in terms of cooperative processes based on nonequilibrium, resonant, long-range interactions involving biological macromolecules (Adey, 1975, 1977, 1981a; Fröhlich, 1968b, 1975b; Kaiser, 1978a,b; Grodsky, 1976; Grundler *et al.*, 1977; Kaczmarek, 1976; Illinger, 1977).

A strongly presumptive site for these interactions, and one considered as a substantive aspect of virtually all these models is the surface of the cell membrane. The molecular biology of cell membranes is a topic of intense continuing research. It is now accepted that older concepts of the membrane as a simple lipid bilayer must be replaced by the view that the lipid bilayer is fluid and encloses a considerable number of "intramembranous particles" (IMPs), which have considerable lateral mobility within the lipid bilayer. These concepts are subsumed under the general title of the "fluid mosaic model" (Singer

and Nicolson, 1972). The IMPs are proteinaceous, with externally protruding terminal strands of amino sugars that bear numerous negative charge sites at fixed locations on the terminal strands. These fixed charge sites thus form a polyanionic sheet on the membrane surface, with a strong affinity for cations, of which H^+ and Ca^{2+} are those with the highest binding affinities in the extracellular fluid (Katchalsky, 1964). This polyanionic sheet appears to form a sensing surface in the first steps in the transductive coupling of a wide variety of weak cell-surface events, including the binding of antibody molecules in an immune reaction (Edelman, 1976; Yahara and Edelman, 1972), in the binding of hormonal molecules (Sutherland and Robison, 1966), and in the weak neurobiological stimulations discussed here.

The sum of observations and constraints does not favor a direct transductive coupling of weak extracellular fields across the plasma membrane, with its extremely high electric gradient probably 12 orders of magnitude greater than these extracellular fields (for review, see Adey, 1981b). Some form of amplification of the initial transductive steps would appear essential. We may also presume that, if this occurs at an extracellular location, it involves systems capable of integrating the weak field over some distance, and would thus occur in the length and area of the membrane surface, rather than in a transmembrane axis (Adey, 1977). This problem has been addressed by Einolf and Carstensen (1971) in a study of the behavior of micro-sized resin particles considered as porous particles with uniformly distributed, fixed-charge sites. Their model is an extension of an earlier formulation by Schwarz (1962), which considered the movement of ions along the surface of solid (rather than porous) colloid particles. At the surface of the particles, the boundary region is characterized by a very large, radially directed static field with a corresponding radial variation in the distribution of mobile ions. Maintaining this distribution has the effect of requiring the ions in the boundary layer to move in a path tangent to the surface of the particle. Porous, charged particles are characterized by a low-frequency dielectric relaxation, leading to large static dielectric constants. A final result is polarization of the ionic atmosphere at the surface of the particle in the presence of an external electric field. This polarization produces an additional *apparent* dielectric constant of the particles, exceeding the actual dielectric constant by several orders of magnitude at low frequencies. The magnitude of the low-frequency dielectric constant is proportional to the size of the particle and the square root of the fixed-charge concentration in the porous material. The relaxation frequency depends directly on counterion mobility and is inversely proportional to the square of the particle size.

The effective dielectric constants of micrometer-sized, ion-exchange resin particles are as high as 10^6 at frequencies below 1 kHz (Einolf and Carstensen, 1971). Similar properties may be expected at the surface of tubular structures with diameters in the micrometer range, including dendrites with polyanionic glycoprotein surface layers. This model provides an avenue for future research into the biological effects cited above in which it appears that thermal noise at normal tissue temperatures is substantially larger than the tissue components of the imposed electric fields. For typical conductors in the biological temperature range, the Boltzmann kT noise is of the order of 0.02 electron volts. However, this expression gives little concept of the extent to which electric gradients in tissue may be established by thermal, atomic, or molecular perturbations, nor of the way in which components of this noise may be transferred to distant sites within tissue. In metallic conductors, the transfer function for this noise energy has an essentially infinite bandwidth, a condition that does not pertain in tissue. The transfer function of thermoelectric noise in tissue has yet to be studied. However, a tentative model does offer interesting points of resemblance to observed neurochemical and behavioral thresholds (Bawin and Adey, 1976). Data from the Einolf and Carstensen study indicate that ionic conductance along a membrane surface in the counterion layer will exhibit an inverse frequency dependence and limited bandwidth due to the very high apparent dielectric constant in this zone. The Boltzmann equation may be written in terms that model the tissue in this region as a low-pass filter:

$$e^2 = kTBR, \tag{11.2}$$

where the transfer function for the root-mean-square noise voltage, e, is a function of the temperature, T, the frequency bandwidth, B, and the specific resistance of the noise pathway, R. With a specific resistance for brain tissue on the order of 300 Ω cm and an effective frequency bandwidth from 0 to 100 Hz, the equivalent, noise voltage gradient would be on the order of 10^{-8} V/cm. This value is in close agreement with observed sensitivities of marine vertebrates, birds, and mammals to certain low-frequency fields, and these thresholds are consistent with a thermal floor as the limiting factor.

Virtually all identified steps in these processes are known to be calcium-ion dependent. In all these events, the observations and models indicate that integrative processes in the coupling of these surface interactions to intracellular mechanisms first occur in the length and area of the membrane, prior to communication of information to the interior of the cell. This, too, has been a significant new concept in models of the molecular biology of excitatory processes.

11.1.3.1 *Quantum Mechanical Models of Long-Range Interactions.* There has been growing interest in models for predictive evaluation of these unexpected biological sensitivites. These models were advanced to resolve two of the more baffling problems of these effects: sensitivity to low-intensity fields and possible bases for molecular interactions in the ELF spectrum below 100 Hertz. There are at least four major groups of models, all of which emphasize phase transitions at extremely low frequencies: charge-pumping models, Lotka-Volterra models of charge-population transitions, models of limit-cycle phenomena, and models of tunneling effects.

11.1.3.1.1 *Models of Macromolecular Phase Transitions at ELF.* There are no known mechanisms to explain ELF biological effects on the basis of direct interactions with component dipoles of molecular systems that oscillate at these low frequencies. Therefore, a structural and functional basis must reside in properties of molecular systems. Grodsky (1974, 1976, 1977) has hypothesized that excitable membranes are energetically equivalent to sheets of giant dipoles bathed in controlled external electric fields. His model examines the role of long-range cooperative processes in latticed mosaic systems of the type first proposed by Ising (1925) to explain mechanisms of ferromagnetism. Grodsky's model encompasses the concept of a "greater" membrane (see below), in which the cell membrane is conceived as extending beyond the phospholipid bilayer by the external protrusion of strongly polyanionic, sialic-acid side chains that are stranded terminals of glycoprotein and ganglioside intramembranous particles (Schmitt and Samson, 1969; Singer and Nicolson, 1972).

In this model, the outer layer of phospholipid polar heads is represented by a two-dimensional crystal mosaic of multipolar sites (*p*-sites), sprinkled with islands of glycoproteins. The "fuzz" of the outer membranes, above the *p*-sites, displays a mosaic of cationic binding sites (*c*-sites). The *c*-sites are less densely packed and less tightly bound mechanically than are the *p*-sites, and their electric charge depends on local, external ionic contributions, which can vary quite rapidly. The prediction of behavior from a knowledge of structure rests on the ability to identify the contributions of *p*-sites and *c*-sites to the total energy of the system in the context of mutual interactions between the two sheets of charges. The *p*-sites are taken to be occupied by ideal dipoles. If the dipoles are densely packed, neighboring interactions will tend to keep them oriented, on the average, perpendicular to the sheet, so that the energy in the *p*-sheet can be expressed as a Hamiltonian integral of the dipole fields. This field decreases as the cube of distances between the sites. The *c*-sites are assumed to be variably occupied by divalent or monovalent cations, or to be unoc-

cupied. The charges interact with each other through Coulombic forces in the *c*-sheet and via the dipoles in the *p*-sheet. Coupling between the sheets falls off rapidly as the distance, *r*, between the sites increases, but the fields set up by the *c*-sites are of much longer range, falling off as r^{-2} instead of the dipolar r^{-3}.

The Hamiltonian expression of the membrane model then becomes mathematically equivalent to that describing the interactions of bands of electrochemical quasiparticle excitations with each other and with a band of phonons, via phonon exchanges, in a complicated combination of dipole rotations, ion exchanges, and mechanical vibrations. The quasiparticle, phonon-coupling constants are negative, because energy is dissipated in the interactions. Negative coupling gives rise to the possibility of new bound states (altogether new bands of quasiparticles of higher frequency), but more importantly, negative coupling always *lowers* the frequency of the existing bands. The direct couplings between the *p*- and the *c*-sheets produce strongly negative contributions to the energy, and are thus capable, under certain conditions, of lowering the uncoupled *p*- and *c*-sheet frequency bands. Grodsky applied his theoretical model to a simplified system consisting of a perfect two-dimensional lattice. At progressively increasing energy levels, this system passes successively through antiferro-like, flop, and para-like phases.

Below a critical level of thermal energy (Neél temperature), at low external field intensities, neighboring interactions and anisotropic fields dominate in the sheet, and the dipoles assume a checkerboard configuration with each neighbor pointing oppositely, on the average, in or out of the sheet; the system is in the antiferro-like phase. At higher field intensities, but below the triple-point energy, the dipoles flop over so that they are perpendicular to the field on the average, but are still in an antiferro-like configuration within the sheet; the system is in the flop phase. With increasingly intense fields below the Neél energy, or at temperatures greater than the critical point, the external field overrides the sheet interactions. The dipoles then follow any external field and the system is in the para-like phase. When the system is in the antiferro-like phase and as the external electric field increases from zero, two bands of oscillations emerge from the initial "degenerate" bands of excitations, one increasing and the other decreasing, until the lowest frequency band (longest wavelength) reaches zero. Grodsky proposed that when the frequency of an allowed mode reaches zero, the system would become a macroscopic quantum-amplification device, and would exhibit long-range-order phase changes that generate into the zero-frequency mode (Einstein-Bose condensation), but occurrence of such a condensation based on this initial

formulation has been questioned (see Adey, 1981b). Grodsky hypothesizes that excitable membranes at physiological temperatures oscillate between antiferro-like and flop phases, with a resting condition close to this first-order phase transition at around zero frequency, and thus associated with spontaneous, intrinsic oscillations in membrane potential. Concurrently, there would be prominent long-range frequency correlation on the surface of the membrane. Energy from extracellular fields matching the natural frequencies would be resonantly absorbed. Such a system, in association with the physical geometry of dendrites of cerebral neurons, might allow information transfer at energy levels far below the excitation energy of an action potential.

As an extrapolation of the Ising (1925) model, Grodsky's formulation necessarily rests on the quite severe constraint of a rigidly ordered, spatially symmetric lattice having certain minimal dimensions. However, a structural counterpart of such a highly ordered lattice remains to be detected in biological membranes. Grodsky's formulation is also applicable to chemically nonreactive systems. In other applications of a linear Ising model to the kinetics of conformational changes in linear polymers (Eigen and de Maeyer, 1973; Schwarz, 1968; Schwarz and Engel, 1972), as many as four relaxation spectra have been found, but only one of them has a finite amplitude for a conformational transition having a strong degree of cooperativity (Schwarz, 1972).

11.1.3.1.2 *Charge "Pumping" and Volterra Models of Charge Population Transitions.* Sensitivity of some biological systems to weak fields suggests that these systems can store signal energy and thus overcome thermal noise. These systems should require relatively small activation energies but would be protected from thermal fluctuations. From an evolutionary viewpoint, the biological membrane can be considered as one of the most elemental of dissipative systems (Nicolis and Lefever, 1975), and membrane properties have been defined in terms of nonequilibrium thermodynamics (Blumenthal *et al.*, 1970). The biological membrane may be considered as a chemically pumped, open, steady-state system (Ismailov and Zubkova, 1977), with energy provided for the membrane system from a sequence of feedback loops linking the steady-state concentrations of oscillatory biochemical reactions (Noyes and Field, 1974). Illinger (1981) proposes that these dissipative processes in a membrane subsystem composed of biopolymers, structural water, and ions may elicit complex and novel interactions, as developed in the model by Frölich (1968a,b, 1972, 1977).

Frölich has hypothesized that ELF electric oscillations in the brain may be connected with such a system requiring relatively small activation energies, but protected from thermal fluctuations. These oscil-

lations cannot arise from a collective mode based on interactions of various molecular groups, because enormous volumes of tissue would necessarily be involved in overcoming their thermal noise. Instead, Frölich has applied a general theory of coherent vibrations in biological systems (Bhaumik *et al.*, 1976; Frölich, 1968a,b, 1972, 1975b, 1977; Kalada *et al.*, 1974) for which there is some experimental evidence (Devyatokov, 1974; Frölich, 1975b, 1977; Mascarenhas, 1975). Frölich envisages collective chemical oscillations in which globular proteins and the surrounding ions and structural water behave as an entity and oscillate between a strongly, electrically polar excited state and a weakly polar ground state. A slow chemical oscillation is thus connected with a corresponding electrical vibration. The strong electrical interaction between the highly polar states in conjunction with strong damping of electric currents then imposes limit-cycle conditions on these polar systems, making the oscillations highly sensitive to external electrical and chemical influences, as described by Kaczmarek (1977).

Frölich's theory of long-range coherence in biological macromolecules describes coherent electric vibrations in the frequency region of 10^{11} Hz when energy is supplied to these molecules above a threshold level. These excitations can cause far-reaching, long-range interactions not seen with static or slowly oscillating electric charges, where they are screened at much shorter range by small ions. Application of this model to enzymatic reactions (Frölich, 1970; Green, 1974) indicates a possible basis for collective enzymatic reactions, with strong polarization of the activated state reducing activation energies, and coherent vibrations causing long-range, selective interactions with other systems.

In the context of field interactions with membrane-surface enzymes that might be a part of a "greater membrane," Frölich (1946) has considered a population of enzymes, of which N are in the excited polar state and Z are not excited, interacting with substrate molecules S. All three are presumed to show long-range, selective interactions that tend to increase their number by influx or excitation. The rate of increase of activated enzymes would be proportional to their concentration N, to the concentration of inactive enzymes Z, and to the number of substrate molecules S (expressed in the function αNZS). Chemical destruction of substrate occurs with each transition from nonpolar to polar state. Spontaneous transitions from excited to ground states may also occur. Nonlinear differential equations describe this model:

$$dN/dt = \alpha NZS - \beta N, \tag{11.3}$$

$$dS/dt = \alpha NZS + \gamma S, \tag{11.4}$$

$$dZ/dt = -\alpha NZS + \beta N - \lambda(Z - A), \tag{11.5}$$

where γS and $\lambda(Z - A)$ result from the long-range interaction, $Z = A$ in the absence of enzymatic activity ($N = 0$, $S = 0$); λ is the rate of long-range substrate attraction, and β is the rate at which an excited enzyme returns to its ground state.

If the equilibrium of nonexcited enzyme concentration is reached very fast (i.e., Z can be considered time independent), the equilibrium values N_0 and S_0 are given by:

$$\begin{aligned} N_0 &= \gamma/\alpha Z, \\ S_0 &= \beta/\alpha Z. \end{aligned} \tag{11.6}$$

Equation (11.5) may then be discarded, and Equations (11.3) and (11.4) are the Lotka-Volterra equations that describe cyclic behavior of populations in predator-prey relationships. For a system close to equilibrium, the concentration N and S may be written:

$$\begin{aligned} N &= N_0 + \nu, \\ S &= S_0 + \sigma. \end{aligned} \tag{11.7}$$

If ν and σ are small, the product $\nu\sigma$ may be ignored, and:

$$\begin{aligned} d\nu/dt &= \gamma\sigma, \\ d\sigma/dt &= -\beta\nu. \end{aligned} \tag{11.8}$$

In this approximation, the periodic enzyme reaction oscillates around the steady-state equilibrium at a circular frequency of $\sqrt{\beta\gamma}$ as a limit-cycle phenomenon of the type proposed by Kaczmarek (1976, 1977). Frölich's model differs from those of Grodsky by incorporating nonlinear dissipative interactions in biochemically reacting systems, rather than the non-reactive systems as developed by Grodsky. Both consider dissipative processes as essential in cell regulatory mechanisms.

11.1.3.1.3 *Limit-Cycle Models.* Turing (1952) predicted that a system of chemical reactions and diffusion may develop a dynamically maintained temporal and/or spatial pattern from an initially steady-state homogenous system of matter (for review, see Katchalsky *et al.*, 1974). Temporal patterns in chemical reactions are well known. Belousov (1959) continuously stirred potassium bromate, ceric sulfate, and citric acid in dilute sulfuric acid and noted oscillations in the ratio of ceric (yellow) to cerous (colorless) ions, producing a recurring temporal pattern. Zhabotinsky (1967) substituted malonic acid for

citric acid and noted similar oscillations. Spatial organization maintained by these dynamic systems of chemical reactions occurs if the Belousov-Zhabotinsky reactions are not stirred, alternating stripes of oxidized and reduced forms of the indicator then propagating through the medium. Viewed as a dissipative structure (Herschkowitz-Kaufman, 1970; Prigogine, 1969; Prigogine and Nicolis, 1971; Prigogine *et al.*, 1969), the spatial patterning of the Belousov-Zhabotinsky reaction behaves in two ways from its initial instability. It develops a limit-cycle oscillation with respect to its chemical constituents, having a defined period and a temporal pattern independent of the initial perturbation. In response to a space-dependent perturbation, it also develops a spatial organization of "dissipative structure" that is distinct from conventional structure found only in systems at dynamic equilibrium. This link between limit-cycle oscillation and dissipative structure may relate to the dynamics of neural populations (Kaczmarek, 1976, 1977).

Kaczmarek has considered the possible occurrence of resonant phenomena in chemical reactions when analyzed as linear systems (Busse, 1969; Hyver, 1973; Ortoleva and Ross, 1972). A simple model of calcium binding to anionic membrane binding sites suggests this possibility:

$$M^{n-} + Ca^{2+} \underset{k_2}{\leftarrow\!\!\rightarrow} X \multimap Y \xrightarrow{k_3} \text{----}$$

Calcium ions bind to the anionic membrane component M^{n-} to form a calcium complex X. The calcium complex may exist in two forms, X and Y. The individual complexes are linked through conformational coupling such that the presence of Y favors the transition $X \rightarrow Y$. As discussed in the previous section, the rate of such a process may be approximated by the use of a "molecular-field" approach in which the rate constant is set equal to βe^{ny} (Blumenthal, 1970). The third step of the reaction scheme would provide for removal of Y, as in its utilization for release of transmitter substances at synapses. The kinetic equations describing the system are:

$$\begin{aligned} dX/dt &= k_1[M^{n-}][Ca^{2+}] - k_2 X - \beta e^{ny} X, \\ dY/dt &= \beta e^{ny} X - k_3 Y. \end{aligned} \tag{11.9}$$

For appropriate values of the kinetic constants and the extent of cooperativity, n, this scheme can display multiple steady states, limit-cycle behavior, or both (Kaczmarek, 1976). In the limit of a very weak field, the effect of an oscillating electromagnetic field on the rate constants for the initial binding of Ca^{2+} to the membrane may be

represented by:

$$k_1 = K_1[1 + \alpha\sin(\omega t + \phi)], \qquad \alpha \ll 1. \tag{11.10}$$

In computer simulations, the dynamics of the system were very sensitive to the frequency of perturbation, ω, when the system was in the limit-cycle mode. Kaczmarek (1977) points out that if calcium binding in neural membranes can exhibit limit-cycle behavior due to reaction steps being maintained far from chemical equilibrium, weak external perturbations could easily disrupt the electrochemical balance. The narrow range of ELF frequencies evidenced in weak field interactions with brain tissue does not support a molecular or dipole-moment interaction at, or close to, equilibrium.

11.1.3.1.4 *Tunneling Models.* There is a possibility, as yet untested, that long-range interactions between membrane-surface, fixed-charge sites may occur at the boundary between zones of fixed charges exhibiting coherence and incoherence (Lawrence and Adey, 1982). This boundary would be an energy barrier for charge movement between the zones. Coherence of charge sites has been observed along the surface of macromolecular biopolymers. From studies of relaxation times in the binding of acridine dyes to poly-1-glutamic acid, Schwarz (1967) postulated a condition of identical energy levels at adjoining fixed-charge sites in the length of the biopolymer sheet. This coherent condition was observed to persist for periods approaching a millisecond. The dimensions of such a coherent "patch" have not been determined.

The possibility of biological tunneling has been considered for excitatory processes (Cope, 1973) and for the hemoglobin molecule in binding oxygen (Hopfield, 1973, 1974). It has been proposed that the "window" phenomena noted in several types of field interactions with tissues (Bawin and Adey, 1976; Bawin *et al.*, 1978a; Blackman *et al.*, 1979) may arise in charge tunneling across an energy barrier (Adey, 1981a; Adey and Bawin, 1982; Bawin *et al.*, 1978a). Most previous schemes have envisaged electrons as the charge carriers in tissue tunneling in conformity with classic observations at semiconductor junctions (Esaki, 1958). Hopfield (1974) points out that the separation between linking sites in biological sites for electron tunneling may be limited to 0.8 to 1 nanometer. Experiments and related models on the role of hydrogen ions in field interactions indicate that protons may offer a basis for tunneling interactions along cell surfaces in brain tissue (Bawin *et al.*, 1978b; Adey and Bawin, 1982).

11.2 Effects of RFEM Radiation on Peripheral and Isolated Nervous Tissues

Investigators have used such techniques as electroencephalograms, evoked electrical responses from the brain, and behavioral approaches to study effects of RFEM fields on the nervous system. Some indications as to what tissues or portions of the nervous system are being affected by the fields has come from other experiments involving exposure of peripheral or isolated tissues. These tissues have ranged from single giant axons of squid to mammalian nerve-muscle preparations in studies conducted over the last two decades. While some results are easy to interpret, many others are difficult to evaluate because of variations in exposure techniques and, in some cases, lack of essential information.

In an early study, McAfee (1962) reported that physiological effects in cats, dogs, rabbits, and rats exposed to 2450-MHz and 10-GHz fields can be duplicated by heating the peripheral nerves with warm water or thermodes. These responses include arousal reactions, blood-pressure and vascular changes, and signs of neurohormonal activation. McAfee concluded that the field effect is a result of thermal stimulation of peripheral nerves, which can occur independently of a significant increase in skin temperature or total body heating.

Kamenskii (1964) exposed frog sciatic nerves to 2450-MHz CW and 3-GHz pulsed fields at an average power density of 1 to 12 mW/cm^2 for 20 to 30 minutes. The center portion of the suspended nerve was exposed in an S-band waveguide and horn apparatus (Presman and Kamenskii, 1961). During CW exposure, there was no change in threshold excitability. However, exposure to CW fields did increase the conduction velocity by 16 ± 4.5 percent, shortened the absolute and relative refractory periods, and affected the amplitude of the action potentials. The maximal temperature rise was less than 2 °C as measured by a thermocouple attached to the surface of the irradiated nerve. The nerve was exposed to pulsed fields at an average 12 mW/cm^2 (1-μs pulses, 100, 200, and 700 pps), but there was a 15 percent increase in excitability only when the repetition rate was 700 pulses per second. At a pulse repetition rate of 10 pps and a power density of 3.5 mW/cm^2, the conduction velocity was increased by 10 percent. In this experiment, heating of the nerve did not exceed 0.2 °C. Kamenskii attributed the changes in CW exposures to thermal effects and in the pulsed exposures to athermal effects of the fields.

Rothmeier (1970) exposed frog sciatic nerves in an X-band waveguide to 10-GHz fields at an input power of 1 mW. The power

measurements showed that 52 percent of the energy was absorbed by the nerve. At an average power density of 0.43 mW/cm^2, he occasionally observed evidence of increases in excitability. Although the total input power was only 1 mW, the *SAR* in a nerve 1 mm in diameter could be as high as 66 W/kg. This *SAR* could certainly cause thermal effects if temperature controls were not employed.

The sciatic nerves of frogs were also studied by Lott and Smith (1977, abstract). They exposed the nerves to 2450-MHz fields at a power density below 10 mW/cm^2 and observed a gradual and prolonged increase in the amplitude of the action potential, followed by a sharp decline after 4 h of exposure, and a gradual and sustained increase in conduction velocity, followed by a decline 4 h after exposure.

In contrast, Deficis *et al.* (1974) found a decreased conduction velocity in frog sciatic nerves exposed to 2.5- and 9-GHz fields, especially at 5 and 6 GHz. They observed no effects on chronaxie or rheobase. The effect on conduction velocity is not explicable on the basis of a thermal effect.

The effect of RFEM irradiation on resting potential in giant neurons of molluscs (*Helix pomatia*) was reported by Arber (1976). The neurons were exposed to 2450-MHz fields for 1 h at an *SAR* of 15.5 W/kg. Exposure caused hyperpolarization of the resting potential. No effect was observed at pH 4, and the effect was reduced when ouabain was used. The author claimed that the fields increased the membrane permeability to K^+ and Na^+. The resulting intracellular accumulation of Na^+ caused an activation of the sodium pump. This activation would account for about 60 percent of the radiation-induced hyperpolarization.

Wachtel *et al.* (1975) and Seaman and Wachtel (1978) exposed abdominal ganglia of *Aplysia* in a strip line apparatus to 1.5- and 2.45-GHz fields for 2 to 3 minutes. The effects on the firing rate of both beating pacemaker cells and "bursting" cells were quite complicated. The threshold *SAR* for producing a slow decrease in firing rate of beating pacemakers was 7 W/kg, and that for producing a rapid change of increased firing rate was 1 W/kg. Although pulsed fields seemed to be more effective than CW fields, the authors reached no definitive conclusion to account for the difference. When nerves were heated in a water bath, both increased and decreased firing rates in beating pacemakers were noted. Comparisons of these results with those produced by RFEM radiation indicates that the field effect is more than a simple heating effect. Wachtel *et al.* (1975) pointed out that these effects occurred only occasionally and represented only extreme cases. Also, thermal controls employed in these studies were quite crude. Although they observed effects on firing rate, no effects were

found on action-potential amplitude, duration or shape, nor on the resting potential or conductance. They discussed the possibility that effects on firing rate were produced by current injected through the microelectrode or rectification across the neuronal membrane.

Kritikos *et al.* (1975) exposed giant axons of squid and myxicola to fields between 10 Hz and 30 MHz. They found no difference between CW and pulsed fields in the triggering of action potentials. Above 20 kHz, it was not possible to excite the nerve by the fields. The DC-evoked action potentials were not affected by the presence of the field. However, if a large field was applied, the field was rectified due to a nonlinear electrode process. Under this condition, change in firing rate was observed.

Bychkov (1974) reported effects at a power density of 5 $\mu W/cm^2$ (5-min exposure) on frog nerve-muscle preparation. Effects included diverse changes in membrane potential, threshold of excitability, latent and refractory periods, rate of conduction, amplitude of action potential of muscle fibers, synaptic delays at myoneural junction, and impulse activity of neurons. Few details are given and it is not possible to evaluate the significance of each of so many effects presented.

Tigranian *et al.* (1980) studied a frog neuromuscular preparation exposed to a 0.8-GHz field (8-ms pulses, 1 pps) at an average power density of 12 mW/cm^2. The preparation was placed in a plastic chamber with humidified air and exposed in a waveguide. The increase in temperature of the preparation was not more than 0.5 °C. While employing repetitive electrical stimulation with the expectation of producing conduction blocking, they observed that the irradiation substantially increased the functioning time of the preparation (i.e., tbere was no blocking). It was postulated that exposure changed the transmembrane transport in the synapses and enhanced the synthesis of neurotransmitters, thus lengthening survival of the preparation.

In an earlier study, Portella *et al.* (1974) exposed isolated frog sartorius muscle to an average 10-mW/cm^2, 2.88-GHz pulsed field for 2 h and found transient changes in muscle membrane resistance, capacitance, ion conductance, conduction velocity, water permeability, space constant, and rise and fall times of action potentials. They also found that these effects were more profound in winter than in summer. However, no permanent changes were observed. In a later report, Portella *et al.* (1979) showed that chronic exposure of frogs to the same field for 6 min/d for 20 to 100 d did not produce any change in the water and solute parameters of cells, nor on membrane permeability. These latter studies were performed during the summer.

When McArthur *et al.* (1977) exposed isolated terminal pyloric segments of rat gut to 960-MHz fields at *SAR*s of 1.5 to 5.5 W/kg,

they observed an increase in peristaltic activity. The preparation was suspended in isothermal, aerated Ringer's solution and was exposed in the field of a parallel-plate, capacitor-type radiator. The increase was thought to be neurally mediated by the release of transmitter substances by the autonomic nervous system. The experiment was repeated in 1-GHz fields by Whitcomb *et al.* (1979). However, no effect was observed at *SAR*s as large as 6.9 W/kg.

Because nervous tissues are very sensitive to temperature change, it is important to differentiate thermal from athermal effects. Matsumoto and Yamamura (1977, abstract) reported only thermal effects of 11-GHz fields on the abdominal ganglia and stretch receptor neurons of American fresh-water crayfish. A minimal effect occurred when temperature was increased by 0.5 °C. Because of the different exposure arrangements in the experiments described above, it is difficult to evaluate the differences in reported effects.

Chou and Guy (1978) exposed isolated frog sciatic nerves, cat saphenous nerves, rabbit vagus nerves and rabbit superior cervical ganglia as well as rat diaphragm muscles in a temperature-controlled waveguide and found no changes in conduction velocity or action potentials of nerves, nor any changes in contractile ability of muscles exposed to 2450-MHz fields at *SAR*s as large as 1.5 kW/kg for CW and 220 kW/kg (peak) for pulsed (1-μs pulses, 1000 pps). A decrease in response latency occurred at a temperature rise of 1 °C brought about by field or by bathing-solution heating. Courtney *et al.* (1975) also exposed rabbit superior cervical ganglia in the same temperature-controlled waveguide at *SAR*s to 1 kW/kg, but failed to influence the transmission latencies of responses recorded from postganglionic fibers. Kritikos and Takashima (1975) also exposed frog sciatic nerves to 2450-MHz fields in a constant temperature bath and found no effect at an *SAR* of 500 W/kg.

Vitality of isolated frog sciatic nerves was studied by McRee and Wachtel (1980). The vitality of nerve tissue was measured in terms of its ability to sustain high firing rates over prolonged periods without changes in the action potential. The nerves that were exposed at 10 W/kg or more showed a prolonged refractory period and decreased amplitude of the action potential. The authors considered this effect to be field-specific because temperature control experiments did not produce this effect. This effect also was irreversible and had a threshold of 5 W/kg. The exposure system was similar to that used by Chou and Guy (1978) except that nerves were exposed while enclosed in polyethylene tubes. Heat transfer processes differ in this case from that when the nerve is in direct contact with Ringer's solution as studied by Chou and Guy (1978).

The effect of exposure of the spinal cord was studied by Taylor and Ashleman (1975) and by McRee *et al.* (1976). The studies involved exposures of the spinal cord of cats to 2450-MHz CW fields at *SAR*s to 1.6 kW/kg. The effect on monosynaptic transmission was studied by stimulating the dorsal root and recording at the ventral root. Both studies showed that the observed effect on action potentials was thermal.

11.3 Effects of RFEM Radiation on Autonomic Nervous Function

The autonomic nervous system strives to maintain uniformity of the internal environment. Smooth muscle, glands and the excitable tissue of the heart, for example, receive motor nerves that, when reflexively activated, alter the functional state of the innervated organ. A reflex alteration of arteriolar diameter, mediated by autonomic motor fibers that supply vascular smooth muscle, is at least partly responsible for the shifting of blood from one vascular bed to another in accord with physiologic demand. Similarly, reflex discharges in autonomic nerves that supply a cardiac pacemaker modulate and regulate the rate of beating, although they do not initiate the heartbeat, so that the varying demands upon the pumping system are automatically met.

The preganglionic autonomic neurons are maintained in a continuous, but quantitatively variable, state of activity by a host of inputs. Some of these inputs are segmental in origin (dorsal roots); others originate in supraspinal structures and descend the neural axis to reach the levels of autonomic outflow. When the spinal cord is transected above the level of T_1, the first thoracic segment, a transient condition of spinal shock ensues in which blood pressure drops precipitously because of a decrease in the sympathetic discharge to the visceral vascular bed and a consequent diminution in the peripheral resistance to flow. Temperature regulation is immediately lacking, sweating ceases, and body temperature falls toward that of the environment. The bladder and bowel are paralyzed, and sexual reflexes are absent.

The contributing role of structures in the medulla oblongata or hind brain to the regulation of autonomic reflexes may be inferred from studies on preparations in which the brain stem is sectioned at the intercollicular level. The status of autonomic reflexes in these preparations resembles in general that of the spinal preparation, with body temperature fluctuating with environmental temperature. But, if the

test section is made at a higher level that removes influences of the cerebral cortex, there is residual autonomic function that gives some indication of the relative participation of supracollicular brain-stem structures in the regulation of autonomic function. In this case, blood pressure is well maintained and temperature regulation is normal.

The full measure of autonomic reactivity in the decorticate preparation is seen, however, when a mildly noxious stimulus such as a light pinching of the skin, is applied. Such stimulation evokes a paroxysm of behavior that, because it so closely resembles anger, is called "sham rage." The presence of sham rage in the decorticate preparation and its absence in the preparation transected at or below the midbrain indicates that structures lying between the cortex and midbrain influence powerfully, via descending connections, the lower brain stem and spinal autonomic centers. Moreover, this control is well integrated, so that discharges over both autonomic and somatic pathways are blended into an effective behavioral pattern. This integrative center lies in the hypothalamus.

Particular regions in the hypothalamus are responsible for the visceral regulatory functions such as regulation of body temperature, water balance (antidiuretic hormone, ADH secretion), oxytocin secretion, regulation of adenohypophysial function, food intake, gastric-acid secretion and cardiovascular regulation, all of which maintain the constancy of the internal environment (Ruch and Patton, 1966).

A number of physiological changes in the autonomic nervous system occur in experimental animals after exposure to RFEM radiation. These effects are discussed in the following sections: endocrine system, Section 8; cardiovascular function, Section 9; and thermoregulatory responses, Section 15.

12. Behavioral Studies

12.1 Introduction

Some of the more challenging questions regarding biological effects of exposure to RFEM fields have stemmed from reports of altered behavior and nervous-system activity. In 1973, for example, at a symposium entitled *Biologic Effects and Health Hazards of Microwave Radiation*, several Eastern European investigators reported that behavioral and neurological anomalies were observed in workers exposed to RFEM fields in industrial settings (Kalada; Klimkova-Deutschova; and Sadcikova; all in Czerski *et al.*, 1974c). With few exceptions, the Western scientific community responded skeptically to the Eastern reports. This skepticism apparently stems from the lack of such positive findings by Western investigators. However, the investigations that produced the positive Eastern European reports have little in common with the Western studies. The Eastern European reports are based on clinical studies of chronically exposed human populations as well as relatively long-term experimental studies of animals at low levels of irradiation. The Western reports are largely based on acute studies of laboratory animals exposed at relatively high levels of irradiation (Justesen, 1979, 1983a, b).

The following review of the behavioral literature is preceded by a brief dicussion of the ways in which behavioral end points can be investigated as well as some methodological considerations pertinent to such investigations.

12.2 Methodological Issues

12.2.1 *Behavioral End Points*

Behavioral techniques can be used to address a variety of end points that range from sensory physiology to the higher mental processes of learning and memory, of judgment and thinking, and of motivation and emotion (Kling and Riggs, 1971). Behavioral observations can be made on organisms in the natural environment, in a clinical setting,

or in the laboratory. In any of these settings, the behavioral datum can range from the extreme of a casual observation to a detailed, highly rigorous, experimental probe.

Behavior is a useful end point in exploring potential toxicity of an agent because it is highly sensitive and because it reflects the integrated nervous, hormonal, and motor activity of the organism.

Behavioral sensitivity often is observed at low levels of RFEM irradiation that do not lead to discernible changes in other biological end points, *in-vivo* or *in-vitro*. As such, behavior frequently can be used to establish thresholds of organismic reactivity. Whether such observed effects are harmful or benign is an independent question that needs to be qualified. As an example, consider the discomfort associated with a headache. Such discomfort may produce observable behavioral alterations that are likely to increase in magnitude with the level of discomfort experienced. However, this discomfort only infrequently is associated with such life-threatening conditions as tumor formation or cerebral aneurism. Direct observation of the behavior does not reveal either the cellular mechanism or the potential harm associated with the discomfort. Interpretation of the behavioral end point is subject to the limitations incumbent with its phenomenological character, with individual differences, and with theoretical biases that may lie implicitly in design of experiments and interpretation of data.

12.2.2 *Behavioral Design*

Of the behavioral end points referred to above, one of the most frequently studied is learning or conditioning. Two classes of conditioning are used, respondent (classical or Pavlovian) and operant (instrumental).

12.2.2.1 *Respondent Conditioning.* Pavlov was the first scientist to study systematically respondent conditioning in animals. A neutral (conditional) stimulus is presented to an animal immediately prior to the presentation of an unconditional stimulus that results in a reflexive (i.e., unconditional) response. After repeated presentations, the animal may respond to the conditional stimulus in the absence of unconditional stimulation. A learned response to conditional stimulation is termed the "conditional response."

12.2.2.2 *Operant Conditioning.* In respondent conditioning, the occurrence of the response is assured because it is directly *elicited* by the unconditional stimulus, which is controlled by the investigator. In operant conditioning, the response to be conditioned is first *emitted* by the organism. If the response operates successfully on the environ-

ment, i.e., if the operant is positively or negatively reinforced, it tends to recur with greater frequency. An example of a positive reinforcer is a food pellet or sugar water. An example of a negative reinforcer is cessation of electrical shock to the feet. Reinforcers of both classes will readily maintain a lever-pressing or a locomotor operant. Operant conditioning involves two categories of behavior, *controlled* and *free*. A controlled operant refers to the case in which the animal can make only one successful response, simple or complex, such as a specifically ordered set of left and right turns in a maze. In the free-operant case, the appropriate response might be to depress a lever or to pull a cord to obtain food or water. The organism is free to depress the lever by any means, but the investigator determines the temporal relations among stimuli, responses, and delivery of reinforcers, which are termed schedules. An effective schedule results in a consistent pattern of responding. Schedules are characterized by this degree of stimulus control and by the nature of the response pattern that they produce. In this regard, schedules differ with respect to sensitivity to alteration of the response pattern of additional conditions placed on the organism, e.g., injection of various drugs.

For an excellent treatment of the traditional experimental approach to psychology as well as a discussion of advantages and limitations of behavioral analysis, see Kling and Riggs (1971), Sheridan (1976), and Honig and Staddon (1977).

12.2.3 *Field Parameters*

Section 2 of this report and NCRP Report No. 67 (NCRP, 1981) discuss in detail the variables relating to exposure conditions that must be considered when evaluating effects of RFEM irradiation on a biological preparation. It has been demonstrated repeatedly that the *SA* threshold of detection of a RFEM field is very small when the field is delivered in discrete pulses (Frey, 1961; Guy *et al.*, 1975) as compared with delivery of a CW or sinusoidally modulated field (King *et al.*, 1971). Reports of behavioral alteration must be evaluated and interpreted carefully with respect to the character of modulation of the carrier, especially when transients or other pulses of high peak power density are generated.

In the review that follows, results from studies of human subjects are treated separately from data on subhuman species; also, data on acute, high-level exposures are distinguished from those associated with long-term exposures at low intensities.

12.3 Clinical Investigations

Most of the reported effects of RFEM fields on human beings have come from Eastern Europe (*cf.* Dodge, 1970; Tolgskaya and Gordon, 1973; Czerski and Siekierzynski, 1974; Klimkova-Deutschova, 1974; Bielski *et al.*, 1976; Gabovich and Zhukovskii, 1976; Gus'kova and Kochanova, 1976; Siekierzynski *et al.*, 1976). A typical set of psychological symptoms identified as the neurasthenic syndrome or "microwave sickness" (Sadcikova, 1974) is a somewhat variable collection of complaints that include irritability, headache, lethargy, insomnia, irascibleness, impotence, mnemonic disorders, and loss of libido. When persistent, this set of symptoms, in whole or in part, is not unlike that labeled the *chronic depressive reaction* in the *Diagnostic and Statistics Manual (DSM-III)* of the American Psychiatric Association (APA, 1980).

Reports of neurasthenia continue to appear in the RFEM literature (Bielski *et al.*, 1980), but neither the definition of the symptoms nor the conditions of exposure under which such symptoms are reported to occur have changed significantly from those of the earlier reports.

Neurasthenia is reported by Eastern European authors to occur in response to irradiation at frequencies that span the electromagnetic spectrum from 50-Hz fields to x rays. For the RFEM portion of the spectrum, the symptoms are associated with field intensities that range from nanowatts to milliwatts per square centimeter. Because neurasthenia is also linked to dust and noise, it is difficult to interpret its specific etiology in evaluating earlier reports from Eastern Europe (see Section 14, and *cf.* Tolgskaya and Gordon, 1973; Djorjevic *et al.*, 1979). The results of more recently reported studies are similar to those of the earlier studies, but provide more information on critical variables of methodology and on statistical analyses. This additional information has led to more attentive assessment of the early reports. "Microwave" or "radiowave sickness" has been cited as a distinct clinical entity in the Soviet Union (Tolgskaya and Gordon, 1973). Clinical responses usually are reported after chronic (approximately 3 to 6 y) exposure at power densities ranging from a few $\mu W/cm^2$ to a few mW/cm^2.

Few studies of the human response to RFEM irradiation have been reported in the Western literature. Individual cases that have attracted public attention are not specific to behavioral effects. One study, that of American employees of the United States Embassy in Moscow, did reveal considerable neurasthenic symptomatology, but these symptoms were not correlated with levels of exposure (Lilienfeld *et al.*, 1978). A more detailed treatment of this study and other human

clinical reports, as well as the methodological problems associated with interpretations of such studies, is presented in Section 14.

Experimental investigations of human subjects in the laboratory are restricted to sensory physiological and psychological studies that are conducted primarily on thresholds of cutaneous and auditory perception (see, e.g., Frey, 1961; Hendler *et al.*, 1963; Lin, 1978; Guy *et al.*, 1975; and Justesen *et al.*, 1982).

12.4 Laboratory Investigations

12.4.1 *Acute Exposures*

More than 6,000 reports of biological effects have appeared in the literature on RFEM radiations (Dodge and Glaser, 1977; Glaser and Dodge, 1977). Most of these reports are based on exposures of small animals to RFEM fields in the microwave spectrum or at lower frequencies, and a substantial number relates in whole or in part to behavioral reactions. As indicated previously, most of the scientific reports from the United States are based on studies in which exposures of short (minutes to hours) duration occurred to highly intense fields well in excess of 10 mW/cm^2. The behavioral data that have emerged are, therefore, associated with acute effects and include (in approximate order of decreasing field strength) death, convulsive activity, work stoppage, work disturbance, decreased endurance, behavioral thermoregulation, aversive behavior, interaction with drugs, and perception of the field.

12.4.1.1 *Lethality.* Numerous studies of subhuman subjects have consistently shown that RFEM irradiation that results in a rise of core temperature to 43 to 44 °C is lethal to the organism. Schrot and Hawkins (1976), for example, reported on 100 male mice and 180 male rats that were exposed to a 150-mW/cm^2 CW field at frequencies of 710, 985, 1700, 2450, and 3000 MHz. At each frequency, the vector of the electric field was either parallel or perpendicular to the long axis of the animal's body. Body masses of a single group of mice ranged from 25 to 30 grams. The rats were assorted into two groups according to body mass: Smaller animals ($n = 110$) ranged from 100 to 125 g, and the larger ones ($n = 70$) from 380 to 420 grams. The animals were restrained during exposure. Latency to initiation of a lethal, tonic-clonic convulsion was recorded and the total duration of the exposure was one hour if the animal survived. The results showed that, for a horizontally polarized electric field, the frequency associated with the

shortest latency to a lethal convulsion was 1700 MHz for the mouse, 985 MHz for the small rat, and 710 MHz for the large rat. In the mice, 55 percent did not survive 1 h of exposure to the 1700-MHz field. The authors concluded that both frequency and polarization of the field interact with an animal's physical dimensions. This conclusion is in agreement with earlier studies of energy absorption (Gandhi, 1974), which revealed that the greatest amount of energy is generally absorbed when the long axis of a target is parallel to the vector of the electric field.

12.4.1.2 *Convulsions.* Non-lethal, *grand-mal* convulsions that are induced by intense irradiation by RFEM fields result from high brain temperatures near 42 °C. Such convulsions have been observed within 30 min in mice and rats under standard environmental conditions at power-density thresholds that cover a considerable range from less than 5 to more than 500 mW/cm^2. Although the power-density thresholds associated with convulsive activity are highly variable, the convulsive threshold as indexed by the whole-body-averaged *SA*s is not highly variable (Justesen, 1975). Under typical environmental conditions, the *SA* threshold lies between 22 and 35 kJ/kg of body mass and holds for exposure durations ranging from less than a second (Guy and Chou, 1978) to 15 min (Dordevio, 1975). Acute *SA* thresholds of convulsions are highly stable under standard environmental conditions, but they are sensitive to basal body temperature at initiation of irradiation and to environmental variables, especially those of ambient temperature and air velocity (Justesen, 1975; Dordevio, 1975; and Phillips *et al.*, 1975b). The critical factor is brain temperature (Guy and Chou, 1978). When brain temperature approaches 43 °C, the probability of a febrile convulsion within a few tens of seconds approaches unity. Convulsions induced by RFEM fields indicate a dangerous condition because morbidity and death frequently follow (Phillips *et al.*, 1975b; Justesen *et al.*, 1977, abstract).

12.4.1.3 *Work Disturbance.* Work disturbance is defined as a positive or negative change induced by some agent in the rate or efficiency of performance. Studies of the squirrel monkey by de Lorge (1979b) not only exemplify the case of behavioral disturbance, but illustrate how animals larger than mice and rats have much higher tolerance for RFEM fields of a given frequency and intensity. de Lorge's monkeys worked at a two-lever task that required adroitness in discrimination and timing to achieve rewards of small pellets of food. After the monkeys had been partially deprived of food until body mass was reduced by 10 percent, which insured strong motivation to perform the two-lever task, they were subjected to unrestricted exposures of the body to 2450-MHz fields that ranged in power density from 0 to

75 mW/cm^2. Performance was not reliably affected until rectal temperatures were elevated by 1 °C or more. The intensity of irradiation required to induce a 1-°C increment in temperature was near 50 mW/cm^2 for a 30-min exposure. Disruption of performance (work stoppage) did not occur in the monkeys until power density was increased above 60 mW/cm^2. Even after exposures at 70 to 75 mW/cm^2, which were strongly disruptive, the impairment of performance was only temporary. The *SAR* at the threshold of disturbance was estimated by de Lorge to lie between 2.5 and 4.5 W/kg (*cf.* de Lorge and Ezell, 1980).

12.4.1.4 *Endurance.* The work-disturbance experiments described above were based on operant lever-pressing responses. Such responding does not necessarily entail sustained, strenuous effort. When forced expenditure of effort at a task is required over a long period of time, an agent can be tested to determine the level at which it degrades performance, i.e., the threshold of endurance. In a study by Hunt *et al.* (1975), rats were required to swim almost continuously in an automated swimway into which the animals were placed after being subjected to 30 min of sham irradiation or of irradiation by 2.45-GHz CW fields that resulted in an *SAR* of 6.3 or 11 W/kg. Rats absorbing energy at the higher *SAR*, which resulted in an *SA* near 20 kJ/kg, were markedly impaired during the initial period of swimming, then recovered and swam about 600 meters at a normal rate before again showing impaired performance. When tested 24 hours after irradiation at the 11-W/kg *SAR*, the rats' swimming speeds were normal for about 1200 m before their performance worsened relative to controls. Some of the controls could swim a distance of 9 km during a 24-h period.

The rats that had been absorbing energy at the rate of 6.3 W/kg for 30 min, when tested immediately after irradiation, swam as well as controls for about 1200 m, then performed more poorly over the next 600 m before again swimming at speeds that fell within control values. The *SA* imparted to these rats, about 11 kJ/kg, was associated with a modest degradation of endurance when the animals were tested immediately after exposure to 2450-MHz fields.

12.4.1.5 *Perception of RFEM Fields.* Introspectively or behaviorally defined perceptibility of RFEM fields is the most thoroughly established datum in the behavioral literature on such fields, but a datum that must be qualified. The qualification is related to modulation of the field. When a field is sharply pulsed so as to produce a burst of RFEM waves of short rise time and high peak intensity, individuals with normal hearing perceive a popping or clicking sound. The earliest report on the auditory perception of RFEM fields appeared as an advertisement of the Airborne Instruments Laboratory (1956). The

advertisement described observations made in 1947 on the hearing of sounds that occurred at the repetition rate of a pulsed radar beam. Later, Frey initiated a series of formal studies that resulted in several reports that detail field conditions associated with perception of pulsed fields (e.g., 1961, 1962, 1963).

12.4.1.5.1 *Human Auditory Perception.* In 1947, several members of the engineering staff of the Airborne Instruments Laboratory heard sounds when they were standing close to the horn antenna of a ground-based radar operating at 1.3 GHz (20-μs pulse width, 600 pps). Power density was not specified.

Several papers by Frey (1961, 1962, 1963) describe experiments on human observers exposed to 0.216-, 0.425-, 1.31-, 2.98-, and 8.9-GHz pulsed fields at various pulse widths from 1 μs to 1000 μs and at different pulse-repetition rates. Depending on pulse parameters, the sensations were perceived as buzzing, ticking, hissing, or knocking sounds that originated within or immediately behind the head. Sound was perceived at all frequencies except at 8.9-GHz. The threshold peak of power density was determined to be in the range of several hundred milliwatts per square centimerer. When converted to energy per pulse, the *SA* threshold is near 20 mJ/kg. Frey also found that the hearing phenomenon is associated with acoustic frequencies in a range above 5 kHz, because subjects that could not hear the pulsed RFEM fields had hearing losses above 5 kHz (*cf.* Justesen, 1975). Another interesting finding of Frey (1961) is that a subject with otosclerosis could hear the RF sound as well as normal subjects; this finding indicates that the ossicles of the middle ear do not play an important role in the perception of the pulsed field.

Frey and Messenger (1973) exposed 4 subjects to 1.25-GHz fields (10- to 70-μs pulse widths) and used a magnitude-estimation method to determine loudness as a function of peak power and of average power density. They concluded that loudness is dependent on the peak of power density, not on the averaged power density. A closer examination of their data reveals that loudness is essentially independent of the peak of power density for pulses that are less than 30 μs in width (*cf.* Lin, 1978; Guy *et al.*, 1975a).

Ingalls (1967) reported results similar to those of Frey and colleagues, except that the RFEM sound was perceived by his observers to be above or at the very top of the head. When the subjects positioned their fingers (presumably in or over their ears) so that ambient noise was reduced, the sound source was reported to be at the very top of the head.

Guy *et al.* (1975a) determined the threshold energy level for human observers exposed to pulsed 2450-MHz fields (0.5- to 32-μs pulse

widths). They found that, regardless of the peak of power density and the pulse width, the per-pulse *SA* threshold for a normal subject is near 20 mJ/kg. The average elevation of brain temperature associated with a just-perceptible pulse was calculated by Guy *et al.* to be about 5×10^{-6} °C.

Cain and Rissman (1978) studied perceptual thresholds associated with 3-GHz pulsed fields (5- to 15-μs pulse widths, 0.5 pps) delivered to each of 8 observers. Five of the subjects were able to hear the pulses, which presented the same subjective sensation reported by Frey (1961, 1962, 1963) and by Guy *et al.* (1975a). Thresholds varied across the 5 perceptive observers from 3.4 to 17.5 μJ/cm^2 and were, in most cases, independent of pulse width. All 3 subjects who were unable to hear the pulses had hearing losses above 8 kHz.

Tyazhelov *et al.* (1979) exposed human subjects to 800-MHz pulsed fields (5- to 150-μs pulse widths, 20,000 down to 50 pps). Relative loudness was determined for different pulse-repetition rates. During an audio- and RFEM-sound matching experiment, a beat frequency could be heard. By adjusting the phase of the audio sound in opposition to that of the RFEM sound, a loss of sensation of the RFEM sound occurred. This cancellation could also be obtained by presenting audio sound at harmonics of the field repetition rate. Lowering a subject's head into water during irradiation did not change the acoustic characteristics of the field-induced sensations unless the entire head was immersed.

12.4.1.5.2. *Auditory Perception of Pulsed Fields by Small Animals.* Frey (1971) attempted without success to record cochlear microphonics in cats and guinea pigs, which led him to propose the hypothesis of direct neural stimulation in explaining the hearing phenomenon. Guy *et al.* (1975) demonstrated that bilateral destruction of the cochlea can abolish all RFEM-induced potentials recorded at higher levels in the auditory pathway. They provided substantial evidence that the cochlea, rather than cortical neurons, is the site of RFEM hearing. The cochlear microphonic was recorded by Chou *et al.* (1975), who used a 918-MHz circularly polarized waveguide for efficient energy coupling, an isolated RFEM-shielded room to minimize artifact, and a wide-band recording system to detect high-frequency responses. In guinea pigs, the cochlear microphonic was observed almost immediately (latency <30 μs) after onset of an incident pulse, which oscillated at a frequency of about 50 kHz for ~200 microseconds. Cochlear microphonics at the same frequency were also produced when the skull of the guinea pig was stimulated by a laser pulse or by excitation of an implanted piezoelectric crystal (Chou *et al.*, 1976). When the recordings were extended to cats and additional guinea pigs, animals

of each species having been selected for a considerable range of body mass, the characteristics of the RFEM-induced cochlear microphonic changed (Chou *et al.*, 1977). Physical parameters of the animals, including body mass, head mass, skull mass, skull dimension, skull thickness, brain cavity dimension, brain volume, bulla dimensions, cerebellar-cavity dimension and cerebellar volume, were plotted as a function of the frequency of the cochlear microphonic. Only the anterior-to-posterior dimension of the brain cavity showed a consistent relation to the frequency of the cochlear microphonic, i.e., as the length of the skull increased the frequency of the microphonic decreased.

When electrodes are attached to the scalp of an animal, RFEM-induced, auditory-brain-stem responses can be recorded during exposure to pulsed fields. Chou *et al.*, (1976) have shown that the field-evoked response is similar to that acoustically evoked. This similarity indicates that excitation occurs in the peripheral nervous system, and that a single auditory pathway in the central nervous system can be activated both by pulsed fields and by acoustic stimuli. Using the same recording technique, Chou and Galambos (1979) studied the involvement of the middle ear in RFEM hearing and found it to be non-critical. The effects of middle-ear inactivation of the bone-conducted, brain-stem-evoked response and on the RFEM-induced, brain-stem-evoked response were highly similar. Hearing of pulsed fields by the animals was only slightly impaired.

In another study by Chou and Guy (1979), the relation between perceptual threshold and RFEM-pulse duration was determined by use of the brain-stem-evoked response. The results indicate that the hearing phenomenon depends on energy content when a pulse is shorter than 30 μs and is dependent on the peak power for pulses longer than 50 microseconds. This relation is consistent with predictions based on thermoelastic-expansion theory (Foster and Finch, 1974).

Cain and Rissman (1978) recorded field-evoked responses, both from the inferior colliculus and from the scalp of cats exposed to 3-GHz pulsed fields. Lin *et al.* (1979c) recorded evoked potentials of cats from indwelling brain electrodes and superficial (epidural) electrodes that were coupled to a small applicator operating at 2.45 GHz. They also found waveforms of the field-induced responses comparable to those evoked by sonic pulses.

Single-cell recordings by Lebovitz and Seaman (1977a, b) revealed a similarity between acoustic and field-induced, post-stimulus time histograms. The threshold *SA* for the effect was about 4 mJ/kg. Lebovitz and Seaman's data are consistent with the thermoelastic

mechanism of the RFEM hearing effect except that a smaller number of fibers with a high characteristic frequency (2.3 to 5 kHz) responded to pulses, which is in seeming disagreement with the thermoelastic-expansion theory and with the cochlear-microphonic data. However, Lebovitz and Seaman used long pulses (250 to 300 μs) to obtain large amounts of energy per pulse. The results of Tyazhelov *et al.* (1979) showed that, for long pulses (>100 μs), lower-pitched RFEM sound is perceived by human observers. Therefore, the results of a single-unit recording in cats are consistent with human perception of pulsed fields when pulse widths are relatively long.

In behavioral studies, Hjeresen *et al.* (1979) explored effects of pulsed fields on shuttle-box behavior of rats, which had been studied earlier by Frey and Feld (1975). Hjeresen *et al.* hypothesized that the position-preference data of Frey and Feld—rats tended to remain in a side shielded from RFEM fields—might be associated with the hearing of pulsed waves. These authors found that rats responded to pulsed sound waves in much the same manner as they responded to pulsed RFEM waves.

A discriminative control study reported by Johnson, R. B. *et al.* (1976) clearly demonstrated that rats can perceive pulsed RFEM fields acoustically. Similarly, sonic-stimulation thresholds of audiogenic seizures in rats were elevated after the animals were chronically exposed to pulsed fields (Stverak *et al.*, 1974), a datum that also can be explained by a mechanism based on thermoelastic expansion.

The thresholds of detection of unmodulated or of sinusoidally modulated RFEM fields are much higher than those of pulsed waves. King *et al.* (1971) utilized a behavioral assay that combines classical and operant conditioning (conditional suppression) to determine sensory thresholds of rats in a 12-cm, multipath, sinusoidally modulated, but nonpulsatile field. They found that threshold *SA*s after 60-s periods of irradiation are near maximal limiting values of 35 to 140 J/kg. The associated *SAR* thresholds were 0.6 to 2.4 W/kg. The range of power densities at 2450 MHz that would result in an *SAR* of 0.6 W/kg in a mature female rat is about 3.5 to 6.0 mW/cm^2.

12.4.1.5.3 *Physical Measurements and Mechanisms of Auditory Perception.* Frey (1962) was the first to suggest possible mechanisms to explain the hearing of pulsed RFEM fields. He considered four possibilities for intracranial sites or structures involved in the transduction of pulsed fields to perceptible sound. The first involved the tympanic membrane and the oval window acting together as a capacitor. Frey ruled out this possibility because rotation of a head in the field did not change the loudness of the RFEM sound. The cochlea was considered, but there were no conclusive data to support its

transductive role. Direct interaction of pulsed fields with cerebral neurons was proposed by Frey, who found the most likely area for the detection of RFEM sounds to be a region over the temporal lobe of the brain. The fourth possibility was multiple avenues of detection, i.e., some combination of the other three candidate mechanisms.

Thermoelastic expansion in response to RFEM pulses was first studied and demonstrated by White (1963) in inert materials, and then was proposed by Foster and Finch (1974) as the mechanism of hearing of pulsed RFEM fields. A pressure wave is generated in most solid and liquid materials by a pulse of RFEM energy—a pressure wave that is several orders of magnitude larger in amplitude than that resulting from radiation pressure or from electrostrictive forces (Guy *et al.*, 1975; Lin, 1978). The characteristics of the field-induced cochlear microphonic in guinea pigs and cats (Chou *et al.*, 1975, 1976, 1977), the relationship of pulse duration and threshold (Chou and Guy, 1979), physical measurements in water (Foster and Finch, 1974) and in tissue-simulating materials (Olsen and Hammer, 1980; Olsen and Lin, 1981), as well as numerous theoretical calculations—all point to thermoelastic expansion as the mechanism of the hearing phenomenon. Virtually all investigators who have studied the phenomenon now accept thermoelastic expansion as the mechanism of acoustic perception of short pulses of RFEM energy.

12.4.1.6 *Aversive Behavior.* Rodents do not develop a strong escape or avoidance response to weak RFEM fields. Frey and Feld (1975) showed that, when rats were presented a choice between staying in an area shielded from irradiation or in an area where they were continuously exposed to pulsed 1.2-GHz fields, they remained in the shielded area approximately 60 to 70 percent of the time. Rats placed in the continuously pulsed field, which averaged about 200 $\mu W/cm^2$, repeatedly probed and re-entered the radiated area even though they developed a general preference for the shielded side. The fields used in these studies were of an acoustically detectable magnitude (Hjeresen *et al.*, 1979).

As mentioned earlier, a rodent can detect the presence of a nonpulsatile 12-cm field of moderate intensity (~20 mW/cm^2) with relative ease. However, Carroll *et al.* (1980) have reported that experimentally naive rats do not readily learn to escape from highly intense irradiation when the field is not pulse modulated and, thus, is not acoustically detectable. When given 8- to 10-min exposures at power densities near lethal levels, i.e., in an acoustically undetectable 918-MHz field that results in an *SAR* of 60 W/kg, rats simply do not learn a simple locomotor response that immediately attenuates or extinguishes the field.

The datum of detectability of fields of low-to-moderate intensity in contrast to failure of escape learning in a nearly lethal field may seem a paradox, but actually demonstrates that the continuous presence of a field and its sudden cessation have quite different stimulus properties. Several minutes of 2450-MHz irradiation at 10 to 25 mW/cm^2 or more can produce detectable warming (Stern *et al.*, 1979). However, sudden cessation of the intense RFEM field does not serve as a negative reinforcer, probably because of the large thermal time constants of the mammal's well-hydrated tissues. The field extinguishes, but the elevated temperatures of tissues in which thermal nocireceptors are situated apparently decline too slowly to provide a discernible thermal cue to reinforce an escape response. In agreement with this explanation are data by Levinson *et al.* (1982), who found that rats will learn to escape from an intense field at an *SAR* of 60 W/kg when a photic cue is presented in synchrony with the field.

12.4.1.7 *Human Cutaneous Perception.* All mammals readily detect warming of the body by radiant energy (see, e.g., Adair and Adams, 1980b; Adair, 1983), but longer latencies to detection are the rule as the wavelength of a RFEM field incident on the body's surface is increased (see the reviews by Michaelson, 1974 and by Justesen, 1983b). Data from a recent psychophysical study of absolute thresholds of human detection of 12-cm (2450-MHz) fields and of far-infrared waves are illustrative of a corollary relation: Given fixed periods of irradiation, much more microwave than infrared energy is required to generate a sensation of warmth (Justesen *et al.*, 1982).

Three male and three female observers, all adults, underwent exposure of the ventral surface of the right forearm (mean surface area ~100 cm^2) to CW fields during a succession of 10-s periods. Thresholds of just-detectable warming were determined for each individual. Four of the same observers (two men, two women) also yielded threshold data on far-(non-luminous) infrared irradiation of the forearm. The means of threshold power densities were 26.7 and 1.7 mW/cm^2, respectively, for the microwave and infrared fields. Dosimetric assays with saline models revealed, as expected, that the infrared energy incident on the arm was virtually perfectly absorbed; in contrast, only a third of the incident microwave energy was absorbed. The authors concluded that the same set of thermal receptors was responsible for detection of warming, but that the more deeply penetrating, more diffusely absorbed 12-cm fields required about five times more energy to elevate the cutaneous thermoreceptors to a detectable elevation of temperature. In conformity with this interpretation are (1) a subjective datum—the sensation of warming was identical under infrared and 12-cm irradiation, and (2) a statistical datum—the correlation between

infrared and microwave thresholds of warming of the four men and women approached unity. [The data of Justesen *et al.* (1982) are discussed also in the context of human and subhuman thermoregulation in Section 15.]

12.4.1.8 *The Special Case of Work Stoppage.* A consensual criterion of harm based on *SAR* thresholds of behavioral incapacitation—work stoppage—formed the empirical rationale of the ANSI C95.1-1982 standard. The data base at time of selection of the behavioral criterion consisted of the 1970 report by Justesen and King (rats; sinusiodally modulated, multipath, 2450-MHz field), the 1977 report of Lin *et al.* (rats; CW, near zone, 918-MHz field), the 1977 report of D'Andrea *et al.* (rats; CW or pulsed, 400-, 500-, 600-, and 700-MHz fields in a simulated far field), and the 1979 report of de Lorge (squirrel monkeys; CW, far zone of a 2450-MHz field). Despite the differing carrier frequencies, field zones, and modulation characteristics, disruption of the murine and primate animals' ability to work was associated with a relatively narrow range of threshold *SAR*s (~4 to 9 W/kg). Corresponding thresholds of power density were much more variable (~8 to 45 mW/cm^2) and reflect in their variation the frequency- and geometry-dependent differences in scatter of the incident fields by biological bodies of varying size—differences predicted earlier by Gandhi (1974).

All peer-reviewed, formal reports of *SAR* thresholds of behavioral incapacitation available in the late 1970s to members of ANSI Subcommittee C95-IV, who formulated the C95.1-1982 standard, are based on acute exposure of small mammals. A justifiable concern for absence of data on disabling thresholds associated with *chronic* exposure led Lebovitz (1981; see also Lebovitz and Seaman, 1980) to observe for behavioral disruption in rats repeatedly exposed 3 h daily to a pulsed, 1.3-GHz, circularly polarized field. Individual rats of 3 groups, 15 animals per group, were respectively exposed at mean *SAR*s of 1.6, 3.6, or 6.7 W/kg for 5 d weekly, over a period of 6 to 9 weeks. Three independent groups of sham-irradiated rats (15 in each group) provided control data. All 90 animals performed in an environment at a temperature of 21 ± 1.5 °C. Disruption of photically cued lever-pressing behavior (1 food pellet per 25 consecutive depressions of a small lever) was not observed at any *SAR*, but rates of responding at the highest *SAR* were "slightly reduced" (Lebovitz, 1981, p. 169). During frequent time-outs of the photic cue (when the lever was not illuminated, lever-responding was not reinforced by food pellets), there was an inverse, *SAR*-related decline in mean rates of lever pressing. That is, the discriminative efficiency of the rats (responding relatively less often when food was not available) *increased* as a positive function of *SAR*, a finding observed in rats earlier by Justesen and King (1970).

The basis and implications of *SAR*-related increases of discriminative efficiency are unknown, but Lebovitz's data clearly reveal that lengthy and repeated exposures of the rat to a field at a substantial *SAR* (one that exceeds the species' diurnally averaged, specific metabolic rate, which approximates 4.8 W/kg), is not associated with disruption of appetitively reinforced operant behavior.

Lebovitz did not report data on temperatures of live animals after a 3-h exposure to a microwave field, but D'Andrea *et al.* (1977) found that rats irradiated at an *SAR* of 6 W/kg exhibited an elevation of colonic temperature near 0.5 °C after a 20-min exposure. Although a linear, time-intensity projection of an elevation after a 3-h exposure (estimated $\Delta T = 4.5$ °C) doubtless would overestimate the animals' steady-state thermal response, it is highly likely that Lebovitz's rats, akin to human beings that acclimate to a hotter environment, exhibited thermal acclimation (Gelineo, 1964), which might have been accomplished in part by reductions of metabolic rate (*cf.* Sacher, 1967; Lovely *et al.*, 1983; Justesen, 1983a; see also Section 15).

Other, earlier concerns over the late-1970's data base on field-induced behavioral incapacitation lay in the relatively narrow range of carrier frequencies (400 to 2450 MHz) and of body masses of animal models (~250 to 700 g). de Lorge (1982, abstract; 1983, 1984)[3] has reviewed data from several experiments in his laboratory that shed additional light on power-density and *SAR* thresholds of behavioral disruption for a larger primate (*Macaca mulatta*) as well as for squirrel monkeys and rats, and for frequencies near 5800 MHz as well as for frequencies at 1300 and 2450 MHz.

de Lorge imposed a highly demanding operant task on his rats and his squirrel and rhesus monkeys, one that requires *vigilance* in spatial and temporal *discrimination* of sensory stimuli if the animal is to obtain reinforcers of food. As indicated in Table 12.1, *SAR* thresholds of behavioral disruption are less variable than are power-density thresholds; the respective ratios of highest-to-lowest average threshold values are 3.4-fold (8.4/2.5 W/kg) and 14-fold (140/10 mW/cm^2), a disparity that reflects both the frequency- and the geometry-dependent differences of energy absorption observed in previous studies by other investigators. The disparity is even greater when *SAR* and power-density thresholds are compared across frequencies for a single primate species. For the rhesus monkey at frequencies between 225 MHz and 5.8 GHz, the range of power-density thresholds of work stoppage (8 to 140 mW/cm^2) is substantially greater than the range of *SAR* thresholds

[3] The results reported in the 1983 and 1984 references were available in 1982 and these references, beyond the cutoff date of 1982, are included for the formal record of the information.

TABLE 12.1—*Comparison of power-density and SAR thresholds of behavioral disruption across species and carrier frequencies*[a,b]

Species and conditions	CW 225-MHz field	Pulsed 1.3-GHz field	CW 2.45-GHz field	Pulsed 5.8-GHz field
Norwegian Rat				
Power Density:	—	10 mW/cm^2	28 mW/cm^2	20 mW/cm^2
SAR:	—	2.5 W/kg	5.0 W/kg	4.9 W/kg
Squirrel Monkey				
Power Density:	—	—	45 mW/cm^2	40 mW/cm^2
SAR:	—	—	4.5 W/kg	7.2 W/kg
Rhesus Monkey				
Power Density:	8 mW/cm^2	57 mW/cm^2	67 mW/cm^2	140 mW/cm^2
SAR:	3.2 W/kg	4.5 W/kg	4.7 W/kg	8.4 W/kg

[a] From de Lorge (1982, 1983, 1984).
[b] Values within ±15 percent.

(3.2 to 8.4 W/kg). When the base of comparison is normalized to threshold values at the rhesus monkey's whole-body resonant frequency (225 MHz), the ratio of respective highest-to-lowest ratios, power-density versus *SAR* thresholds, approximates a 7-fold difference, i.e., 17.5/2.6 = 6.7. Given de Lorge's field parameters, the whole-body-averaged *SAR* is, therefore, nearly 700 percent less variable than is power density in predicting the rhesus monkey's threshold of behavioral incapacitation. Also worthy of note in de Lorge's data is evidence that the larger (rhesus) monkey has a higher *SAR* threshold of disruption at supraresonant frequencies than do the smaller (squirrel) monkey and the still smaller rat.

The lowest *SAR* threshold of disruption reported by de Lorge (1983) is based on rats exposed to pulsed, 1.3-GHz fields. The threshold value, 2.5 W/kg, is less than half the highest *SAR* to which Lebovitz's rats were subjected (6.7 W/kg). Because Lebovitz also exposed his rats to pulsed, 1.3-GHz fields but did not observe behavioral disruption, the variable or variables responsible for the difference warrent comment. One can speculate that electrical or thermal hot spots in the brain, or that environmental conditions, especially that of higher ambient temperature, may have been responsible for de Lorge's findings of disruption (his rats performed in an average temperature of 24 °C; in contrast, the temperature in Lebovitz's laboratory was 21 °C). Alternately, or in addition, are the factors of acclimation and demand; de Lorge's rats were exposed for shorter daily durations and less often, and were challenged by a more effort-requiring task than were Lebovitz's rats. Finally, the experimental *history* of the animals may have played a role in their differing *SAR* thresholds. Each of Lebovitz's rats was repeatedly exposed under the same set of field and environmental conditions throughout the tenure of his experiments. In contrast, de

Lorge's rats had earlier been subjected to alternating periods of sham exposure and RFEM irradiation at 5.7 GHz and then, after a 6-month interval, underwent a period during which sham exposures alternated with exposures to a 1.3-GHz field.

The factor of experimental history, embracing, as it were, the potentially interacting variables of aging, shifts in wavelength of applied fields, acclimation and dis-acclimation, and intermittency of exposure, is one of the most neglected aspects of research on the biological response of animal models to RFEM fields. To the extent that subhuman subjects provide valid models of the human condition—and there is little choice but to assume validity when fields at high intensities are at issue—implementation and analysis of differing exposure regimens in the laboratory over the long term offer one of the surest means of simulating exposures of human beings in the industrial and medical settings and of isolating specific etiological factors for further analysis.

The end point of behavioral incapacitation, notwithstanding the incursion of variables associated with differing conditions of exposure over the long term, has emerged as a highly stable, repeatedly reconfirmed marker of field-induced, *SAR*-dependent deficits of function. As an indicant of an effect that is associated with quantities of energy absorbed rather than with quantities of incident energy across a sizable span of species and carrier frequencies, behavioral incapacitation has served as a highly useful criterion and benchmark in the formulation of protective exposure limits. These virtues notwithstanding, the end point of incapacitation (or of any dependent variable based solely on behavior) has a weakness that lies in its empirical rationale—no distinction can be made between thermal effects and effects arising from athermal events, or from thermal-athermal complexing—and in the corollary matter of mechanisms. Disrupted behavior is a smoking gun, but the physiological, biochemical, and biophysical mechanisms associated with altered function are critical factors that require independent analyses. As noted elsewhere (Justesen *et al.*, 1978), behavior is an important sign post, a sensitive phenomenological marker that signals circumstances in which fruitful multidisciplinary inquiry might take place and, indeed, must take place, if the causes of scientific and hygienic advances are to be served.

12.4.2 *Long-term Exposure*

As is true of the reports on human subjects, the earliest reports of CNS and behavioral effects of RFEM fields on animals originated in

Eastern European countries. Many of these reports are based on long-term exposures to radiation at low levels (Dumanski and Shandala, 1974; Lobanova, 1974; Stverak *et al.*, 1974). Several of these studies were presented at the 1973 Warsaw Symposium (Czerski *et al.*, 1974). Alterations of conditional reflexes (Lobanova, 1974) and differences in latency to onset of an audiogenic seizure (Stverak *et al.*, 1974) were reported. The Eastern European investigators in general reported studies in which rats or rabbits were exposed for one to several hours daily over periods of weeks or even months. Power densities are reported to range from as low as 0.6 $\mu W/cm^2$ to as high as 30 mW/cm^2. Both CW and pulsed sources were used.

In one of the first attempts to confirm Eastern European findings, Ferri and Hagan (1975) exposed rabbits to 2.45-GHz CW fields at 10 mW/cm^2 for 8 h daily 5 d weekly over an 8- to 17-week period. The only differences observed between exposed and control rabbits were slight reductions in food and water intakes during the first week of exposure. In another early study, rats were exposed for two weeks to 9.4-GHz pulsed fields at 7 mW/cm^2 (Gillard *et al.*, 1976). The authors state that the exposed rats were slower to move about, i.e., exploratory activity was depressed, when they were subjected to a standard, open-field test.

Moe *et al.* (1976) exposed male rats to 918-MHz CW fields at *SAR*s of 4 to 7.5 W/kg for 10 h per night for 3 consecutive weeks (*cf.* Lovely *et al.*, 1983). The animals showed decreased food consumption and lower blood-glucose levels. The animals were fed diurnally during periods between exposures. During 3 separate nocturnal periods, the exposed animals, as compared with sham-exposed controls, showed lower overall activity as well as a different activity distribution as a function of circadian period. In a follow-up study (Lovely *et al.*, 1977, abstract, 1983) male rats were exposed for 10 h per night for 13 weeks to 918-MHz CW fields at an *SAR* of ~2 W/kg. Exposure at the lower *SAR*s did not result in any of the previously observed changes of behavior.

In contrast to the finding that irradiation reduced activity, Mitchell *et al.* (1977) reported increased locomotor activity by and disrupted performance of rats on an operant schedule that differentially reinforced low rates of responding (DRL). The female rats were irradiated at power densities of 5 mW/cm^2 5 h/d over 22 weeks at a frequency of 2.45 GHz. Activity in this study was measured on an activity platform, whereas activity in the studies mentioned above (Moe *et al.*, 1977; Lovely *et al.*, 1977, abstract) was measured by scoring an animal's behavioral repertoire, i.e., resting, eating, drinking, grooming, and activity during selected periods of time.

The differences that can be obtained by different methods of measuring activity were further confirmed in an investigation by D'Andrea *et al.* (1979). They exposed Long-Evans male rats for 16 weeks to 2450-MHz CW fields at an average power density of 5 mW/cm^2 (*SAR*, 1.23 W/kg). All animals were exposed 8 h/d, 5 d weekly in a Plexiglas holding cage that restricted movement. A variety of measures was taken, including two tests of activity. During the 12-h periods between exposures, locomotor activity was measured by the number of revolutions made by an animal in a running wheel that was adjacent to the home cage. At 14-d intervals, animals were placed on a stabilimetric platform immediately after exposure. Movement by an animal on this platform triggered a microswitch, each closure of which was recorded as a single unit of activity. The analysis of the two measures showed that stabilimetric activity was reduced in the RFEM-exposed group, but that home-cage activity, as assessed by the revolutions of the running wheel, did not differ between sham- and field-exposed subjects.

12.5 Effects of Prenatal Exposures

Results of studies in which subjects were exposed *in utero* to irradiation are presented in Section 6 on Reproduction, Growth, and Development. However, several of these investigations included postnatal behavioral measures of prenatally exposed animals. Teratogenic effects and learning ability were assessed in one of three separate studies conducted on C3H/HeJ mice exposed to 2450-MHz fields (Chernovetz *et al.*, 1975). In these studies, 10-min exposures (*SAR*, 38 W/kg) were factorially combined with dosing of primagravid dams with an established teratogen, cortisone. Dams in the survival and reversal-learning studies were treated on gestational day 14. There were 15 litters of pups in each of 4 treatment conditions. Only 2 fetuses survived the cortisone treatment as compared with 25 survivors in the combined-treatment group, 93 in the exposed-alone group, and 81 in the sham-exposed group. The difference in survival between the cortisone and the cortisone-and-exposed groups was unexpected in light of the findings from the prior teratology study: The combined treatment resulted in the highest incidence of structural abnormalities. The reversal-learning study, which consisted of original learning plus 3 consecutive reversals, was conducted with 3 groups of surviving pups. Performance was measured in a Lashley-III maze as modified for swimming. The combined treatment, but not the exposure-alone treat-

ment, was associated with a modest impairment in learning of the original habit. Performance across the 3 reversals was statistically indistinguishable among the 3 groups of offspring.

In another study, Johnson, R. B. *et al.* (1977) exposed rats *in utero* to 918-MHz CW fields at an *SAR* of ~2 W/kg. The animals subsequently were tested as adults. The prenatal exposures continued 20 h/d during 19 d of gestation. As adults, the male offspring that had been individually housed and the female offspring that had been group housed demonstrated a defect in acquisition of a conditioned-avoidance habit; a rat was required to traverse the runway of a shuttlebox within 10 s after the presentation of an auditory signal to avoid a footshock. Frequency of escape from the shock and of responses to extinction of the avoidance were also recorded but no statistically significant differences were observed. Individually housed female rats as well as group-housed male rats showed no impairment on any of the tasks as compared with sham-exposed controls. Evaluation of these data is difficult because the small samples involved render the majority of the comparisons of doubtful statistical reliability. However, the study was repeated at 2450 MHz and similar results were obtained (Mizumori *et al.*, 1979).

12.6 Behavioral Thermoregulation

As indicated in Section 15, exposure to RFEM fields can alter the ongoing thermoregulatory behavior of an animal. Adair and Adams (1980b) studied squirrel monkeys (*Saimiri sciureus*) that had been trained to regulate environmental temperature during exposure to a 2450-MHz CW field. During periods of exposure, a monkey was restrained in a chair in an anechoic chamber. The monkey had been trained to pull a response cord to select an alternating flux of air at 15 and at 55 °C to achieve a preferred core temperature. All experimental sessions were conducted in the presence of a 73-dB-SPL (standard pressure level) masking noise to control for any auditory cues as to presence or absence of the field. Power densities ranged from 1 to 22 mW/cm^2 (*SAR*, 0.15 to 3.25 W/kg). Ten minutes of exposure at power densities of 6 to 8 mW/cm^2 resulted in the selection of a lower temperature. This threshold (6 to 8 mW/cm^2) corresponds to a whole-body *SAR* of 1.1 W/kg, which is approximately 20 percent of the resting metabolic rate of the squirrel monkey in a thermoneutral environment. Thermoregulatory behavior was highly efficient, and skin and rectal temperatures remained stable.

More information on temperature regulation is given in Section 11 on Interactions with the Nervous System. Other studies dealing with models of thermoregulation and specifically with physiological and behavioral mechanisms of thermoregulation in human beings and laboratory animals are covered in detail in Section 15.

12.7 Drug-Field Interactions

A series of studies that has sparked considerable interest and controversy focused on alteration of schedule-controlled behavior in animals trained to respond under the influence of psychoactive drugs. Thomas and Maitland (1979) reported that a 30-min exposure to pulsed 2450-MHz fields (2-μs pulse width, 500 pps) at an average power density of 1 mW/cm^2 following injection of varying doses (0.25 to 5.0 mg/kg) of dextroamphetamine produced a reduction in the dose necessary to alter performance on a DRL schedule. The authors reported that the *SAR* was near 200 mW/kg.

Thomas *et al.* (1979) extended the work on field-drug interactions by dosing rats with chlordiazepoxide. Rats were trained to make an operant response on a 1-min, fixed-interval schedule of reinforcement. The exposure parameters were the same as those of the Thomas and Maitland (1979) study. A 30-min exposure to the pulsed field following injection of chlordiazepoxide resulted in potentiation of the drug effect.

One problem in interpreting these drug-field-interaction studies is that, to date, they have not been confirmed independently. Also, the studies were performed in the near field, and so it is difficult to determine the *SAR* associated with these near field exposures. Lovely *et al.* (1981) attempted to extend the chlordiazepoxide findings to the far field. Except for the distance from the source and for the animal holder used by Thomas *et al.*, all conditions of their study were replicated. No drug-behavior interactions were observed in these studies. Attempts by Sessions (1981) to produce an effect on fixed- or variable-interval responding by rats following exposure to a 2450-MHz pulsed field in a waveguide also yielded no evidence of drug-field interaction.

12.8 Summary and Conclusions

Several conclusions regarding the behavioral response to RFEM irradiation can be drawn that enjoy a substantial consensus among

scientists of many disciplines:

1. Behavior not only provides a highly sensitive index of field-body interactions, but a broad spectrum of end points. A single pulse of RFEM energy can be heard by human beings and experimental animals, the threshold of perception requiring but a few millijoules per kilogram of body mass. The threshold of convulsive activity, which anchors the near-lethal side of the behavioral spectrum, requires absorption of energy six orders of magnitude greater.
2. Lying between the extremes of auditory-perception and convulsive thresholds are intermediate end points of threshold sensitivity that include detection of cutaneous warming, field-drug interactions, endurance, impaired performance, and work stoppage. It is within this intermediate range of end points that consensus is lost and controversy begins. At least for acute exposures, the problem lies not in stability of thresholds—*SA* and *SAR* thresholds are often remarkably stable within animals of a species in a controlled environment—but in the interpretation of the implications of an altered behavior. Perception of warmth is an effect, but is it indicative of insult and injury? Enhancement of the pharmacologic activity of a drug is an effect, but is it evidence of facilitation or debilitation? The behavioral incapacitation that is reflected in the work-stoppage end point could be an indicant of harm, but where below this threshold does a body of scientific or medical experts draw a definitive line for permissible levels of irradiation? That is a question that cannot be answered solely in the behavioral laboratory; only a concerted and integrated effort involving researchers of many disciplines—and many experiments yet-to-be performed—can provide answers that will summon an unimpeachable consensus.
3. Among the experiments yet-to-be performed are those that address at all levels of biological analysis the greatest void of scientific knowledge: The systemic and functional responses of the organism that are observed over the long term after intense (acute) or low-level (chronic) exposures to fields that range the spectrum and that are evaluated for modulation-specific influences.

13. Cataractogenesis

13.1 Theoretical and Experimental Models

The absorption of RFEM energy at microwave frequencies has been shown experimentally to result in damage to ocular tissues. The site of damage depends on the radiation frequency and on the mode of exposure, whereas the magnitude primarily depends on the power density of the field, the quantity of absorbed energy, and the duration of exposure (Cleary, 1970). The lens is the ocular tissue of greatest sensitivity to fields at frequencies in the range of 1 to 10 GHz. This sensitivity arises from the absorption characteristics of mammalian ocular structures and from the mitotic and metabolic status of lens fibers and their avascularity, which predispose them to thermal damage. The lens fibers, being from post-mitotic cells of limited metabolic capacity, are subject to a relatively greater degree of irreversible damage than are most other tissues. The high detectability of lens changes resulting from microwave fields and other types of radiation such as ionizing radiation is attributed to the fact that damage to lens fibers, which is manifested in opacification of the lens, is readily observable because of the transparency of the pre-retinal ocular struc-because of the transparency of the pre-retinal ocular structures.

The paracrystalline state of the soluble proteins that comprise most of the interior of the lens fibers confers the high degree of spatial order in the intact fibers, which accounts for their transparency (Trokel, 1962). Opacification of lens fibers may thus be attributed to any physical, chemical, or metabolic stress that alters the paracrystalline state of lens proteins. A number of such agents has been demonstrated to produce lens opacification, but the basic mechanisms are not well understood.

Although subject to various interpretations, the term "cataract" generally refers to a degree of lens opacification that results in loss of visual function and, in its extreme manifestations, in blindness. In addition to metabolic stress and to physical and chemical trauma, cataracts also have been associated with congenital anomalies of genetic or viral origin, and with senescent changes in many individuals. Recently, it has been recognized that in the case of sugar-induced cataracts, polyol accumulation leads to osmotic imbalance in the lens fiber, indicating a possible involvement of lens-fiber membranes in

cataractogenesis (Kinoshita, 1974). In senile cataracts there is evidence that the opacification is due to light scattering by aggregates of soluble lens proteins (Roy and Spector, 1976). There has never been a direct demonstration of the involvement of an alteration in protein synthesis in cataract formation. Piatigorsky and Shinohara (1977) have found, however, that the synthesis of the principal crystallin of the embryonic chick lens, δ-crystallin, is reversibly affected during the initiation of cataract formation *in vitro*. That a reversible biochemical event has been shown to occur during the development of cataracts indicates that the study of the etiology of cataracts cannot be limited to lenses in which mature cataracts have formed (Piatigorsky and Shinohara, 1977).

Immediate ocular effects of acute irradiation of rabbits include lacrimation, edema of lid and conjunctiva, enophthalmos, miosis, pupillary constriction, and anterior chamber turbidity, the extent of which depends on the field intensity and exposure duration. Such reactions also include hyperemia of limbal and iris vessels and vitreous floaters and filaments, all of which are reportedly transient in nature, persisting for a few days following cataractogenic RFEM exposures (Williams *et al.*, 1955; Carpenter, 1958; Guy *et al.*, 1975). The latent period for the development of lens changes that are detectable by slit-lamp biomicroscopy has been found to be inversely related to exposure intensity. Typically, following exposure to 2.45-GHz fields in the range of 100 to 300 mW/cm^2, lens changes in rabbits are first seen 24 to 48 h post exposure. At the lower end of this intensity range, minor degrees of lens change, which are often reversible, consist of a milky band in the posterior cortex immediately adjacent to the posterior capsule, which extends to the equatorial zone. In addition, a chain of vacuoles or small vesicles is observed in the vicinity of the posterior suture. Guy *et al.* (1975b) have reported that higher intensity microwave fields cause more pronounced and permanent changes consisting of denser banding, of an increase in the number of vacuoles, and of a well-defined circumscribed opacity in the posterior-lens cortex that is detectable with an ophthalmoscope. In some instances, large vesicles appear at the equator of the lens, and, in some cases, the posterior cortical opacity involves not only the equator but extends to the anterior subcapsular cortex. Usually, however, microwave cataracts in the rabbit are confined to the cortex of the posterior lens. When irradiation is highly intense, the entire lens becomes opacified (Guy *et al.*, 1975b).

Histopathological changes associated with the development of RFEM cataracts have been described by Carpenter (1977a). Lens fibers in the posterior subcapsular cortex become hydropic and slightly

swollen. Small vesicles are seen during the first two days post exposure. By the fourth day post exposure, the epithelial cells have migrated posteriorly from the equator under the lens capsule, and numerous mitotic figures indicate cellular proliferation. During the subsequent 5-d period, swollen "balloon" cells appear at the equator or in the posterior cortex, which reportedly represent abortive attempts of damaged cells to differentiate into lens fibers. During the third to fifth week post irradiation, many nucleated cells and lens fibers are found in the posterior cortex, as are cysts that contain protein aggregates and cellular debris. Regions of highly swollen or denatured fibers are histopathological characteristics of lens opacities. Carpenter concludes that such histopathological changes are not characteristic of lens changes induced by conventional heating.

Cataract induction in experimental animals, principally New Zealand white rabbits, has been described by a number of investigators that have used a variety of exposure modalities (Appleton *et al.*, 1975; Carpenter, 1958; Guy *et al.*, 1975b). In general it has been reported that field intensities associated with acute induction of cataracts in the rabbit are of such a magnitude that whole-body exposure results in hyperthermic lethality. Consequently, most investigations have involved the use of focused or near-zone fields that have limited the exposure to the head or eye. Even under such exposure conditions, thermal trauma to the animals is of such a magnitude that local or general anesthesia has generally been necessary. Corneal irrigation has also been employed in such studies to prevent corneal damage due to dehydration during exposures greater than one hour. Schwartz and Feller (1962) have shown that anesthesia and corneal irrigation, as well as air temperature and humidity, significantly affect the temperature of ocular structures. Because it has generally been assumed that cataract induction is wholly or predominantly a thermal effect, such factors complicate the interpretation and comparison of results of experimental studies. These factors also introduce a degree of uncertainty in application of results to assessment of cataract induction in human beings.

The extrapolation of results of animal experimentation to the human case is further complicated by marked anatomical differences in the head and in the position of the eye in the skull. Carpenter *et al.* (1974) have shown that at a frequency of 2.45 GHz, the measured field intensity at the position of the head of a rabbit was reduced 40 percent by the presence of the animal in the field, and a further reduction in field intensity of 40 percent was effected by fastening the animal's ears against its back. A direct comparison of cataractogenic thresholds in rabbits and rhesus monkeys exposed in the same 2.45-GHz, cavity-

backed, resonant-slot radiator has been reported by Kramar *et al.* (1978). In this study, cataracts were induced in rabbits exposed for 140 minutes at 180 mW/cm^2, whereas the monkeys sustained facial burns but no lens damage at power densities to 500 mW/cm^2. The difference in thresholds is attributed to species' differences in the anatomical configuration of cranial and ocular structures.

Frequency- and orientation-dependent factors have not been investigated with respect to field distributions in the eyes of human models exposed to RFEM fields. It is well known that absorption of RFEM fields by a lossy dielectric scatterer, such as the mammalian head, is a function of its shape and dimensions. The heating potential of RFEM radiation at a given frequency may, therefore, differ significantly both with respect to location and magnitude for an experimental animal such as a rabbit as compared with man. Because it is not possible to determine experimentally RFEM heating patterns in the human eye, the only alternative is to apply theoretical methods and to simulate ocular-tissue geometry and thermodynamics. Although a number of investigators has attempted to determine theoretically field-induced heating patterns in human (Taflove and Brodwin, 1975) and rabbit ocular structures (Al-Badwaihy and Youssef, 1975; Emery *et al.*, 1975) limitations of computer methodology and/or mathematical complexities have not permitted detailed determinations of such patterns.

Theoretical methods applied to the calculation of RFEM heating patterns in the rabbit eye by Emery *et al.* (1975) have revealed frequency-dependent temperature distributions that agreed well with experimental determinations. Frequency-dependent heating patterns in the rabbit are attributed to resonances of the eye-scatterer and of the head as a whole. At frequencies below approximately 1.5 GHz, the dimensions of the orbit-eye combination are too small to result in field concentrations. Consequently, any peaking of energy absorption would be due to whole-head resonance. At frequencies greater than 1.5 GHz, it has been theoretically determined that the eye-scatterer can support resonance independent of possible field-concentration effects of the head. It may be concluded that peaks of heating may occur within rabbit ocular tissues at frequencies greater than 1.5 GHz (Taflove and Brodwin, 1975). The limitations imposed on the applicability of data derived from animal studies of field-induced ocular damage resulting from frequency-dependent resonance phenomena must be taken into account in the assessment of human cataractogenic potential of RFEM exposure.

The effects of acute exposure of the eyes of experimental animals, predominantly rabbits, have been found to depend on the field frequency and intensity and on exposure duration. Pulse-modulated fields

have not produced ocular effects that differ qualitatively or quantitatively from those produced by CW fields of equal average intensity (Birenbaum *et al.*, 1969a).

13.2 Cataractogenesis in Experimental Animals

Time-intensity relations in the induction of cataracts in rabbits have been determined for fields at frequencies of 2.45, 5.4, 5.5, 8.2 and 10 GHz (Guy *et al.*, 1975b; Birenbaum *et al.*, 1969b; Carpenter *et al.*, 1960a,b; Carpenter and Van Ummersen, 1968; and Williams *et al.*, 1955). These experiments, which were conducted in the near field on animals under anesthesia, involved a variety of field-measurement techniques such that a quantitative comparison of the data from different laboratories is not possible. The general procedure employed in these studies was to determine the minimal exposure time required to induce rapid opacification of the lens (i.e., changes detectable within the first few days post exposure) at a given field intensity. Although exact comparisons of results are not possible, when similar dosimetric methods were used by different investigators, there was a high degree of concordance in the relation between time-intensity and opacification (Guy *et al.*, 1975b). In all instances, however, the hyperbolic form of the curves is indicative of a dose-reciprocity relationship, i.e., lens opacification in the rabbit, when arising from a single exposure, is a threshold phenomenon related to the *SA*. Figure 13.1 summarizes time and power-density thresholds of cataract formation in rabbits exposed to near-zone, 2.45-GHz radiation as determined by various investigators (Guy *et al.*, 1975b; Carpenter and Van Ummersen, 1968; Williams *et al.*, 1955). Under these conditions of exposure, cataracts were not produced at intensities below 100 mW/cm^2 during exposures as long as 100 minutes.

The effects of multiple exposures of the rabbit eye to 2.45-GHz radiation under duration-intensity parameters that are non-cataractogenic for single exposures were reported by Carpenter *et al.* (1960a, b). Having established that the minimal duration of a cataractogenic CW irradiation at 420 mW/cm^2 was 5 minutes, they reduced the exposure period to 4 minutes but repeated it at 24-h intervals for a total of 4 exposures. Of the 8 animals thus irradiated, 4 developed marked cataracts and 4 showed only slight effects. When 4-min exposures were carried out at weekly intervals in 7 animals, extensive cataracts developed in 2 cases after 2 exposures, minimal changes were noted in 3 lenses after 4 exposures, and in 2 cases there was no effect. When the interval between the 4-min exposures was increased to 2

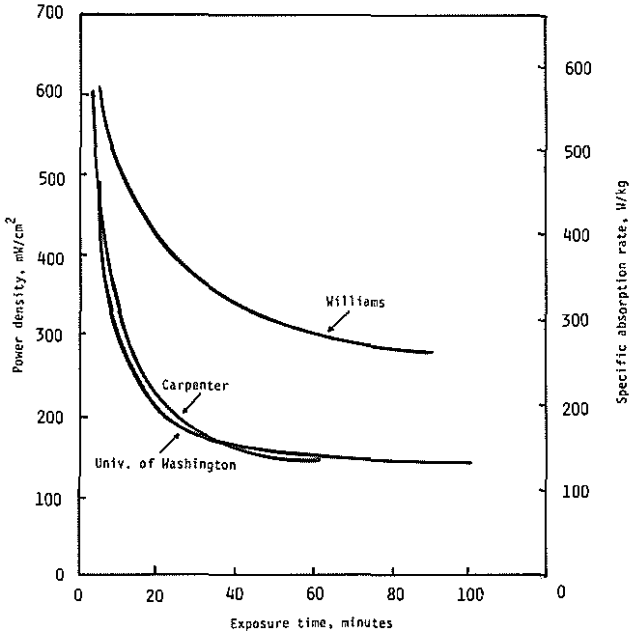


Fig. 13.1. 2.45-GHz, near-field, intensity-time and calculated retrolental-*SAR*-time thresholds for lens-opacity induction in rabbits by acute exposures. (After Emery *et al.*, 1975.)

weeks, opacities developed in 3 of 8 rabbits after 3 exposures. When the eye was irradiated for only 3 min, which was 60 percent of the cataractogenic threshold for a single exposure, lens opacities developed after 5 such exposures given at daily intervals or after 3 exposures given at 4-d intervals. However, when the interval between exposures was increased to 1 week, 5 successive weekly exposures failed to have a cataractogenic effect on the lens in all of 5 experiments.

Carpenter *et al.* (1977) concluded from these results that the cataractogenic effect of the radiation involves initiation of a chain of events in the lens, the visible end result of which is an opacity, and that this chain of events must itself be initiated by a field of adequate power density acting for a sufficient duration of time if it is to produce an opacity. If either the power density or the duration of the irradiation are below a certain threshold value, then the damage done to the lens is reparable and recovery can occur, providing that sufficient time elapses before a subsequent similar episode. In the experiments described in the previous paragraph, it appears that the interval necessary for recovery after the damage done by a 3-min exposure must be greater than 4 d but need not be longer than a week. The authors, therefore, reached the general conclusion that, if the interval of time

between successive sub-threshold exposures is not adequate for repair of the radiation inflicted damage, then the residues of damage accumulate and cause the development of an opacity. In this sense, therefore, it can be said that RFEM fields may exert a cumulative effect on the lens, so that irradiation causing no apparent effect when applied a single time can inflict permanent damage when repeated at daily or even weekly intervals.

Carpenter *et al.* (1974) performed additional experiments in which lower power densities and a longer duration of exposure were employed. Nine rabbits were exposed 20 to 24 times for 1 h daily at a power density of 142 mW/cm^2. A lens opacity was induced in only 1 rabbit. Four of 10 animals developed opacities when the eye was exposed 18 to 32 times for 1 h daily at 178 mW/cm^2. At an intensity of 219 mW/cm^2, 13 to 20 daily exposures of 1 h each resulted in opacities being formed in 8 of 10 rabbits, although a single 1-h exposure at this intensity produced no opacities in 7 rabbits. However, when the duration of a single exposure at 219 mW/cm^2 was increased to 4 or 4.5 h, a small central opacity did develop. On the other hand, a single exposure lasting 5.5 h was without effect. A 1-h exposure at these power densities did not require anesthesia of the animal.

It should be noted that the values given for power densities in all the experiments on cumulative effects represent a correction of previously reported data (Carpenter, 1979).

Most investigations of experimental RFEM-induced cataractogenesis have, as indicated, involved single or multiple sub-threshold exposures in the intensity range of 80 to 500 mW/cm^2. In a chronic study at low intensities, Ferri and Hagan (1975) exposed 6 unanesthesized rabbits to 2.45-GHz CW radiation in the far field at an intensity of 10 ± 3 mW/cm^2 for 8 h/d, 5 consecutive days a week for 8 to 17 weeks. Six months of observation failed to reveal any abnormal ocular changes in the exposed animals.

The results of investigations of the time-intensity relation for cataract induction in the rabbit, as well as experimental determinations of microwave-induced ocular heating, indicate the involvement of thermal damage to lens tissue. For single, acute, near-field exposures of the rabbit there is an apparent temperature threshold near 41 °C for lens opacification; the effect also has been shown to depend on the duration of temperature elevation. Repeated exposures at intensities that do not induce elevations of temperature to 41 °C, however, have been shown to induce opacification depending on the duration and number of exposures, which indicates a cumulative component of RFEM-induced lens damage that depends on the time-temperature history of the exposed tissue (Cleary, 1970). Elevations of the lens

temperature to a comparable level by conventional means has, on the other hand, failed to result in cataracts. Radiation, therefore, appears to exert a unique time-intensity component of thermal stress in the induction of opacification of the mammalian lens.

The involvement of thermal phenomena in cataractogenesis has been investigated by the alteration of ocular temperatures by means of whole-body or localized hyper- or hypothermia. Whole-body hypothermia of dogs was used to limit the elevation of intraocular temperature during exposure to cataractogenic, 2.5-GHz fields. Cataracts were induced in normothermic eyes by Baillie (1970) but not in the eyes of animals subjected to whole-body hypothermia at 22 °C, which led the investigator to conclude that RFEM-induced cataractogenesis is directly or indirectly a thermal phenomenon occurring when intraocular temperature exceeds 43 °C. Similar conclusions were derived from studies of whole-body hypothermia of rabbits in which a 2.45-GHz field was used to induce intraocular temperatures below 41 °C, and no lens opacification was detected (Kramar *et al.*, 1975).

The hypothesis that lens opacification is solely due to heating was subsequently investigated by Kramar *et al.* (1976), who subjected rabbits to localized or whole-body hyperthermia by heating them in water jackets. The water was hot enough to raise retrolental temperature to 42 °C for a period of 30 min or more. No detectable lens opacification resulted from such treatment despite intraocular temperatures (and temperature distributions in the case of localized ocular heating) that attained levels associated with field-induced cataracts.

The effects of localized heating and the combined effect of localized heating and RFEM exposure at sub-threshold cataract intensities have also been investigated by Carpenter *et al.* (1977). In these experiments, it was found that when the rabbit eye was heated at the same rate, to the same temperature, and for durations equal to those experienced during cataractogenic RFEM exposures, localized heating did not produce cataracts with the exception of one case, which was attributed to severe uveitis rather than to a direct lenticular effect. Cataracts were not observed during a 10-day post-exposure period in eyes of 5 rabbits heated to 59 °C for 30 min, in contrast to the effects of ocular heating by microwaves. In another series of experiments, the rabbit's body temperature was increased by raising the environmental temperature of the ears in conjunction with RFEM exposure at an intensity sufficient to increase the retrolental temperature to a level normally associated with cataractogenic insult. In only 3 of the 10 animals so exposed were opacities induced in the posterior cortex of the lens, and, in two instances in which there was opacification, the RFEM exposures were 90 and 91 percent of the 40-min cataractogenic exposure. In the

third case, the eye exposed to 76 percent of the cataractogenic exposure developed opacities in the posterior subcapsular cortex of the lens 4 d post exposure (Carpenter *et al.*, 1977). The results of these experiments indicate that microwave cataractogenesis is not solely a thermal effect, but that it also depends on other, undetermined factors that are specifically related to the mode of absorption of radiation by the mammalian eye.

Experimental studies of exposure to RFEM radiation in the frequency range of 0.385 to 107 GHz have revealed qualitative, frequency-dependent differences in the effects on ocular tissues. Of those frequencies that have been investigated to date, the induction of lens opacities has been restricted to the range from 0.8 to 10 GHz. Although the majority of the studies in this frequency range has been at 2.45 GHz (Carpenter, 1958; Carpenter and Van Ummersen, 1968; Carpenter *et al.*, 1974; Kramar *et al.*, 1973; Williams *et al.*, 1975; Richardson *et al.*, 1948; Daily *et al.*, 1952; Imig and Searle, 1958; Guy *et al.*, 1975b), opacities have been reported to result from exposure at 800 MHz (Birenbaum *et al.*, 1969b); at 2.8 GHz (Seth and Michaelson, 1965); at 3 GHz (Appleton *et al.*, 1975; Belova and Gordon, 1956); at 4.2, 4.6, 5.2, 5.4, 5.5, and 6.3 GHz (Birenbaum *et al.*, 1969a); at 5.5 GHz (Birenbaum *et al.*, 1969b); at 8.23 and 9.37 GHz (Carpenter, 1962); and at 10 GHz (Carpenter and Van Ummersen, 1968; Carpenter, 1962; Richardson *et al.*, 1957).

Although the rabbit was the subject in these experiments, the differences in the experimental procedures, such as the mode of application of the RFEM energy and the field-measurement techniques, precludes a comparison of the relative cataractogenic potential of these radiation frequencies except in the case of the series of experiments reported by Birenbaum *et al.* (1969b). In this investigation a dielectric-waveguide-insert adapter was used to apply pulsed fields at various frequencies directly to the corneal surface of the eye. The field strengths at various frequencies that ranged from 4.2 to 6.3 GHz were held constant, and the exposure time was varied to establish cataractogenic thresholds. An inverse relation was found between frequency and exposure time such that as frequency was decreased, longer exposure times were needed to produce lens opacification. These results indicate that as frequency is increased (in this range), the field intensity required to produce opacification decreases. However, it should be noted that, in these experiments, the opacities developed in the anterior cortex of the lens, in contrast to those in the posterior subcapsular lens, when microwave energy was applied across an air space (see Carpenter, 1962). Cataractogenic thresholds depend, therefore, on the mode of application of the microwave field.

A comparison of cataractogenic effects of 2.45- and 10-GHz fields was carried out by Hagan and Carpenter (1975), who used dielectric lenses to concentrate the radiation on eyes of rabbits. Based on the results of this study, it was concluded that, when the rabbit eye is subjected to a single acute exposure, the cataractogenic potential decreases as the frequency is increased from 2.45 to 10 GHz. At the higher frequency, temperature measurements revealed that the aqueous humor of the anterior chamber (anterior to the lens) was heated to a greater extent than it was at the lower frequency, for which the maximal temperature elevation occurred in the vitreous body posterior to the lens (Hagan and Carpenter, 1975). The results of this study agree qualitatively with theoretical predictions based on the inverse relation between RFEM frequency and penetration depth in lossy dielectric material such as tissue.

The inverse relation between frequency and penetration depth has been demonstrated by Rosenthal *et al.* (1975) in an experimental study of effects on the rabbit eye exposed to 35- and 107-GHz fields. Effects of acute exposures at these frequencies were limited to the corneal stroma, indicating that maximal field absorption and heating occurred in the superficial regions of the eye, as predicted by theory. The 107-GHz radiation was found to be more effective in producing immediate stromal damage to the cornea. The damage was repaired within 24 h post exposure, in contrast to the effects of 35-GHz radiation, which was more persistent and was associated with a significant degree of epithelial damage. At both frequencies, field-induced keratitis occurred at intensities lower than those required to produce other ocular effects such as iritis or lens opacification (Rosenthal *et al.*, 1975). The experimental conditions employed in this investigation prevent exact comparisons of field-intensity thresholds for corneal damage at higher frequencies with cataractogenic thresholds at lower frequencies, except to the extent that intensities and exposure times were of the same order. That no ocular effects were detected in experiments conducted by Cogan *et al.* (1958) at 385 and 468 MHz is consistent with the hypothesis that ocular damage is directly dependent upon localized energy deposition, which, in turn, is determined by the relation between the physical characteristics (i.e., dimensions and shapes) of ocular tissues and the wavelength of the radiation.

Biochemical techniques have been employed in the study of the etiology of RFEM-induced cataracts. A 23-percent reduction in ascorbic-acid concentrations was detected in rabbit lenses 6 to 18 h post exposure to radiation (Merola and Kinoshita, 1960). Cultured rabbit lenses were found to lose ascorbic acid in an intensity-dependent fashion that was interpreted by Weiter *et al.* (1975) as being thermally

induced. Rabbit lenses were maintained in a culture medium and were exposed either to pulsed or to CW S-band radiation for 10 to 15 min at intensities to 200 mW/cm^2. Ascorbic acid in the lens was measured 1 to 3 d post exposure. Control lenses treated under the same time-temperature conditions as the irradiated lenses exhibited the same decrease in ascorbic acid as did the irradiated lenses. No difference was noted between ascorbic-acid levels in lenses exposed at a given average field intensity by pulse modulated or by CW radiation. The authors concluded that the change in ascorbic-acid concentration is a sensitive index of lens injury, even if the decrease is not a primary event in RFEM-induced cataractogenesis.

The effects of single and multiple RFEM exposures on ascorbic-acid levels in the vitreous, lens, and aqueous humors, at post-exposure times ranging from 5 min to 5 weeks, have also been reported (Ferri, 1977). Lens concentrations were unaltered with the exception of a 25 percent decrease at 1 week post exposure, at which time lens opacification appeared. Ascorbate levels in the vitreous humor were unaltered by the exposures, but the levels in the aqueous humor decreased continuously following acute exposures for periods to 1 week, after which time the levels increased, reaching normal values at 2 weeks post exposure. In an attempt to relate biochemical alterations to the mechanism of lens opacification, Ferri (1977) studied the relative effects of RFEM exposure and conventional hyperthermia on ascorbic-acid levels in the aqueous humor under *in-vivo* and *in-vitro* conditions. When the aqueous humor was conventionally heated, the ascorbate levels increased; in contrast, decreased levels resulted from RFEM exposure. These findings led the investigator to reject the hypothesis that temperature alone causes reduced levels of ascorbate in the lens. The hypothesis advanced by Ferri (1977) is that cataractogenesis is a secondary reaction and that the primary or initiating damage by exposure may not be at the site of the lens but might occur at some other sensitive site and ultimately appears as lens opacification.

The effect of cataractogenic doses of 2.45-GHz CW radiation on the mitotic activity of the lens epithelium of the rabbit was investigated by Van Ummersen and Cogan (1976) by the technique of autoradiography. Two patterns of response were detected as defined by the presence or absence of strings of vesicles in the exposed lenses. Lenses in which vesicle strings were not induced showed an initial, pronounced suppression of mitotic activity followed by a gradual return to normal levels by 20 d post exposure. Lenses with vesicle strings, on the other hand, showed a precipitous transient increase in mitotic activity on the fourth to fifth day after exposure that returned to normal levels by 30 d post exposure. The results were interpreted as indicating that

the vesicles represented hydration of the lens and acted as a stimulus that caused the overlying epithelial cells to proliferate at an accelerated rate. In irradiated lenses in which equatorial vesicles did not develop, the mitotic activity of the lens epithelium followed a course similar to that observed after exposure to ionizing radiation. It was concluded that the earliest effect of RFEM radiation on the rabbit lens epithelium is inhibition of DNA synthesis and mitosis during the 6-h to 25-d period post exposure. Forty-eight hours after exposure, the level of DNA synthesis and mitotic activity indicated some recovery of the epithelial cells and in 2 weeks returned to normal.

The results of Van Ummersen and Cogan's study indicate that RFEM-induced cataractogenesis involves alteration of lens epithelial cells. The transient nature of this epithelial effect may be interpreted as evidence of a recovery period of 10 to 20 d during which time cellular damage is repaired. The existence of a transient alteration in cell function after irradiation is consistent with experimental studies of cataract induction by repeated exposure at sub-threshold levels in which cataract-induction was found to depend inversely on the interval between successive exposures (Carpenter and Van Ummersen, 1968).

The induction of ultrastructural alterations in rabbit lenses exposed to RFEM fields has been described by Williams *et al.* (1975). Electron-microscopic assay of lenses exposed to cataractogenic doses of S-band radiation revealed marked deformation of cells of the immediate subcapsular region of the lens. The cells were swollen and vacuolated, and many contained coarsely granular and clumped cytoplasm. In some instances, the only detectable abnormality involved the interdigitating processes of the cell membrane, which were noted to be unusually electron dense and irregular with some evidence of membrane reduplication and degeneration.

In rabbits exposed to 165-mW/cm^2 fields 20 min/d, twice daily, 5 d/week for a total of 36 exposures, the lenses appeared normal by slit-lamp examination at the time of sacrifice, 5 d after the last exposure. Morphological alterations were detectable, however, by electron microscopy, which revealed that the fibers of the posterior subcapsular cortex were enlarged and contained large intercellular clefts. The outermost cortical fibers of the lens equator were also found to be extensively altered. In this region, cells containing several cysts or vacuoles, and surrounded by thickened and fragmented membranes, were also found, indicating the destruction of organelles that are found in abundance in this region of the cell (Williams *et al.*, 1975). The results of this study indicate that RFEM exposures at levels that induce cataracts result in extensive damage to the membranes of lens

fibers, and that less severe, but still obvious, damage may be induced by exposures that do not result in lens damage detectable by slit-lamp biomicroscopy.

The great majority of experimental reports of RFEM-induced cataracts has involved the rabbit, usually while the animals were irradiated under anesthesia. Work on a species more closely related to man (*Macaca mulatta*) was performed without the complicating factor of anesthesia by McAfee *et al.* (1979). To achieve reinforcers of apple juice, each of 12 monkeys exposed its head to a 9.3-GHz field at an average power density of 150 mW/cm^2. Once-daily exposures approximating 10 to 15 min took place 5 d/week for a total of 30 to 40 exposures. Neither before experimental treatments began nor after termination of the series of exposures were cataracts observed in any of the animals. Assessment was performed via slit-lamp microscopy. The total quantities of incident energy at the monkeys' eyes, as expressed in units of energy density, ranged from 79 to 180 kJ/cm^2 and averaged 144 kJ/cm^2. Neither *SAR*s nor *SA*s were reported by the authors.

13.3 Cataractogenesis in Human Beings

Cataract induction is the most prominently reported irreversible effect of RFEM exposure of human beings. In all, over 50 cases of cataract induction have been attributed to microwave exposures, principally in occupational settings in which workers were presumably exposed acutely to high-intensity fields. In most instances, it has not been possible to obtain sufficient information regarding the exposure conditions to determine, with any degree of certainty, power-density thresholds of human cataractogenesis. Indeed, the inadequacies in the existing data even cast doubts about the validity of some of the reported incidents of RFEM-induced cataracts in human beings.

The first case of microwave cataractogenesis was reported in 1952 and involved a 20-y-old radar worker, but no details of the exposure were presented (JAMA, 1952). Hirsch and Parker (1952) described bilateral cataracts in a 32-y-old worker who had been intermittently exposed over a 1-y period to radiation in the frequency range, as originally reported, of 0.2 to 3 GHz. Exposures of various durations to fields at 100 mW/cm^2 or higher resulted in the subsequent development of nuclear and bilateral-posterior-subcapsular cataracts in addition to the appearance of cellular debris in the aqueous and vitreous

humors, of vitreous opacities, and of choroiditis in the left eye. A subsequent re-examination by Hirsch (1970), after the lens of the left eye had been surgically extracted, revealed a persistent degree of uveitis and chorioretinitis in the left eye, and an apparently non-progressive cataract in the lens of the right eye. In this later report, the exposure frequencies were indicated to be in the range of 4 to 5 GHz and the range of power densities was re-estimated to be 40 to 380 mW/cm^2, with possible near-field exposures at intensities as high as 1.16 W/cm^2. Hirsch (1970) noted that the exposures leading to cataract formation occurred primarily during a 3-d period immediately preceding the onset of symptoms, which indicates a short latency for cataract induction in human beings exposed to high-intensity fields.

Shimkovich and Shilyaev (1959) reported the development of bilateral cataracts in a worker during a one-month period following microwave exposure. In this instance a 22-y-old technician was reportedly exposed several times to 3-GHz radiation at an estimated intensity of 300 mW/cm^2 for durations of 3 min per exposure.

Zaret and coworkers (1970) reported 42 cases of RFEM-induced cataracts that were presumed to result from occupational exposure. The initial site of lens pathology in some of the patients in this group was the posterior lens capsule rather than the lens substance in which opacification was detected in subsequent examinations. Exposure parameters are available for only one case in this series. In this instance, the exposures were for durations of approximately 50 h per month over a 4-y period at a variety of frequencies and at power densities estimated generally to be less than 10 mW/cm^2, but with 1 period of 6 months or more during which the average density was on the order of 1 W/cm^2.

Zaret (1974a) has also reported a case of cataract induction in a 50-y-old woman. The cataract was attributed to intermittent exposure to leakage radiation from a 2.45-GHz microwave oven. The exposures, which presumably occurred over a period of approximately 6 y prior to the detection of lens opacification, consisted of leakage radiation at approximately 1 mW/cm^2 during oven operation but at levels to 90 mW/cm^2 when the oven door was opened. The exposure conditions and clinical manifestations of this case have generated significant controversy with respect to the involvement of microwave exposure. Bouchat (1974), however, has indicated that the clinical observations reported by Zaret (1974a) correspond to a case previously reported by Bouchat and Marsol (1967). They attributed capsular cataracts to microwave exposure of a 23-y-old worker exposed over a period of 44 months.

The limited data on RFEM-induced cataracts in human beings following acute, high-intensity exposure indicates the involvement of thermal damage to lens tissue. The estimated acute cataractogenic dose in human beings is in reasonable agreement with data derived from experimental irradiation of rabbits, indicating, at least to a first approximation, a similar sensitivity of rabbits and human beings to RFEM induction of cataracts. It may further be anticipated that a qualitatively similar time-intensity relation exists in the case of human exposures, which may be interpreted to mean that a threshold intensity for cataract induction in man may exist for acute, single-exposure conditions.

Epidemiological methods have also been employed to assess the ocular effects of occupational exposure to RFEM fields. A retrospective study of minor or non-cataractous lens changes in military and industrial workers by Cleary and Pasternack (1966) revealed an apparent, exposure-related increase in the incidence of such defects as compared with that of an age-matched control group. The most statistically significant finding was an increased incidence of minor defects in the region of the posterior pole of the lens of the workers, which appeared to be related to job specialization. In general, individuals employed in research and development had a higher incidence of such changes than those in other occupational categories. The incidence of non-cataractous changes was correlated with several exposure parameters. However, the most significant correlation of lens defects in both workers and controls was with the age of the individual, such that a linear increase in the mean number of defects occurred with increasing age (Cleary and Pasternack, 1966). The results of this study were interpreted by Cleary and Pasternack as indicating that occupational exposure to RFEM fields increased the rate of aging of the lens, but because the study was not designed to assess incidence of cataracts, no relation was drawn between the incidence of other lens defects and that of cataracts.

Cleary *et al.* (1965) investigated the relationship between occupational RFEM exposure and cataract formation in a retrospective study of 3,000 military personnel with diagnosed cataracts and a control group of 2,000 cataract-free military personnel. The results of this study provided no evidence that occupational RFEM exposure of military personnel was related to an increased risk of cataract induction. These results indicate that, in situations in which exposures were presumed to be less than 10 mW/cm^2, the risk of cataracts from exposure is not detectably increased.

No indication of lens damage attributable to occupational RFEM

exposure was detected in a 5-y survey of workers in which the lenses of potentially exposed workers and controls were examined biomicroscopically for lens defects that are considered to be the precursors of cataracts (Appleton, 1974). In another investigation by Siekierzynski *et al.* (1974), the incidence of lenticular opacities was determined in 841 workers after occupational exposures of various durations. The worker population was subdivided into two groups, one consisting of 507 individuals exposed at estimated power densities in the range of 0.2 to 6 mW/cm^2, and the other group of 334 workers exposed at estimated power densities below 0.2 mW/cm^2. Intergroup analyses of the incidence of lenticular opacities were performed, as well as intragroup comparisons based on age and duration of employment. The incidence of lenticular opacities was found to be significantly correlated with age, but not with exposure level or with duration of employment.

Detailed, double-blind ophthalmological examinations of 477 military RFEM-exposed workers and 340 controls with no known history of occupational RFEM exposure were conducted by Shacklett *et al.* (1975) to determine the relative incidence of lens opacities, lens vacuoles, posterior subcapsular irridescences and lens changes that were equated with early stages of cataract formation. No statistically significant differences were detected in the incidence of any of the types of lens changes between the workers and controls. Medical-surveillance ocular examinations of 705 RFEM-exposed workers revealed no lenticular or retinal defects that could be attributed to microwave exposure in the most recently reported study of the effects of occupational RFEM exposure on the eye (Hathaway *et al.*, 1977).

The results of epidemiological studies of the relation between occupational RFEM exposure and ocular changes do not provide evidence of deleterious effects. If the assumption is made that human exposures in such environments are generally limited to power densities below 10 mW/cm^2, it may be assumed that this is a practical limit for ocular damage from intermittent exposure to microwave fields. The inherent limitations on the interpretation of data of this type, namely the inadequacies in exposure histories and biasing effects such as the removal from employment of any individuals who have, in fact, experienced ocular pathology, preclude the conclusion that long-term occupational exposures of human beings to power densities in the range of 10 mW/cm^2 do not result in any degree of ocular change.

14. Studies of Human Beings

14.1 Epidemiologic Approach to Investigate Effects of RFEM Radiations

Reports of epidemiologic studies of RFEM fields are few in number and are generally limited in scope. Persons occupationally exposed in the military services or in industrial settings have been the principal groups studied (often without systematic observations after termination of employment). A few other populations living or working near generating sources or exposed to shortwave or microwave (medical) diathermy (Hamburger *et al.*, 1983; Ruggera, 1980) have been or are being investigated. Information about health status has come from medical records, questionnaires, physical and laboratory examinations, and vital statistics. Sources of exposure data include personnel records, questionnaires, environmental measurements, equipment-emission measurements, and (assumed adherence to) established exposure limits. Although there have been recent advances in dosimetry, the dosimetry of RFEM fields presents formidable problems for meaningful assessment in most epidemiologic studies. There is at present no practical way of determining cumulative *SA*s or averaged *SAR*s—or even the average of field strengths—for large numbers of individuals. In investigations involving prior exposures, it is a difficult, and often impossible, task to reconstruct exposure data from available records or from recall by study subjects.

Two populations have been the subject of cohort studies in the United States and are described below.

14.1.1 *U.S. Naval Personnel Occupationally Exposed to Radar*

A pilot study by the Bureau of Radiological Health under the sponsorship of the Office of Naval Research determined that it was feasible to study a variety of long-term health effects among enlisted men occupationally exposed to RFEM radiation at different exposure levels during military service. Because of fiscal restraints, the end points of the study were reduced to those that could be investigated through the use of military and veterans' record-keeping systems,

which are largely automated. The three-year study was conducted by the National Academy of Sciences (Robinette *et al.*, 1980).

The study population was drawn from the thousands of enlisted men trained in the use and maintenance of radar and related equipment (for navigation and gunfire control) in technical schools maintained by the Navy since World War II. Other technical schools also graduated large numbers of technicians similarly selected for educational achievement, general intelligence, and specific aptitudes, thus offering the possibility to select valid comparison groups. The men selected for this study graduated from technical schools during the period 1950 through 1954. The Korean-War period was chosen for two reasons: Wartime service ensured virtually complete ascertainment of mortality, and exposure in the early 1950s provided a reasonable period of time for many long-term effects to develop.

Measurements made by the Navy offered a guide for selecting the occupations involving the highest exposures. On the basis of a consensus by naval personnel involved in training and operations, occupational groups were classified as probably maximally exposed (those repairing and testing radar equipment) and probably minimally exposed (those operating radar equipment). Technical occupational groups probably non-exposed (such as engine-room personnel) were considered unsuitable because of their exposure to the stresses of high temperature and excessive humidity. Men selected for the study were drawn from six Naval Enlisted Classifications of occupations.

The high-exposure cohort is made up of men who were Electronics Technicians (13,078), Fire-control Technicians (3,298), and Aviation Electronics Technicians (3,733). The groups in the low-exposure cohort, which consists of men who were trained to operate equipment, are classified as Radioman (9,253), Radarman (10,116), and Aviation Electrician's Mate (1,412). The study population of approximately 40,000 consists of about 20,000 in each of the two cohorts. The groups were composed predominantly but not exclusively of young men who entered the service shortly after graduating from high school; the high-exposure groups had more older men who were veterans of World War II and had re-enlisted. The mean age in 1952 of the total group of low-exposure men was 20.7 y whereas the average age of the high-exposure group was 22.1 years. The airmen in both the high- (mean age 23.4) and low- (mean age 24.6) exposure groups were older than the seamen.

Follow-up medical information was derived from search into and linkage of Navy and Veterans Administration (VA) records. The death of almost every war veteran is a matter of record in VA files, because applications for burial benefits are made by survivors of nearly 98 percent of the deceased veterans. The application usually includes a

copy of the death certificate, from which a certified cause of death may be obtained. The Navy's records of hospital admissions were searched, and records of admissions to VA hospitals were available for computer search, as were current awards for disability compensation. The cohorts of over 40,000 men were followed through extant records for the following end points and period of ascertainment:

Mortality	1955–1974
Morbidity (in-service hospitalization)	1950–1959 (excluding 1955)
Morbidity (VA hospitalization)	1963–1976
Disability Compensation	1976

The study had a 90-percent chance of detecting 50 percent excess mortality at a significance level of $p = 0.05$ for comparisons between the total low- and high-exposure groups.

Precise estimates of exposure were not available for any of the individuals in this study. The only measurements possible were those of the general shipboard environment or those that arose from efforts to reconstruct the circumstances of an accidental overexposure. There have been enough accidental exposures at estimated power densities exceeding 100 mW/cm^2 to indicate that there are occupations in which some men at some times on certain classes of ships have been exposed well in excess of the 10-mW/cm^2 limit (Glaser and Heimer, 1971). Shipboard monitoring programs in the Navy since 1957 show that men in other occupations rarely, if ever, are exposed at power densities in excess of this limit. Radiomen and radar operators, whose duties keep them far from radar pulse generators and antennae, were generally exposed at levels well below 1 mW/cm^2, whereas gunfire-control technicians and electronics technicians were sometimes exposed at higher levels in the course of their duties.

In addition to occupation *per se*, other relevant elements of exposure were included in the analysis, namely, length of time in the occupation, class of ship, and periods of likely exposure. An index of potential exposure of individuals, called the hazard number, was constructed for a sample of men in the high-exposure group. This index consisted of the sum of the power ratings of all gunfire-control radars aboard the ship or of all search radars aboard the aircraft to which the technician was assigned, multiplied by the number of months of assignment. Data on navigational radars, which had very low output powers by comparison, were not available. A technician with a low hazard number had little opportunity for substantial exposure to RFEM fields; men with large hazard numbers might have had substantial opportunity for such exposure. The distribution of hazard numbers by specific occupational

rating showed that, within the high-exposure group, the fire-control technicians and the aviation-electronics technicians had much larger proportions of men with large hazard numbers than did the electronics-technician group. Study constraints prevented the determination of hazard numbers for the low-exposure groups.

Because no measures of actual, as opposed to potential, exposure were available, the so-called "high-exposure" rosters were made up of a mixture, in unknown proportions, of men whose actual exposures may have varied from high to negligible. If a large proportion of the men had, in fact, received negligible exposures, the consequence would have been to obscure by dilution any differences that might have been found had it been possible to study a large group of men who actually received high-level exposures. Further, it is possible that effects involving the cardiovascular, endocrine, and central nervous systems are transient, disappearing with the termination of exposure or soon thereafter, or are not perceived to be of sufficient consequence to result in admission to sick bay or hospital.

Of the four indices studied—mortality by specific cause of death, hospitalization during military service, later hospitalization in VA facilities, and VA disability compensation—differences were found among the occupational classes for some diagnoses but, on overall analysis, no adverse effects were detected that could be attributed to potential exposure to RFEM radiation. It should be noted that the study subjects were very young (early 20s) when exposed, and even a 20-year follow-up period may not be sufficient to detect long-term mortality effects.

It was not possible, in this study, to determine hospitalization outside the Navy and VA systems, non-hospitalized medical conditions during and after service, reproductive performance and health of offspring, or employment history after discharge from service. A subsample of living men with presumed high- and low-exposure indices during service, however, can be identified for intensive individual follow-up. Such a subsample would make it possible to obtain additional information about occupational exposure by reviewing individual service files and by making direct inquiries of the men.

As an extension of a classified experimental study of possible behavioral and physiological effects of RFEM radiation in primates called the Pandora Project, a study named Big Boy was initiated in 1969 to investigate psychological and physical effects in human beings (U.S. Senate, 1977). The Big-Boy study involved selected Navy crewmen from the carrier U.S.S. Saratoga. Three small groups of ship's crew were selected for seagoing and dockside (control) tests: flight-deck crew (8 men) who were expected to have the highest levels of

exposure, hangar-deck crew (15) with expected low-level exposure, and look-out crew (8), with no expected exposure. No significant differences among the three groups were found, either in the dockside or seagoing tests, with respect to task performance, psychological tests, or biological effects. Blood findings were within normal ranges. Although it was expected that maximal power density would reach 10 mW/cm^2 over 80 percent of the carrier deck, measurements disclosed a maximum of 1 mW/cm^2 and, generally, levels less than one-third of that maximum.

14.1.2 *American Embassy Personnel in Moscow*

The long-term (1953–1976) RFEM irradiation by the Soviets of the American Embassy buildings in Moscow was highly publicized in 1976 and led to a two-year epidemiologic study of possible adverse effects on health (Lilienfeld *et al.*, 1978). This study had been preceded by several unpublicized efforts (U.S. Senate, 1979) to investigate the biological effects. An internal survey by the State Department in 1965 of the medical records of 139 employees and 268 dependents assigned to the Moscow Embassy was inadequate and inconclusive. A contract study, performed by the George Washington University School of Medicine for the Department of State from March 29, 1966 to June 30, 1969, was a cytogenetic evaluation of mutagenic exposure, known as the Moscow Viral Study. Approximately 250 blood samples were provided by some 71 State Department employees and by family members before, during, and after exposure to RFEM radiation at the Moscow Embassy. It was concluded that no genetic or other adverse biologic effect on employees and dependents attributable to RFEM radiation had been established.

From February of 1976 to June of 1978, a study authorized by the Department of State was conducted by the Massachusetts General Hospital (Boston, Massachusetts) to determine, to the extent possible, the blood lymphocyte counts of adult employees, including dependents, of the American Embassy in Moscow. Approximately 350 adult males and females who were Embassy employees during the study period were examined, and approximately 1,000 foreign-service personnel in the United States served as a comparison group. A higher average lymphocyte count was found in the Embassy population, but it did not correlate in time or space with irradiation of the Embassy, and this count is believed to have had a microbial etiology (U.S. Senate, 1979).

The purpose of the epidemiologic study sponsored by the Depart-

ment of State and conducted by the Johns Hopkins University School of Hygiene and Public Health (Lilienfeld *et al.*, 1978) was to compare the morbidity and mortality experience of U.S. Government employees at the Moscow Embassy during the period 1953 to 1976 with the experience of employees who had served in other, selected, non-irradiated Eastern European embassies or consulates during the same period. Eight comparison posts were selected for their similarity to Moscow in climate, diet, geographic location, disease problems, and general social milieu: Budapest, Leningrad, Prague, Warsaw, Belgrade, Bucharest, Sofia, and Zagreb.

Primary attention was given to the employees, but spouses and children (whether or not at the embassies) and other dependents who had resided in the embassies during the study period were included in the investigation. A major effort was required to construct a basic list of all personnel who had served in any of the selected posts at any time during the 23-y study period and to identify their dependents who might have been with them during their tours of duty at any study post. The final identified population consisted of 1,827 employees at the Moscow Embassy and over 3,000 of their dependents, and 2,561 employees at the 8 comparison posts and 5,000 of their dependents. The total study group was comprised of 4,388 employees and 8,283 dependents.

The strength of RFEM fields incident on the Moscow Embassy varied during the period of the study. The direction and intensity of the RFEM signal changed in 1975 but it was always directed toward the upper floors of the Chancery. Maximal power densities and the maximally exposed areas by time period were estimated by the State Department (Lilienfeld *et al.*, 1978) as follows:

Exposure Period	Exposed Area of Chancery	Maximal Exposure
January 1, 1953 to May 3, 1975	West Facade	$\leq 5\ \mu W/cm^2$, 9 h/d
June, 1975 to February 7, 1976	South and East Facades	$15\ \mu W/cm^2$, 18 h/d
February 7, 1976 to June 30, 1976	South and East Facades	$<1\ \mu W/cm^2$, 18 h/d

Maximal power densities were measured at or near the windows of the upper central building. Potential exposures according to time period were determined for individual floors in the living and working areas. Apartment complexes in Moscow distant from the Chancery were monitored every few months and only background levels were

found. Tests for RFEM radiation (between frequencies of 0.5 GHz and 10 GHz) at all Eastern European comparison posts were made periodically. Only background levels (~1 $\mu W/cm^2$) were detected at these Eastern European embassies.

Once a person was identified as a member of the target population, tracing was done by means of questionnaire and telephone interviews, with nearly complete success despite the extraordinary mobility of the study population. Medical information was abstracted from the records of the numerous physical examinations required of the foreign-service employees and their dependents. Additional health data, as well as family and detailed occupational information, were sought by means of an extensive Health History Questionnaire mailed to all employees and certain dependents, followed by telephone interviews. Information on mortality experience (living or dead) was reasonably complete because of the high tracing success; specific causes of death were obtained from death certificates and from other sources.

For purposes of the study, persons in the Moscow population were divided into three exposure subgroups: the exposed (above background levels near 1 $\mu W/cm^2$), the unexposed, and those of questionable exposure status. Information about individual working and living locations was not available in personnel records and had to be obtained from the participants by the mailed Health History Questionnaire and by personal telephone interviews. Exposure data, estimated from location during assignments in the Moscow Embassy, were provided by the State Department for only two periods: from 1953 until May 1975 and after May 1975. Many individuals remained in the questionable category due to the nature of their employment at the embassy or because they could not remember exactly where they worked or lived in the embassy compound.

About one-third of the employees were followed by means of records and inquiries for periods of 15 to 20 years and over half of them for periods longer than 10 years. There were approximately 50,000 person years of observation of the total employee group and 18,000 person years of observation of employees who served in Moscow at any time.

Limitations of the study have been noted by the investigators: identification of the entire study population was thought to be very nearly complete, but confirmation of completeness was not possible; compilation of dependents was incomplete to an unknown degree; death certificates could not be obtained during the limited period of the study for approximatley one-third of the employees known to have died; response rates to the Health History Questionnaire were relatively low, no higher than 59 percent for the most responsive subgroup; classification of exposure status was inadequate; the highest exposure

levels were the most recent; and the size of the study population was not suffficient to detect relatively small excess risks for many of the medical conditions of interest. It should be noted that the study population was relatively young and that the follow-up period may have been too short to detect long-term mortality effects.

Hundreds of factors were examined in terms of two basic comparisons: Moscow-post versus comparison-post individuals, and the Moscow-post population divided into subgroups by various measures of exposure to RFEM radiation. No differences between the Moscow-post and comparison populations were found with respect to various components of the study such as success of tracing the ascertained study population, abstracting the medical records, response to the Health History Questionnaire, validation of the conditions and diseases reported on the Questionnaire, and ascertainment of deaths and acquisition of death certificates. Excess risk ratios that could be detected with a power of 80 percent at a significance level of 0.05 varied widely, depending on the person years of observation for various mortality or morbidity event ratios.

Exhaustive comparative analyses were made of all symptoms, conditions, diseases, and causes of death among employees and dependent groups of adults and children. No differences in health status by any measure could be attributed to RFEM radiation. An independent analysis of the RFEM field that had been incident on the Moscow Embassy was performed later by engineers and physicists of the Johns Hopkins University Applied Physics Laboratory (Mallalieu, 1980). They estimated uniformly lower power densities than those provided by the State Department except for one recording of 24 $\mu W/cm^2$ in one room during a 2-h period on 24 January 1976.

14.2 Specific Health Effects

14.2.1 *Ocular Effects*

In laboratory rabbits there is clear evidence that selective exposure of the head and of the eyes to RFEM radiation under controlled environmental conditions will cause not only minor lens changes but also cataracts (see Section 13 for more detailed discussion). Cataracts develop following a single, high-threshold dose or following repeated subthreshold doses to the eye in close succession (Carpenter, 1977).

In man, over 50 cases of alleged RFEM-induced cataract have been accumulated, mainly by a single investigator (Zaret, 1974a).

Numerous surveys of ocular effects in man have been made, especially in the United States. Most investigations have involved service personnel and civilian workers at military bases and civilian workers in industrial settings. The principal subject of interest has been the significance of minor lens changes in the cataractogenic process; cataracts (opacities impairing vision) have been infrequently investigated; and only rarely has evidence of retinal changes been sought.

14.2.1.1 *Minor Lens Changes.* Lenticular defects too minor to affect visual acuity have been studied as possible early markers of RFEM exposure or precursors of cataracts. The studies have been mainly prevalence surveys, but the time periods are often variable or are not specified; re-examinations are rarely done, are sporadic and do not permit estimates of incidence. These occupational studies have generally emphasized careful clinical eye examinations, including the use of slit-lamp biomicroscopy and photographs, but without comparable attention to study design and follow-up plans for exposed and comparison groups.

The following generalizations can be made about observations of lens changes in RFEM-exposed workers and in comparison groups:

a. Lens imperfections occur normally and increase with age among the general population and the male employees that have been studied. There is evidence that lens changes accelerate with age, even during the childhood years (Zydecki, 1974). By about age 50, lens defects have been reported in most comparison subjects, based on data from various studies (Silverman, 1980).
b. Although a few suggestive differences have been reported (Cleary and Pasternack, 1966; Zydecki, 1974; Majewska, 1968), there is no clear indication that minor lens defects are a marker for RFEM exposures in terms of type or frequency of changes, exposure factors, or occupation. The possible earlier appearance of lens defects in RFEM-exposed workers as contrasted with workers of comparison groups cannot be assessed adequately because there is considerable variation in the type, number, and size of recorded defects, in the scoring methods used by different observers, and in the numbers of individuals examined (Silverman, 1980).
c. Clinically significant lens changes, which would permit selection of individuals to be followed, have not been identified (Zaret *et al.*, 1963).
d. There is no evidence from ophthalmic surveys to date that minor lens opacities are precursors of clinical cataracts.

14.2.1.2 *Cataracts.* Although there has been much interest in the cataractogenic effect of RFEM radiation, only a minimal effort has been made to investigate cataracts as such, as distinct from their precursors. The only epidemiologic study of cataracts in exposed workers, a case-control study of World-War-II and Korean-War veterans with negative findings, was reported in 1965 (Cleary *et al.*, 1965).

Neither definitions nor methods of detection of cataracts are standardized. The common meaning of cataract, a lens opacity that interferes with visual acuity, is open to many interpretations as to degree and nature of the opacity and of loss of visual acuity. Specific disorders, physical agents, and traumatic injury are known to cause cataracts, but many cataracts of unknown etiology are loosely called "senile" when they ocur after middle age, implying that they result solely from aging of the lens. Cataracts resulting from RFEM exposure are not distinguishable from other cataracts in the opinion of most observers.

The most prominent characteristic of cataracts is their age distribution. Although estimates of frequency are not comparable because of differences among surveyed populations and because of nonuniform methods of detection and definition, all point to low prevalence until about the fifth decade of life, when sharp increases occur.

One or more cataract conditions were found in 9 percent of the U.S. population (Ganely and Roberts, 1983). For the various age groups under 45, frequency of the condition increases gradually from 0.4 percent in those 1-to-5 years of age to 4 percent in the 35- to 44-y age group. The marked increase that occurs after age 45 reaches a maximum in the oldest group examined: of those 65 to 74 y of age, more than half had cataracts.

Cataract data on active-duty personnel in the armed services (who are mainly healthy, relatively young males) are available as incidence rates and show age dependence to age 55. Mean annual incidence rates are extremely low, on the order of 2 per 100,000 (Odland, 1972).

In the only case-control study of cataracts, which was mentioned earlier (Cleary *et al.*, 1965), armed-services personnel with cataracts that were ascribable to a non-RFEM factor were eliminated from the sampling plan—that is, all congenital, traumatic, diabetic, and other specified types were excluded. The sampling plan also eliminated veterans greater than 55 y of age, to minimize dilution of the study group with data on senile cataracts. The study was designed to detect a 2-fold increase in relative risk, with a probability of 0.80 at a significance level of 0.05. No excess risk of developing cataracts was found among radar workers.

Studies of RFEM-exposed workers have been designed to determine whether cataract formation is accelerated in younger persons. It is

necessary to look for possible increases in the frequency of cataracts in various age groups, as well as in high-risk groups excluded from the study described above, to detect possible heightened field-induced susceptibility. The determinants of the RFEM cataractogenic effect are not fully understood (Carpenter, 1977b), and the epidemiology of cataracts has been inadequately studied (Sommer, 1977). Longitudinal data are needed to examine adequately the risk of cataractogenesis.

14.2.1.3 *Retinal Lesions.* Until recently, retinal lesions have not been considered a possible field-induced effect. There is some reason to think that ophthalmologists examining RFEM-exposed workers have observed, but have not reported, retinal changes, because of no known relation to RFEM exposure (Baranski and Czerski, 1976). A small Swedish study (Aurell and Tengroth, 1973), which included examinations for retinal as well as for lens changes, was prompted by preliminary findings of paramacular and macular pathology in industrial radar workers. A significantly higher proportion of retinal lesions in the central part of the fundus was found in exposed workers aged 26 to 40 y than in comparably aged controls. The retinal lesions had resulted in decreased vision in two cases. No further reports are available.

14.2.2 *Nervous and Behavioral Effects*

As discussed in Section 12 on behavioral studies, nervous-system and behavioral changes in experimental animals following low-level exposures have been reported for many years by investigators from Eastern Europe (Petrov, 1972). Clinical laboratory studies of groups employed in the operation, testing, maintenance, and manufacture of RFEM-generating equipment have also been reported in large number by authors from the Soviet Union and other Eastern European countries (Gordon, 1966; Sadchikova, 1974; Baranski and Czerski, 1976). Exposures have been mainly low-level (microwatts to a few milliwatts per square centimeter) and long-term.

With few exceptions (Siekierzynski *et al.*, 1976; Djordjevic *et al.*, 1979), functional disturbances of the central nervous system have been described as a typical kind of radiowave sickness, termed the *asthenic* or *neurasthenic syndrome.* This syndrome is described in the section on behavioral studies. This clinical syndrome is reported generally to be reversible if exposure is discontinued.

Another frequently described manifestation is a set of 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. More serious but less frequent neurologic or neuropsychiatric disturbances have been described occasionally as a *diencephalic syndrome.*

The only American epidemiologic study to date of some of the neurasthenic effects is the cohort study of American Embassy employees in Moscow and other Eastern European capitals (Lilienfeld *et al.*, 1978). Although much symptomatology was found in American personnel, no differences were attributable to RFEM exposure at the intensities measured outside the Moscow embassy. The levels of exposure, however, were even lower than those reported in the Soviet and Eastern European occupational studies.

In an occupational health study in Yugoslavia (Djordjevic *et al.*, 1979), the frequency of subjective complaints related to the central nervous and cardiovascular systems was determined for a group of 322 workers in radar stations and for a comparison group of 220 non-radar workers. This was part of a comprehensive investigation of health status that included clinical examinations and laboratory tests. The radar workers, who had been exposed for periods of 5 to 10 y to pulsed fields at many frequencies and at power densities generally less than 5 mW/cm^2, were matched with the non-exposed workers on age (25 to 40 y of age), radar-unrelated working conditions, and social and living conditions.

Clinical, hematological, biochemical and ophthalmologic findings were similar in both groups. Of the six subjective complaints studied (headache, fatigue, irritability, sleep disturbance, impaired libido and memory deficits), three were found more frequently in radar workers. Headache, fatigue and irritability occurred in about 15 percent of the non-exposed workers but occurred in 28 percent of the radar workers. The excess of subjective complaints in radar workers was ascribed to unfavorable environmental conditions of work in the radar stations such as high noise level, poor lighting, the necessity of paying attention to the radar screen, and inadequate ventilation.

The prevalence of subjective complaints and a concern for noise and other factors in the industrial setting where RFEM fields are present has also been voiced by Pazderova-Vejlupkova (1981), which raises some complex and essentially unanswered questions: To what degree is exposure *per se* to RFEM fields responsible for these complaints? To what extent do the multiple stresses in the industrial environment complex and interact with RFEM fields to induce symptoms? And to what extent has adverse publicity about RFEM radiation created anxiety among industrial workers? Clearly, there is a need for investigations and surveys that can shed light on the factor or factors

responsible for the many reports that link symptoms of neurasthenia with exposure to RFEM fields.

The identification and assessment of poorly defined, nonspecific complaints, symptom complexes and illnesses is extremely difficult; these considerations compound the problems of study design and case and control selection (Silverman, 1973). In the future, in addition to medical examinations, consultation with behavioral scientists and psychiatric specialists is needed. The use of health questionnaires designed to detect emotional illness, and objective psychologic tests for specific types of symptomatology, can provide relevant information. Useful data may also come from attendance rates at clinics or physicians' offices, absentee rates due to illness, accident liability, and job performance.

14.2.3 *Congenital Anomalies*

Section 6 on reproduction, growth and development presents data on teratogenesis in laboratory animals. In human beings there is no evidence of anomalies following exposure *in utero* other than some case reports (Marha *et al.*, 1971).

A case-control study of *Down's syndrome* (mongolism) in Baltimore, Maryland (Sigler *et al.*, 1965) yielded an unexpected finding regarding paternal exposure to RFEM radiation. Fathers of children with mongolism gave more frequent histories of occupational exposure to radar during military service than did fathers of unaffected children, a difference that was of borderline statistical significance. Exposure during military service occurred prior to the birth of the affected child. After publication of the first report in 1965, expansion of the study group, follow-up of all fathers to obtain more detailed information about radar exposure, and search of available armed-forces records were undertaken. The suggested excess of radar exposure of fathers of mongoloid children was not confirmed on further study, but occupational exposures were difficult to document (Cohen *et al.*, 1977).

A study of congenital anomalies in Alabama (Peacock *et al.*, 1971) showed that, during a 3-y period (1968–1971), the adjoining counties of Dale and Coffee, in which Fort Rucker is located, had a reported number of clubfoot cases among Caucasian babies that greatly exceeded the expected number based on birth-certificate notifications to the state. A more detailed investigation revealed that in the six-county area surrounding Fort Rucker, there was, during the same time period, a considerably higher rate of anomalies (diagnosed within 24 hours of

delivery) among births to military personnel than to parents in the state as a whole. Fort Rucker is a training base for fixed-wing and helicopter aircraft and is situated within 35 miles of dozens of radar stations. Errors in malformation data on birth certificates and probable overreporting from Fort Rucker led to the conclusion that convincing evidence is lacking that radar exposure is related to the congenital malformations (Burdeshaw and Schaffer, 1976). The high malformation rate across a group of counties of the state was presumably environmentally induced but no specific agent was identified. It was not possible to do a more detailed study.

The use of shortwave and microwave diathermy, to relieve the pain of uterine contractions during labor, was reported from Belgium (Daels, 1973) and is discussed in detail in Section 6. Recent studies have been made of occupational exposures of physiotherapists to shortwave equipment (diathermy), suggesting a possible increase in congenital defects among offspring of female therapists (Kallen *et al.*, 1982) and a possible increase in heart disease among male therapists (Hamburger *et al* ., 1983).

14.2.4 *Cancer*

RFEM-induced cancer has not been reported, but the role of RFEM radiation in cancer promotion has been suggested (Szmigielski *et al.*, 1982). The two cohort-epidemiologic studies (Robinette *et al.*, 1980; Lilienfeld *et al.*, 1978) have focused on the question systematically with regard to morbidity and mortality. Although excesses of some forms of cancer were found, neither study revealed an excess that can be interpreted as RFEM-related. Recent analyses of occupational statistics have reported increased proportional mortality and morbidity ratios for leukemia among workers with potential exposure to electric and magnetic fields (Milham, 1982; Coleman *et al.*, 1983). Further discussion of the laboratory studies can be found in Section 4. See also Section 17.6.2.

15. Thermoregulatory Responses in Human Beings

15.1 Introduction

Were the title of this section taken at face value, there would be few words to set down herein. While human beings have been exposed inadvertently to ultra-low "background" levels of both naturally-occurring and man-made sources of RFEM radiation, few individuals have voluntarily exposed themselves to significant levels for the scientific assessment of any responses, thermoregulatory or otherwise. The few quantitative data in hand relate to man's thermal sensations derived from stimulation of restricted body areas by a few discrete RFEM frequencies. These have been compared with similar sensations derived from stimulation by frequencies in the infrared. Because thermal sensation is the initial event that often underlies one of the important regulatory systems of the human body, thermoregulation, these data are tantalizing and precious. However, given the prevailing climate of fear of RFEM held by some of the scientifically sophisticated as well as the layman, together with the current reluctance of funding agencies to support research using human subjects, the prospect for future research in this area is bleak. Therefore, in order to discuss human thermoregulatory responses to RFEM radiation, use is made of current knowledge of how these same responses change, (1) in the presence of conventional thermal stimuli in the environment, (2) during exercise-induced hyperthermia, (3) from predictions made by sophisticated computer models of the human thermoregulatory system, and (4) on the basis of the best quantitative data derived from animal subjects.

15.2 Fundamentals of Thermoregulation

Thermoregulation is the term used to describe the maintenance of the body temperature within a prescribed range under conditions in which the thermal load on the body may vary. In man, these thermal

loads derive from alterations in ambient conditions (temperature, ambient vapor pressure, air velocity, clothing, and other environmental variables which may alter the temperature of the skin) and from changes in heat production within the body. The deposition of thermalizing energy in the body core by exposure to RFEM radiation is a unique exception to the energy flows normally encountered by man, although metabolic activity in the muscles can also deposit large amounts of thermal energy directly into deeper tissues.

Most of the vital internal organs of human beings function most efficiently when they are maintained at a relatively constant temperature near 37.0 °C. Although the temperature of individual body parts may depart somewhat from this norm, significant departures are associated with vigorous exercise, disease states, or possibly lethal conditions. The usual range of body temperatures (35.5 to 40 °C) encompasses circadian variation, vigorous exercise, variations in ambient temperature, sequelae of food intake, age factors, menstrual variation in women, and emotional factors. Temperatures outside of this range must be related to disease states, unusual activity, or extraordinary environmental conditions.

Body tissues are extremely vulnerable to excessive changes in temperature, particularly to overheating. The intricate system of mechanisms in human beings for regulating internal body temperature is therefore not surprising. In man, a warm-blooded (endothermic) organism, two distinct control systems are available to accomplish this regulation: a behavioral system involving conscious, voluntary acts that adjust the characteristics of the air-skin interface, and an autonomic (or physiological) system involving the involuntary responses of the body that generate and dissipate body heat. In man, behavioral regulation (supplemented by highly sophisticated technology) allows the organism to survive such environmental extremes as the heat of a re-entering space vehicle or the cold of a lunar night, whereas physiological regulation provides for the fine control of body temperature in the resting state and is the principal control during exercise.

15.2.1 *Body Heat Balance*

An important principle involved in the study of physiological thermoregulation is the law of conservation of energy. In the steady state, heat produced in the body is balanced by heat lost to the environment such that storage of heat is minimal. This condition can be expressed by a generalized heat-balance equation:

$$M \pm W = \pm R \pm C \pm E \pm S \qquad (15.1)$$

where

M = the rate at which thermal energy is produced through *metabolic* processes

W = power or the rate at which *work* is produced by or on the body

R = the rate of heat exchange with the environment via *radiation*

C = the rate of heat exchange with the environment via *convection*

E = the rate of heat loss due to the *evaporation* of body water

S = the rate of heat *storage* in the body.

It is important to note that all terms in Equation 15.1 must be in the same units, e.g., watts. As the equation is written, negative values of R, C, and E all may cause a rise in body temperature; positive values may cause a fall. Work (W) is positive when accomplished by the body (e.g., riding a bicycle), and this potential energy must be subtracted from metabolic energy (M) to find the net heat developed within the body. When W is negative (e.g. walking downhill), this heat is added to the metabolic heat. Usually, E, evaporative heat loss, is positive; when E is negative, condensation occurs and thermal injury is possible.

No term appears in the above equation for heat transfer by *conduction* which is usually insignificant in man under normal conditions. However, conduction, combined with mass transfer, forms the mode of heat transfer called *convection*, a significant form of heat loss in man. Convective heat transfer in air (H_c) is a linear function of the body's surface area (A), and the convective heat-transfer coefficient (h_c) is a function of ambient air motion (velocity, v) to the 0.6 power ($v^{0.6}$). The amount of heat lost by the body by convection depends on the difference between the surface temperature of the skin (T_{sk}) and the air temperature, which is usually taken as the dry-bulb temperature (T_{db}). Thus the expression for heat loss, H_c, via convection is:

$$H_c = kv^{0.6}A(T_{sk} - T_{db}), \tag{15.2}$$

where the heat-transfer coefficient (h_c) equals $kv^{0.6}$, and k depends on certain properties of the surrounding medium such as density, viscosity, etc., as well as a shape-dimension factor for the body. Clothing complicates the analysis and is often evaluated in terms of insulation (clo) units (Gagge *et al.*, 1941; Winslow *et al.*, 1940; Sprague and Munson, 1974).

Heat transfer by *radiation* is independent of the air temperature. The quantities of the radiation exchanged between two objects are related to their respective surface temperatures, and the net heat transfer by radiation is proportional to the difference between their absolute temperatures to the fourth power and to the relative absorptive and reflective properties of the two surfaces. In general, the net radiant heat exchange between a nude person and the environment

involves estimation of the mean radiant temperature (MRT). In practice, MRT can be derived from the temperature of a 15.4-cm-diameter black globe (T_g) having heat-transfer characteristics similar to those of the human body (Woodcock *et al.*, 1960). Thus:

$$MRT = (1 + 0.222\ v^{0.5})(T_g - T_{db}) + T_{db}. \qquad (15.3)$$

Clothing complicates the analysis as it does for heat transfer by other modes. A solar heat load poses other special problems that have been analyzed in detail by Roller and Goldman (1967). Presumably, heating by RFEM radiation provides further complications to the analysis of radiant heat exchange between a person and the environment. For a preliminary analysis, see Berglund (1983).

The fourth avenue of heat loss available to man is *evaporation* of water. The latent heat of vaporization of water at normal body temperature is 0.58 kcal/g. Thus, the body loses ~2.4 kJ of thermal energy when 1 g of water is evaporated from its surface. Water in the expired air is continuously being lost from the respiratory tract as is water that continuously diffuses through the skin ("insensible" perspiration). These respiratory and diffusion losses account for a total heat loss of ~25 percent of the resting metabolic heat production (M) in a thermoneutral environment. However, the major avenue of evaporative heat loss in human beings is sweating (*cf.* Section 15.2.3.2). The efficiency of evaporative cooling depends on the vapor pressure of the ambient air and of the evaporating surface, and, thus, is a direct function of both dry-bulb (T_{db}) and wet-bulb (T_{wb}) temperatures. For a body under conditions of $T_{db} = T_{wb}$, the air is at 100 percent relative humidity and no water can be evaporated from the skin surface. When the ambient air is at less than 100 percent relative humidity, evaporation can take place. The interrelationships among these variables, as well as tolerance times for heat and cold exposure by human beings, can be determined from a standard psychrometric chart.

Evaporative heat transfer (H_e) for a human body can be expressed as:

$$H_e = 2.2\ h_c A(P_{sk} \cdot \phi_a P_a) F_{pcl}, \qquad (15.4)$$

where the evaporative area (A) is taken as 1.8 m^2 for a standard man, P_{sk} is the vapor pressure of water at skin temperature, P_a is the ambient vapor pressure at a relative humidity of ϕ_a, h_c is the convective heat-transfer coefficient, and F_{pcl} is a dimensionless permeability factor. Once again, this relationship is applicable to a nude person and will be confounded by the insulative value and permeability of clothing. It should be noted also that H_e represents the evaporative cooling allowed by the environment (E_{max}) and is in no way related to the

level of evaporative cooling required (E_{req}) by the person (see Section 15.3).

15.2.2 *Endogenous Heat Production*

The basal metabolic rate (*BMR*) is defined as the heat production of a human being in a thermoneutral environment, who is at rest mentally and physically, after an interval of time exceeding 12 h from the last meal. The standard *BMR* for man is 250 ml/min of oxygen or 84 W or 0.8 MET (where 1 MET = 58.2 W/m^2). The *BMR* can be altered by changes in active body mass, diet, and endocrine levels but probably not by living in a hot environment (Goldman, 1980). In resting man, most of the heat is generated in the core of the body—in the trunk, viscera, and brain—despite the fact that these structures represent only about a third of the total body mass. The heat generated in the central organs of a resting person is conducted to the other body tissues, and the elimination of this heat from the body is controlled by the peripheral vasomotor system. The range of metabolic heat production (M) for human subjects, considering work performed and assorted physiological variables such as age, sex, and size, is roughly 40 W/m^2 to 800 W/m^2 depending on physical fitness and the level of activity. If deep-body temperature is increased, either by heat storage in warm environments or by febrile disease, there is, within limits, a compensatory change in M (Stitt *et al.*, 1974). Similar changes can be expected if deep-body temperature rises during exposure to RFEM radiation (Adair and Adams, 1982).

In cold environments, active shivering is usually preceded by a generalized increase in muscle tone and piloerection, which can increase M by about 35 percent (Swift, 1932). Active shivering begins locally and over time recruits more and more of the body's skeletal musculature, eventually increasing heat production to as much as 4 to 5 times the resting level (i.e., to 160 to 200 W/m^2). However, if cold exposure lasts for several hours, a doubling of the resting M in the steady state is all that can be expected, thus establishing the limit for regulation by heat production in the cold (Iampietro *et al.*, 1960). Increases in M during exercise are discussed in Section 15.3.2.

15.2.3 *Avenues of Heat Loss*

Both changes in vasodilation and sweating must be considered as mechanisms of body-heat loss. Generally speaking, vasomotor control

normally operates to achieve regulation of the body temperature when a person is in thermoneutral environments, sweating being activated in warmer environments and during exercise.

15.2.3.1 *Vasomotor Control.* Convective heat transfer via the circulatory system is under the control of the sympathetic nervous system. In the cold, vasoconstriction of the peripheral vasculature in arm, leg, and trunk skin minimizes heat loss from the body core to the skin, leaving a residual heat flow by conduction of 5 to 9 W/m^2 per °C of temperature difference between body core and skin. In thermoneutral environments, when the peripheral vessels are vasodilated, each liter of blood at 37 °C that flows to the skin and returns 1 °C cooler allows the body to lose ~1 kcal or 1.16 W h of heat (Hardy, 1978). In warm environments, during vigorous exercise, peripheral blood flow can increase almost 10-fold, and this increase is essential to eliminate the increased metabolic heat production in the working muscles.

Tissue conductance represents the combined effect of two channels of heat transfer in the body: conduction through layers of muscle and fat, and convective heat transfer by the blood. Conductance can be estimated for resting human beings if it is assumed that all the heat is produced in the core of the body, and is transferred to the skin and thence to the environment. Thus,

$$H_l = K(T_{re} - \bar{T}_{sk}), \tag{15.5}$$

where H_l represents the heat loss (neglecting that lost through respiration), K is conductance, T_{re} is rectal (or core) temperature, and $\bar{T}_{sk}$ is the average skin temperature. In the cold (22 to 28 °C), conductance is minimal for both men and women, ranging between 6 to 9 $W\ m^{-2}\ °C^{-1}$. In warm environments, conductance increases markedly, with women showing a faster increase than men (Cunningham, 1970). In general, measurements of heat transfer made at the skin's surface yield only minimal rates of blood flow because countercurrent heat exchange between arteries and veins in the peripheral tissues affects the observed heat flow.

15.2.3.2 *Evaporative Water Loss Through Sweating.* Evaporation of sweat from the skin is an efficient way of losing heat, even in environments warmer than the skin. Thus, evaporative heat loss must compensate both for metabolic heat production and that absorbed by radiation and convection from the hot environment. Thermalizing energy from RFEM fields will be dealt with in a manner similar to heat produced by normal metabolic processes in a resting person or by exposure to warm environments.

Normal secretory functioning of the ~2.5×10^6 eccrine (sweat) glands in the skin of a human being is essential to prevent dangerous

levels of hyperthermia. Secretion is under the control of the sympathetic nervous system and is activated when the ambient temperature climbs above 30 to 31 °C and/or the internal body temperature rises above 37 °C (Nadel *et al.*, 1971a). Local sweating rate has also been found to depend on the local skin temperature (Nadel *et al.*, 1971b). Both physically fit individuals and those acclimated to warm environments show a lower threshold of internal-body temperature for sweating and also show an increased responsiveness of the sweating mechanism when challenged by exercise (Nadel *et al.*, 1974). Factors such as dehydration or increased salt intake will alter plasma volume and decrease the efficiency of the sweating response during exercise (Greenleaf, 1973).

15.2.4 *Neurophysiological Control of Thermoregulation*

The operating characteristics of the thermoregulatory system have much in common with those of an automatic control system involving negative feedback. The body temperature appears to be regulated at a set or reference level (Hammel *et al.*, 1963). Temperature sensors located in various parts of the body detect thermal perturbations and feed this information to a central integrator and controller. Not only does this central controller integrate sensory information from various parts of the body, but it also controls the effector systems for heat production and heat loss. If a thermal disturbance shifts the body temperature away from the set or reference level, this change will be detected by the controller through signals from the temperature sensors, and appropriate effector responses will be mobilized to return the body temperature back to the set level.

15.2.4.1 *Thermosensitive Neural Tissue.* Because the type and level of thermoregulatory effector activity depends on the temperature of the skin, it has long been felt that specialized receptors must exist in the outer layers of the skin, which detect changes in their own temperature (Hensel *et al.*, 1960). Two populations of free-nerve endings have been found in the skin that increase their activity both to warming (warm receptors) and to cooling (cold receptors) (Hensel, 1974). This 2-fold mechanism was demonstrated definitively by Hensel and Kenshalo (1969), who heated and cooled the facial skin of cats while recording from single fibers in the infraorbital nerve that innervates this skin area, thereby determining response functions for both types of sensor. An increase in skin temperature ($\bar{T}_{sk}$) from the cat's thermoneutral level (~33 °C) produced a sharp increase in impulse frequency of warm fibers while that in cold fibers decreased. A sharp

cutoff in warm-fiber response occurred at a $\bar{T}_{sk}$ above 45 °C indicative of thermal death of the fibers. Cooling the facial skin below 33 °C produced an increase in impulse frequency of cold fibers while suppressing activity of the warm fibers.

Extensive neurophysiological research, beginning with studies of lesioned animals a century ago (Aronsohn and Sachs, 1885; Ott, 1887), has shown that certain tissues of the central nervous system (CNS) are essential for, or at least are involved in, the control of autonomic mechanisms of heat production and heat loss in endothermic species. As early as 1912, Barbour showed that a thermode implanted in the anterior brain stem of rabbits could be used to trigger many thermoregulatory responses. When Barbour warmed this device, heat-loss responses were initiated; when he cooled it, heat production and conservation responses were stimulated. Although Barbour's methods were very primitive, his experiments provided the impetus for more than 60 years of research in the neurophysiology of thermoregulation. Much of this work has involved the search for temperature sensors in the CNS that, it was felt, must exist in those areas where lesions or thermal stimulation influenced thermoregulatory-effector responses.

Beginning with work in Hardy's laboratory in 1961, many CNS sites in experimental animals have been explored with microelectrodes revealing the existence of single neurons whose firing rates depend on the temperature of the tissue in which they are located (Nakayama *et al.*, 1961, 1963; Guieu and Hardy, 1971). Local tissue temperature was controlled routinely with implanted thermodes (Hammel, 1968). The activity patterns of these thermal sensors resemble in many respects those of the thermal sensors in the skin. Tissue sites that have been shown to exhibit such thermosensitivity include the medial preoptic area of the hypothalamus, lateral hypothalamus, midbrain reticular formation, medulla, motor cortex, thalamus, spinal cord, and deep viscera (Hellon, 1967; Cabanac *et al.*, 1967, 1968; Cunningham *et al.*, 1967; Simon, 1974; Rawson and Quick, 1970). Many cells in the preoptic area have been shown to respond to temperature changes in, e.g., the skin and spinal cord as well as in their own vicinity (Wit and Wang, 1968; Hellon, 1969; Wünnenberg and Hardy, 1972). On the basis of such data, many investigators believe this to be evidence not only for the hypothalamus as the site of the central body "thermostat" but also as the site of the integrator-controller as well. Unfortunately, there is still no direct evidence that these thermally responsive neurons are actually the thermal sensors involved with thermoregulation. Furthermore, we can only assume that the CNS of human beings contains thermal sensors in sites analogous to those that have been found in

experimental animals. The strongest evidence marshalled for this assumption is the uniformity of the neurophysiological findings for ectotherms and endotherms alike.

Temperature changes localized to several of the thermosensitive sites mentioned above can trigger behavioral thermoregulatory responses as well as physiological responses (Satinoff, 1964; Adair, 1974; Lipton, 1971; Cabanac, 1972; Carlisle and Ingram, 1973). It is clear that any means by which such central nervous system structures may be thermally stimulated has the potential to alter the normal thermoregulatory-response strategy of an endotherm. Clearly, RFEM radiation, known to be absorbed in extremely complex configurations by man and lesser animals, is such a potential stimulus.

15.2.4.2 *Characteristics of the Thermoregulatory Controller.* The integration of neural signals from the various thermal sensors in the body by a controller located (perhaps) in the hypothalamus, the comparison of the integrated signal with a reference level, and the generation of neural-effector commands—all are hypothetical constructs that aid in the understanding of thermoregulatory processes. There are about as many models of the thermoregulatory controller as there are researchers in the field, and more are being proposed all the time. Many early models featured two centers for thermoregulation rather than one: one controlling body-heat loss, the other body-heat production (Ott, 1887; Meyer, 1913). However, the current consensus among thermophysiologists is that one center or controller can accomplish both types of regulation. All models have other features in common: The controlling center resides in the brain and contains some kind of reference against which error signals of various types are compared.

There have been many types of controller models: verbal descriptions (Ott, 1887; Rubner, 1902; Meyer, 1913), pictorial models of the neurophysiological system (DuBois, 1948; Benzinger, 1959; Hensel, 1952; Chatonnet and Cabanac, 1965), physical analogs of the thermoregulatory system or portions thereof (Aschoff and Wever, 1958), electrical analogs (MacDonald and Wyndham, 1950), mathematical models (Burton, 1934; Wissler, 1961; Smith and James, 1964; Stolwijk and Hardy, 1966, 1977), neuronal models (Hammel, 1965; Hardy and Guieu, 1971; Bligh, 1972), and chemical or neuro-transmitter models (Feldberg and Myers, 1964; Myers, 1970). A comprehensive account of the development of modeling in thermal physiology is discussed by Hardy (1972). Details of one mathematical model of the human thermoregulatory system are presented in Section 15.5.

15.3 Limits of Human Heat Tolerance to RFEM Radiation

The human thermoregulatory response to the deposition of significant amounts of thermalizing energy by RFEM radiation (i.e., sufficient to elevate the temperature of tissues in all or part of the body) probably will not differ substantially from the response to heat generated in the body tissues by other means. The basic problem posed by excessive body heating from any source is whether the heat-loss capability of the thermoregulatory system is sufficient to prevent heat storage in the body. Thus, for a human being exposed to an RFEM field, Equation (15.1) may be rewritten as:

$$(M \pm W) + A_{rf} = R + C + E \pm S, \tag{15.6}$$

where A_{rf} represents the rate of energy absorption from the RFEM field. Neglecting the work factor, the sum of the heat production, of the heat exchange by radiation and convection, and of the absorbed RFEM energy provides a useful estimate of the evaporative cooling required (E_{req}) as:

$$E_{req} = M \pm H_c \pm H_r + A_{rf}. \tag{15.7}$$

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

In general, the degree of heat stress placed on the body can be predicted by the simple ratio of E_{req}/E_{max}, which yields a measure of the percentage of the skin surface that is wet with sweat (Gagge, 1937). Values of E_{req}/E_{max} <20 percent yield a state of thermal comfort, while higher percentages indicate tolerance limits. This same ratio has been called the Heat Stress Index (HSI) (Belding and Hatch, 1955). HSI values in excess of 30 percent are judged to be uncomfortable and may interfere with concentration and fine motor performance, but are also judged to be tolerable; values from 30 to 60 percent result in finite tolerance times and interfere with work; values from 60 to 100 percent represent severe, intolerable conditions.

The amount of heat storage in the body calculated from the heat balance equation can also be used to predict tolerance times to heat (Goldman, 1978b). Thus, a heat storage of up to 25 kcal may not even be noticed if incurred slowly enough; a value >80 kcal represents the usual voluntary tolerance time; double this value (160 kcal) incurs a 50 percent risk of collapse; and triple this value (240 kcal) is intolerable.

15.3.1 *Environmental Variables: Temperature, Vapor Pressure, and Clothing*

As has been mentioned in Section 15.2.1, tolerance times for human subjects can be determined from a standard psychrometric chart that diagrams the vapor pressure of the ambient air as a function of both wet-bulb and dry-bulb temperatures. Certain information has been extracted from such a chart to produce a Comfort-Health-Index (C-H-I) for human responses shown in Table 15.1 (adapted from Hardy, 1970). The table depicts the thermal sensations, physiological thermoregulatory responses, and associated health hazards as these variables relate to dry-bulb temperature at 50 percent relative humidity. This level of relative humidity prevails in much of the United States

TABLE 15.1—*Human responses to comfort-health-index for prolonged exposures*[a]

C-H-I T_{db} at 50% RH	Sensations	Physiological Responses	Health Hazard
°C			
50			
	Unbearable	Rapid body heating	Circulatory collapse
45		Failure of body temperature regulation	
	Very uncomfortable Hot		Temporary exposure dangerous
40		100% wetted area	
	Uncomfortable Hot		
		50% wetted area	
35			
	Slightly uncomfortable		"Danger line" for heat stroke
30			
	Warm	25% wetted area	
	Comfort zone	Zone of vasomotor regulation	No health hazard
25	Cool		
	Slightly uncomfortable		
20		Vasoconstriction of hands and feet	Muscular pains Peripheral circulation impaired

[a] After Hardy (1970)

(except for certain high-altitude and desert regions); therefore, the T_{db} depicted will be appropriate for a high percentage of the U.S. population and can be applied to sedentary man in the indoor environment. No data exist on exposure to RFEM radiation that can be added to this table, but it is certain that exposures that provide significant rates of energy deposition in the body core will alter the C-H-I in much the same way as would an equivalent metabolic load. Stolwijk (1982) has used his mathematical model to predict, for example, that, at an air temperature of 30 °C and at a relative humidity of 50 percent, deposition of 500 watts for 30 min into the trunk core of sedentary man would elevate the temperature of the central blood by ~1.5 °C when thermoregulation is fully operational. This energy deposition would be the equivalent of a moderate work load (5 MET) such as pedaling a bicycle ergometer at 50 rpm (Gagge *et al.*, 1971). If, on the other hand, the sweating response were disabled (as would be the case if the body were immersed in water or the relative humidity were equal to 100 percent), the deposition of the same amount of energy into the trunk core would produce a rise in central blood temperature in excess of 4 °C. Stolwijk has used his mathematical model in similar fashion to predict not only changes in the temperature of the body core but also shifts in many other thermoregulatory parameters (body temperatures, heat storage, metabolic rate, evaporative water loss, skin blood flow, cardiac output, and effective thermal conductance) that may occur when significant amounts of energy are deposited in the head core or leg.

A somewhat different approach has been taken in the *Radiofrequency Radiation Dosimetry Handbook* (Durney *et al.*, 1978). An upper limit of 39.2 °C for rectal temperature as a criterion of heat-stress tolerance and an arbitrary 60-min exposure period were used to determine the values of the irradiation parameters that would fulfill these criteria under different environmental conditions (i.e., T_{db} from 30 to 68 °C and $\phi_a = 0.8$, 0.5, and 0.2). The intent was to predict the maximal, whole-body *SAR* (based on thermal considerations) that a healthy man could tolerate for 60 min in a specified environment (SAR_{60}) under the assumption that the thermoregulatory mechanisms are all functioning normally. The basis of the calculation is, therefore, the standard heat balance equation. One such calculation yielded an SAR_{60} of 3.11 W/kg for $T_{db} = 40$ °C and 80 percent relative humidity. Then the *SAR* curves for an average man in the *Handbook* were used to calculate the incident power density for any given frequency and polarization that will produce this SAR_{60}. Thus, an SAR_{60} of 3.11 W/kg corresponds to an incident power density of ~13 mW/cm^2 for irradiation by a plane wave (*E* polarization) at the resonant

frequency of 70 MHz. The authors of the *Handbook* emphasize, however, that SAR_{60} values calculated in this manner are not to be interpreted as safe exposure limits—they are simply estimates of the upper tolerance levels for a healthy man with normal heat loss capabilities.

The variety of calculations described above has assumed that the subject is a healthy nude male in a resting state. The clothed human body presents a resistance to the flow of heat from the skin to the environment that is a direct function of the thickness of the air layer trapped by the clothing (Gagge *et al.*, 1938). The standard insulation unit, called the clo (Gagge *et al.*, 1941), was empirically derived and equals 0.18 °C m^2 h $kcal^{-1}$ or 0.155 °C m^2 W^{-1}. The insulation value of a standard business suit is defined as 1 clo. Typical indoor clothing worn in offices today range from 0.4 clo in summer (short, light dress; light slacks and short-sleeved shirt) to ~1.0 clo in winter (heavy slacks, blouse, light sweater, and jacket; heavy trousers, sweater and shirt, jacket) (Goldman, 1978a). It has been suggested as a rule of thumb (ASHRAE, 1974) that for each 0.1 clo deviation from the usual 0.6 clo insulation baseline for sedentary persons doing light office work (1 MET), the air temperature for comfort can be offset by 1 °F (0.55 °C). This temperature offset can be doubled when the workload is increased to 4 to 5 MET.

The limiting factor to lowering office temperatures for energy conservation appears to be related to cold hands and, to a lesser extent, cold feet. It is difficult to design practical mittens that warm the hands and still allow the manual dexterity required for most jobs. The recent proposal by Pound (1980) to provide heating of human beings in otherwise cold interior spaces by radiant energy at microwave frequencies is a potential solution to the problem of energy conservation. On the other side of the coin, as we have seen, the avoidance of thermal discomfort in hot environments that may include a source of RFEM radiation is accomplished primarily by minimizing the percentage of the body surface area that is wetted by sweat. There is little that can be done with clothing to accomplish this objective other than to remove as much of it as possible consistent with acceptable social norms.

15.3.2 *Exercise*

Physical exercise produces a condition under which the human thermoregulatory system must function in the presence of an internal disturbance. When a proportional, negative-feedback control system (such as the thermoregulatory system) is faced with such a disturbance,

the system usually functions with an offset in its regulated variable (the regulated internal body temperature, in this case). This seems to be the case during muscular exercise. Upon initiation of activity, heat production in the skeletal muscles rises rapidly, producing a temporary large increase in heat storage within the body. The rising body temperature generates an error signal relative to the "set" body temperature, which drives the mechanisms of heat loss at an ever-increasing rate until heat loss equals heat production. When a balance is attained, the body temperature will equilibrate at a hyperthermic level that is characteristic of the level of exercise being performed (Nielsen, 1938). Nadel (1977) has observed that exercise represents the single condition that provides a maximal strain to the thermoregulatory system under normal circumstances and that allows measurement of the various modes by which the body adjusts to this strain. The reader is referred to Nadel's comprehensive work that discusses current knowledge in this complex area of thermal physiology.

It has been demonstrated that exercise changes neither the "set point" for body temperature nor the normal operating characteristics of the thermoregulatory system (Wyndham, 1973). Nielsen and Nielsen (1965) used diathermy, frequency unspecified, to deposit heat directly into the deep tissues of the trunk in human subjects. In other experiments, the same subjects exercised on a bicycle ergometer at a work rate that was adjusted so that the heat load during cycling and diathermic heating were the same (~5 MET). In the steady state, the rectal temperature increased by the same amount during the two procedures as did thermal conductance as assessed by changes in skin blood flow. Sweating rates were also comparable. These findings indicate that passive heating by shortwaves and the heat generated during active exercise produced the same kind of thermal disturbance in the body as a whole, although the distribution of heat in individual body tissue compartments was certainly very different in the two cases. Nielsen and Nielsen's data also demonstrate that the thermoregulatory consequences of whole-body energy deposition by RFEM radiation may be predicted by the consequence of equivalent heat loads via exercise. This rationale underlies the predictions of changes in thermoregulatory responses to RFEM energy deposition made by Stolwijk (1982) using his mathematical model of the human thermoregulatory system. A similar rationale provided the basis for the prediction by Tell and Harlen (1979) that the equilibrium rectal temperature of a resting man (~0.7 clo) exposed to 75 MHz in a thermoneutral environment (25 °C, RH = 50 percent, v = 0.13 m/s) will not exceed 1 °C above normal unless the power density exceeds 15 mW/cm^2.

15.3.3 *Febrile States*

It is important to differentiate between elevated body temperatures produced by exercise and those occurring during febrile disease. Strenuous exercise may produce an elevation in body temperature to a level above the normal, regulated (or "set") level. The magnitude of the heat-dissipation response that is stimulated during exercise is directly related to the magnitude of this temperature offset (Robinson, 1949). On the other hand, during fever there is an increase in the regulated body temperature that is defended as is the normal body temperature during euthermia. The behavior of the thermoregulatory system during the generation and maintenance of fever is consistent with an elevation of the "set" temperature (von Liebermeister, 1875). This elevation was demonstrated by Macpherson (1959) in a human subject during daily bouts of exercise and rest. When the subject contracted a febrile disease, his rectal temperature rose and fell, respectively, during periods of exercise and rest, but at an overall level about 2 °C higher than that of the other healthy subjects. Nadel (1977) has also demonstrated an upward shift in the internal temperature at the threshold for vasodilation in a febrile subject.

The elevated body temperature of fever is generated differently depending on the thermal environment in which the subject is located. In warm environments, heat loss will be curtailed and vasoconstriction will occur; if these responses are inadequate to increase heat storage, an increase in heat production will be initiated. In cold environments where heat loss responses are already minimal, greatly increased heat production via vigorous shivering (chill) is the only way to raise the body temperature. Stitt (1979) has shown that once a pyrogenic substance is introduced into the body and displaces the set temperature, the controller for thermoregulation will mobilize any appropriate effector mechanism to increase the storage of body heat. Behavioral thermoregulatory responses that increase the temperature of the skin (by selection of a warmer environment or by increasing body insulation) generate a fever identical to that produced by changes in physiological responses when a given dose of pyrogenic substance is administered (Crawshaw and Stitt, 1975).

The evolution of a febrile episode is well understood, although the actual mechanism by which the set point is elevated by the pyrogen remains a mystery. When the set temperature is elevated by a circulating pyrogen, a large load error is generated because the body temperature is below the new set point. Heat loss is curtailed, vasoconstriction occurs, and metabolic heat production increases in an attempt to raise the body temperature to the new set level. This "chill"

phase gives way to a "plateau" phase once the body temperature has risen to the febrile level. At this point, the error signal no longer exists and the effector responses return to magnitudes that existed before fever onset, regulating in normal fashion around the new elevated set point. When the disease runs its course or an antipyretic drug is given, the normal set point is restored, giving rise to a new load error of opposite sign to that occurring at fever onset. During this "crisis" phase, vigorous heat-loss responses are stimulated (vasodilation and sweating) which rapidly return the body temperature to normal. From this description, it should be clear that hyperthermic states that result from exposure to RFEM radiation differ greatly from those occurring during febrile episodes and resemble much more closely the hyperthermias of exercise.

15.4 Thermal Sensation and Thermoregulatory Behavior

Because measurable thermalization can occur in body tissues that are exposed to RFEM radiation, such radiation must be considered as part of the thermal environment to which man and animals may potentially be exposed (Pound, 1980). Although physiological responses (e.g., vasodilation, sweating) may be triggered automatically by thermal stimuli, sensory appreciation of tissue heating is considered to be necessary for the initiation of appropriate behavioral action. The excitation of temperature-sensitive neural structures residing within the outermost 0.6 mm of mammalian skin (Hensel, 1973) is believed to underlie the sensation of changes in skin temperature. Whether exposure to RFEM radiation produces a threshold sensation of warmth will depend on many parameters of the signal (e.g., frequency, modulation, intensity, duration, and the surface area of the exposed body). Extensive psychophysical research has shown that many of these same physical parameters influence the magnitude of both threshold and suprathreshold thermal sensations associated with infrared radiation (Cain, 1973; Hardy and Oppel, 1937; Herget *et al.*, 1941; Kenshalo *et al.*, 1967; Marks and Stevens, 1973; Stevens and Marks, 1971; Stevens *et al.*, 1973; Stevens *et al.*, 1974). Indeed, Stevens (1983) has concluded that it is reasonable to anticipate comparable results in experiments involving shortwave and microwave stimuli.

15.4.1 *Thermal Sensations Produced by RFEM Fields*

Absolute thresholds for the detection of RFEM radiation by human observers have been determined in several studies (Schwan *et al.*, 1966;

Cook, 1952; Eijkman and Vendrik, 1961; Vendrik and Vos, 1958; Hendler *et al.*, 1963; Hendler and Hardy, 1960; Hendler, 1968; Justesen *et al.*, 1982), all of which have involved brief exposures (a few seconds to a few minutes) and restricted areas of the skin of the forehead or forearm. Many of these studies have been reviewed by Michaelson (1972). In general, it has been found that the shorter the wavelength of radiation, the less energy is required to provoke a just-detectible sensation of warmth. Hendler *et al.* (1963) found that when a 37-cm^2 area of the forehead was irradiated for 4 s, the mean, absolute, power-density threshold of warmth was 33.5 mW/cm^2 at 3 GHz, 12.6 mW/cm^2 at 10 GHz, and 4.2 mW/cm^2 at >1000 GHz (far-infrared). Hendler *et al.* (1963) and Eijkman and Vendrik (1961) also demonstrated that irradiation of small skin areas by 3- or 10-cm pulsed microwaves had to last at least 5 s (termed the "critical duration") in order for the minimal intensity to evoke a thermal sensation. At shorter durations, stimulus intensity had to be greatly increased in order to evoke comparable sensations of warmth. A comparable critical duration (~1 s) must be surpassed in order for the minimal intensity of infrared radiation to evoke a sensation of warmth.

An unusual aspect of the thermal sensation derived from exposure to RFEM fields is its persistence following cessation of irradiation (Hendler *et al.*, 1963; Schwan *et al.*, 1966). This property, together with excessively long latencies to detection, probably derives from the continued existence of an effective temperature difference between the subcutaneous tissue layers (Hendler, 1968), the thermal inertia of the tissues involved (Hendler and Hardy, 1960; Justesen, 1983b), and the greater volume of tissue that may be heated when deeply-penetrating radiation is involved.

A recent study reported by Justesen *et al.* (1982) has incorporated indirect assessment of the energy absorbed during 10-s exposures of the forearm (average area = 107 cm^2) of human subjects to 2450-MHz CW fields. Sensations of warmth were experienced by the subjects when the energy density of the incident field was about 29 mJ/cm^2 as opposed to about 1.8 mJ/cm^2 when the same skin area was exposed to far-infrared radiation. These threshold values correspond to power densities of 27 mW/cm^2 and 1.7 mW/cm^2 respectively, and, thus, are similar to results reported in the earlier studies cited above. Because the far-infrared waves were virtually perfectly absorbed by the observer's skin, and because nearly two-thirds of the 12-cm RFEM energy was scattered, the actual difference in means of threshold quantities of absorbed energy was 5-fold.

Infrared and RFEM radiation will be absorbed very differently by the skin and yield different thermal gradients in both superficial and subcutaneous tissues. Because the thermal receptors are strategically

located within the first millimeter of skin, they will be most efficiently stimulated by thermal energy that is deposited directly in their vicinity. Energy deposited in deeper tissues, unusual thermal gradients, and abnormal patterns of heat flow in the tissues will conspire against efficient receptor stimulation and contribute to altered thermal sensations in the presence of RFEM fields. Although changes in skin and muscle blood flow will occur as tissue temperature rises (Cunningham, 1970; deLateur *et al.*, 1970), the amount of thermal averaging produced thereby is largely unquantified and warrants experimental investigation.

15.4.2 *Changes in Thermoregulatory Behavior in the Presence of RFEM Fields*

Thermoregulatory behavior refers to those voluntary actions by an organism that control the thermal characteristics of the air-skin interface, thereby facilitating regulation of the body temperature at a characteristic, stable level. Very few experimental data exist that relate changes in thermoregulatory behavior of human subjects to imposed RFEM fields. However, results derived from various experimental protocols involving animal subjects afford meaningful insights with good predictive value. In a qualitative sense, RFEM fields will influence thermoregulatory behavior as other heat sources do. Lizards will bask under a microwave source and regulate their body temperature thereby (D'Andrea *et al.*, 1978). Rats, trained to press a lever for infrared heat in a cold environment, will reduce the rate of lever pressing when a 2450-MHz field is present (Stern *et al.*, 1979). The higher the intensity of the field to which they are exposed (range, 5 to 20 mW/cm^2), the smaller the amount of infrared radiation demanded by the rats. Squirrel monkeys will select a cooler environment when irradiated for 10-min periods by 2450-MHz plane waves at a power density of 6 to 8 mW/cm^2 (Adair and Adams, 1980b). Radiation at higher power densities stimulates correspondingly greater reductions in selected air temperature, thereby assuring regulation of skin and deep-body temperatures at the normal level. Except during the first irradiation period of a series or during the early minutes of a single long (2.5-h) exposure, duration of irradiation has no significant effect on the air temperature selected by a behaving animal or on the body temperatures achieved thereby (Adair and Adams, 1983).

Extensive training of the experimental animal in the thermoregulatory behavioral response (Adair and Adams, 1980b) is certainly advantageous and may be essential to survival (Carroll *et al.*, 1980).

The presence of visible or auditory cues correlated with RFEM irradiation facilitates learning of appropriate responses leading to escape from potentially lethal fields (Levinson *et al.*, 1981, 1982), while careful shaping of appropriate responses accelerates such learning dramatically (Justesen, 1983b). Previous experience with similar stimulus-response contingencies has also been demonstrated to be helpful (Bruce-Wolfe and Adair, 1981). Extrapolation of these general findings to the human condition, especially in industrial settings that incorporate high-power sources of RFEM fields, leads to the conclusion that education of the worker and preventive hygiene of the most comprehensive sort should aid recognition of the symptoms of untoward exposure and insure timely retreat from the field.

15.5 Mathematical Models of the Human Thermoregulatory System

All animals, of which man is the example under consideration, exhibit a substantial response to changes in body temperature, and each species is characterized by a preferred level of body temperature at which its functioning and well-being is optimal. Although cold-blooded animals (ectotherms) regulate their body temperatures largely through behavioral selection of a preferred micro-climate, warm-blooded animals (endotherms) have available, in addition, an involuntary physiological system that functions to produce and dissipate thermal energy. Although physiological thermoregulation maintains a much narrower range of body temperature, even endotherms rely to a considerable extent on behavioral thermoregulation. When behavioral responses, which include the thermostatic control of the immediate micro-environment, are rendered difficult or inoperative, the body temperature of endotherms will be regulated by physiological mechanisms that control metabolic heat production, the distribution of heat in the body, and the avenues and the rate of heat loss from the body to the environment (Adair, 1976; Adair and Wright, 1976; Corbit, 1970; Hardy, 1972; Stitt *et al.*, 1971).

The physiological mechanisms that the human body uses to maintain a stable internal temperature are well-described and well-understood quantitatively. Further, because the thermal characteristics of the various tissues of the human body are reasonably well known, it is possible to develop mathematical simulation models of physiological thermoregulation in reasonable detail and validate them against experimental data (Stolwijk and Hardy, 1966, 1977). Many such models

have been constructed (Burton, 1934; MacDonald and Wyndham, 1950; Crosbie *et al.*, 1961; Stolwijk and Hardy, 1966; Wissler, 1961, 1964, 1970). In some cases, such models have been adapted for purposes other than the original ones for which they were formulated [e.g., Montgomery's adaptation (1972) of the Stolwijk (1971) model for the simulation of heat transfer in divers wearing diving suits]. Because heat production and body-heat loss can occur and can be described in a wide variety of specific circumstances, there is a special usefulness in evaluating such specific conditions through simulation. The disposition of absorbed RFEM energy as heat in all or certain parts of the human body is one of the specific conditions that lends itself uniquely to a preliminary evaluation through simulation modeling.

15.5.1 *Characteristics of Models of Human Thermoregulation*

As in any simulation model, models of human thermoregulation are based on simplification of the actual system. The simplifications are usually applied to less relevant parts of the system that are not considered critical to the understanding or prediction of the modeled responses.

It is useful to recognize the separation of the thermoregulatory system into two major components: the regulated or passive system, and the regulatory or controlling system. In all models, both of these systems are simplified.

The controlled or passive system consists of the simplified representation of the thermal characteristics of all the body tissues including metabolic heat production, heat capacitance, local tissue temperature, heat transfer by conduction and convection inside the body and via evaporation, conduction, convection, and radiation between the skin and the external environment (*cf.* Section 15.2.1).

The regulatory or controlling system consists of the structures that sense body temperatures and their response characteristics, the central neural integrator, the neural effector pathways, and the effector mechanisms themselves (e.g., shivering muscles, secreting sweat glands, and the tone of peripheral blood vessels in the skin and elsewhere, which control convective heat transfer between different organs and structures of the body).

Normally, the events that are to be evaluated by such models, and that provide validation of the model, are heat production by exercise and modification of normal heat loss patterns by unusual environmental temperatures, water vapor pressure, clothing characteristics, etc.

15.5.2 *The Controlled System*

The model to be discussed here is that developed by Stolwijk and Hardy (1966, 1977) because it forms the basis for more recent extensions (Emery *et al.*, 1976; Spiegel *et al.*, 1980). In this model the human body is represented by six elements, each consisting of four concentric cylinders and a central blood compartment. The exact details of the specification and the validation of the controlled system have been presented elsewhere (Stolwijk and Hardy, 1977). The concentric cylinders in each element are made to correspond to the mass of skin, subcutaneous fat, muscle, and core tissues of the head, trunk, arms, hands, legs, and feet. Together with a central blood compartment, which exchanges blood and heat with each of the tissue compartments, there is a total of 25 tissue compartments. Each of these compartments is characterized by a heat capacitance, a basal and exercise-related heat production rate, a blood-flow rate indicating its convective connection to the central blood compartment, a heat conductance to adjacent compartments, and for the skin, evaporative, radiant, convective, and conductive heat exchange with the environment.

The simulation model provides, for each of the 25 compartments, a temperature based on the initial condition and the integrated flows of heat into and out of the compartment.

15.5.3 *The Controlling System*

The controlling system receives from the controlled system the instantaneous temperature of each of the 25 compartments, which temperatures are compared with reference or set-point temperatures, summed and weighted in accordance with physiological measurements. In the current version of the model (Stolwijk and Hardy, 1977), temperature sensors in the skin and head core (hypothalamus) feed into the central integrating structure. Although temperature sensors are known to exist in other CNS structures, their participation in human thermoregulation is largely unknown. In the model, signals from the skin and head-core receptors are integrated, with a relative weight of 0.1 for the skin and 0.9 for the head core, and are converted into effector commands to the sweat glands, to the peripheral muscles, and/or to the peripheral blood vessels. The resulting effector action will then produce changes in heat production, heat loss, and heat transfer to counteract the effects of internal or external loads that would otherwise change body temperatures from the preferred, regulated levels.

15.5.4 *Performance and Validation of the Model*

For such a model to have maximal utility, it must contain all the changes in physiological responses that may occur within the ranges of imposed environmental heat stress, metabolic heat production, and body temperature that encompass its anticipated uses. Underlying the model described here is a great deal of experimentation on human subjects that was designed specifically to elucidate the structure and quantitative characteristics of the physiological thermoregulatory system. The model has been found by many investigators to predict accurately changes in observed responses both to sudden changes in environmental temperature (Stolwijk, 1971) and to bouts of exercise at many levels (Stolwijk and Hardy, 1977). The model seems well suited for the prediction of changes in thermoregulatory responses that may result from deposition of RFEM energy in the body and has provided the basis for several such analyses (Emery *et al.*, 1976; Spiegel *et al.*, 1980; Way *et al.*, 1981).

15.5.5 *Application of Simulation Models of the Human Thermoregulatory System to Deposition of RFEM Energy in the Body*

It is natural and appropriate to use thermoregulatory simulation models for the evaluation of special conditions of thermal stress. This is especially true for conditions that are difficult to evaluate experimentally, such as localized or whole-body deposition of RFEM energy. Although animal studies can provide useful insights and guidance, formidable difficulties are encountered in attempting to extrapolate results derived from subhuman animals to human beings (Gordon, 1982a, 1983; Adair *et al.*, 1983). Both inadvertent and unrestricted exposure of the body to low-level radiation and the controlled focal applications of high-intensity fields in clinical hyperthermia are of concern and, as such, are suitable conditions for modeling.

In recent years, considerable progress has been made in the quantification of the absorption of RFEM energy by mammals ranging from mouse to man (Guy *et al.*, 1974; Kritikos and Schwan, 1979; Gandhi, 1982). Many studies have pointed out nonuniformities of energy deposition within exposed tissue volumes and the potential for electrical and thermal hot spots, especially in the cranial cavity (Burr and Krupp, 1980). Mathematical models embodying considerable detail (e.g., Gandhi, 1982; Burr *et al.*, 1980; Johnson and Guy, 1972; Lin *et al.*, 1973; Shapiro *et al.*, 1971; Kritikos and Schwan, 1972, 1975,

1976; Weil, 1975) are now available to simulate the deposition of RFEM energy in the human body. Thus, it is logical to combine the two types of models so as to evaluate physiological thermoregulatory responses to energy deposition by RFEM fields (Way *et al.*, 1981; Stolwijk, 1980). Excellent reviews have been offered by Durney (1980) and Gandhi (1980a). A word of caution is in order, however. The interweaving of two simulation models, each of which was developed for different purposes and was based on different rationales and objectives, poses particular problems. Prior assumptions and simplifications of different types that may have been incorporated into the separate models may lead to internal incompatibilities that may not be readily apparent.

In general, in the energy-deposition model, the mathematical treatment of energy deposition will be sensitive to shape and dimensions, electrical conductivity, and dielectric constant. The formulation of the thermoregulatory model will be designed to accommodate the location of thermal sensors and effector mechanisms as well as sources of metabolic heat and patterns of blood flow. The descriptions of the body are different in these two models, and special limitations apply to their combined use, as acknowledged in studies by Way *et al.* (1981) and Stolwijk (1980). Other attempts to combine the two types of models (e.g., Spiegel *et al.*, 1980; Emery *et al.*, 1976) have encountered certain difficulties that result from either internal incompatibilities or inadequate representation of the convective heat transfer that may occur due to changes in blood flow (deLateur *et al.*, 1970).

Stolwijk (1980) has used a combined-simulation model to derive useful insights about special cases of localized RFEM-energy deposition in the human body. In one example, the model predicts that the consequences of depositing energy at 100 W in the human brain include a relatively modest (<0.7 °C) initial rise in brain temperature, less than would be expected from assumed rates of brain blood flow [~50 mL $(100g)^{-1}$ min^{-1}]. Even this relatively limited rise in brain temperature stimulates the thermoreceptors in the brain to mobilize vigorous sweating, which produces a rate of body-heat loss that exceeds even the total RFEM energy input. The result is a fall in all body temperatures, even the temperature of the brain. A modification of the basic Stolwijk model by Way *et al.* (1981) that provides for focusing of RFEM radiation in the hypothalamus predicts an even stronger reduction in core temperatures under similar exposure conditions and an enhanced evaporative-heat loss, skin-blood flow, and core-to-skin conductance.

A combined simulation model has been used by Spiegel *et al.* (1980) to predict steady-state changes in body temperatures in a nude, 70-kg

man at rest in a thermoneutral environment (T_{db} = 30 °C, RH = 30 percent, velocity unknown) and exposed to a unilateral plane wave (80 or 200 MHz, E polarization). At a power density of 10 mW/cm^2 (SAR = 2.25 W/kg or ~2 MET), the 80-MHz field, deposited uniformly, was predicted to produce very modest temperature increments (e.g., 0.2 °C in the trunk) in specific parts of the body. However, energy from the same field, deposited nonuniformly, was predicted to elevate the temperature of the trunk core 0.3 to 0.8 °C above a 37-°C "average" body temperature but also predicted a significant hot spot (41.6 °C) in the core of the lower thigh. Data of Lehmann *et al.* (1968), deLateur *et al.* (1970), and Cunningham (1970), among others, confirm a substantial increase in local tissue blood flow at temperatures in excess of 40 °C, a factor not yet incorporated into the model of Speigel *et al.* While greatly elevated temperatures in the limbs or brain may conceivably occur, even when elevations of core temperatures are slight, recent laboratory investigations have failed to confirm the existence of such hot spots in living animals with thermoregulation intact (Krupp, 1983).

It is clear that the amount of thermal averaging over all body tissues of locally deposited RFEM energy occurs by convective heat transfer via blood flow. The result is the protection of individual tissues. Thus, it is rather difficult to raise the temperature of a small volume of tissue to a high level unless the radiation is highly focused or very intense.

Of course, it is possible that poorly perfused tissues or regions such as resting muscle or the ocular lens may increase in temperature if high SARs at focal sites occur. In such cases, there is for many of these tissues, especially for well vascularized tissues such as skeletal muscle, a tremendous increase in local blood flow as soon as temperatures of 40 to 42 °C are exceeded. This dramatic increase was demonstrated by Cunningham (1970) as well as by others (Lehman *et al.*, 1968). Indeed, Spiegel *et al.* (1980) admitted that certain hot spots predicted by their model would be of smaller magnitude if appropriate alteration of tissue blood flow at temperatures above 39 °C were incorporated in their model.

15.6 Supporting Data from Animal Studies

Several studies of the thermoregulatory consequences of exposure to RFEM fields in experimental animals have been reported. Nearly all of these studies have involved exposure to fields at a frequency of 2450 MHz. In addition to the behavioral experiments summarized in

Section 15.4, some studies have been performed to assess individual physiological responses of heat production and heat loss with varying degrees of success. Experimental animals must be restrained to afford the opportunity to monitor body temperatures and other thermoregulatory variables, and restraint in and of itself often imposes a stress that can interfere with normal thermoregulation. There is a clear and present need for definitive, unconfounded experiments based on higher primates including human subjects, and involving a wider spectrum of frequencies (including simultaneous irradiation at several different frequencies) with especial emphasis on exposure at resonant frequencies.

15.6.1 *Threshold Effects*

RFEM exposure can lower the metabolic heat production of animals in thermoneutral and cool environments. This result was reported for the mouse by Ho and Edwards (1977) and for the rat by Phillips *et al.* (1975a). In neither study were the thermoregulatory consequences of the absorbed energy evaluated while the 30-min exposures were in progress. This was precluded by the exposure geometry employed: the mice were held inside a waveguide and the rats in a multimodal cavity (microwave oven). Although *SAR*s were varied in both studies, the environmental temperature during exposure was uncontrolled in the cavity and held at 24 °C in the waveguide. The general conclusion drawn from both studies was that the metabolic reduction produced by exposure is dose dependent, although in the mouse study postural adjustments (undocumented because the waveguide was opaque) may have reduced energy absorption (Monahan and Ho, 1977). In addition to hypometabolism, Phillips *et al.* also observed bradycardia and arrhythmia in the rats and concluded, interestingly, that these response changes may have resulted from significant localized heating in the brain as a consequence of high localized *SAR*s. A follow-up study by Ho and Edwards (1979) in which the environmental temperature in the waveguide was varied (range, 20 to 35 °C) showed no difference in oxygen consumption from that at sham-exposed temperatures when the animals were in cool environments. However, an increase in metabolic rate was measured in mice exposed to an average *SAR* of 10 W/kg and above in a waveguide temperature of 35 °C, a result that would be expected during hyperthermal stress.

Adair and Adams (1982) exposed squirrel monkeys in the far field of a horn antenna to both brief (10-min) and prolonged (90-min) periods of 2450-MHz CW fields with T_{db} held constant at 15, 20, or

25 °C. The power density ranged from 2.5 to 10 mW/cm^2, representing a range of whole-body *SAR*s from 0.4 to 1.5 W/kg. Reliable reductions in metabolic heat production (M), calculated from oxygen deficit in the monkey's expired air, were initiated at all T_{db} by 10-min, whole-body exposures at power densities of 4 mW/cm^2 (2 monkeys) or 6 mW/cm^2 (1 monkey) and above. The magnitude of the reduction of M was linearly related to power density above the threshold level. Termination of the field was followed by a rapid rebound of M. The change in M produced at a given power density was the same at all T_{db}. During 90-min exposures, M first decreased rapidly and then more slowly as it approached a new steady state, ensuring continued precise regulation of the internal body temperature. These experiments demonstrated clearly that cold-exposed endotherms compensate readily for field-induced body heating by reducing endogenous-heat production.

Experiments by the same authors (Adair and Adams, 1980a) have probed the potential of RFEM radiations to alter peripheral vasomotor tonus in the squirrel monkey. Vasomotor activity in cutaneous tail veins was indexed by changes in local skin temperature during unrestricted exposure of the monkey's body to 2450-MHz CW fields. At an ambient temperature (26 °C) just below that at which tail vessels normally vasodilate, vasodilation was initiated by 5-min exposures at a power density of 8 mW/cm^2. Radiation at this intensity deposited energy equivalent to ~20 percent of the monkey's resting metabolic heat production but produced no observable change in deep-body temperature. For each 1-°C reduction in ambient temperature below 26 °C, a power density increment of 3 to 4 mW/cm^2 will produce an identical threshold response. That no vasodilation occurred during infrared exposures of equivalent power density suggests that noncutaneous thermosensitive structures may mediate the activation of thermoregulatory responses in the peripheral vasomotor system.

In another experiment, Gordon (1982a, b) has measured the whole-body evaporative water loss of mice exposed to 2450-MHz fields inside a waveguide held at 20 °C. He found that irradiation at 29 W/kg (equivalent to 3 MET) was required before the water lost by the mice was significantly elevated. Because rodents neither pant nor sweat, the animals may have been spreading urine or saliva over their fur but this could not be observed because the waveguide was opaque. The import of the measurements could not be determined because body temperatures were not recorded. Furthermore, the prevailing T_{db} (20 °C) was well below thermoneutrality for mice; the most likely response to have been altered at *SAR*s below 29 W/kg was metabolic rate, not measured by Gordon.

A preliminary report by Adair (1981) describes other experiments designed to determine the minimal power density of 10-min exposures to a 2450-MHz CW field that will reliably initiate thermoregulatory sweating from the foot of squirrel monkeys restrained in ambient temperatures just below the upper critical temperature (36 °C) at which sweating occurs spontaneously in this species. For 4 animals, the threshold power density was 6 to 8 mW/cm^2 (SAR, ~1.1 W/kg), a value comparable to thresholds found by the same investigator for other thermoregulatory responses. Above the threshold, the magnitude of the change in sweating rate at a given T_{db} was directly related to the power density of the imposed field. Indeed, the sweating data for the monkey are qualitatively similar to human data reported by Nadel *et al.* (1971a). The local sweat rate of exercising human beings increases linearly as body-core temperature rises during exercise at a given ambient temperature. But a higher core temperature is necessary to initiate sweating as skin temperature falls, and the rate of increase in sweating during exercise is lower and lower in cooler and cooler environments. This quantitative comparison indicates that, in the monkey, the rate of thermoregulatory sweating initiated by exposure to an RFEM field depends not only on the ambient (skin) temperature but also on the temperature of the body core as it is directly increased by the absorbed energy.

Many investigators have recorded RFEM-induced changes in the deep-body temperature (usually measured in the colon) of experimental animals and have characterized these data as "thermoregulatory responses" to RFEM fields. A word of caution is in order in this regard. The body temperature is *not* a thermoregulatory response and measurement of the colonic temperature of an animal subject may or may not reveal anything about ongoing processes of heat production or heat loss (*cf.* Equation 15.1). If the deep body temperature of an animal rises during a certain period, this may reflect increased endogenous heat production, decreased heat loss to the environment, passive heating from RFEM or other radiation in the absence of active thermoregulation, an altered set point due to febrile disease, a hormonal imbalance, an influence of drugs, greatly reduced body-water content, circadian variation, a generalized stress response, etc. Frequently, a measured rise in deep body temperature is held to be a breakdown in the thermoregulatory system, an interpretation that may often be erroneous. A case in point is a study reported by Lotz (1983) in which the change in body temperature of rhesus monkeys during microwave exposure was influenced by the circadian rhythm of body temperature. Although the measured increase in rectal temperature (ΔT) caused by identical exposure (1.29-GHz pulsed fields at 4.1

W/kg for 8 hours) conducted either in the day or at night was the same, the peak level of that temperature was ~1 °C lower at night. Thus the constant-load error produced by an RFEM exposure was added to a different level of thermoregulatory set point as it exhibited circadian variation. This study also demonstrated that RFEM exposure had no effect on the control of the basic circadian rhythm of body temperature.

Any change in body temperature measured during RFEM exposure will also be a function of animal species (particular responses characteristic of species), of insulation (fur, fat, feathers), of ambient conditions (temperature, vapor pressure, air movement), of parameters of the RFEM field (frequency, polarization, intensity, duration, pulsed *vs* CW, near *vs* far field, etc.), of the presence of other environmental stressors, etc. To catalogue here the ΔTs measured by many investigators on several species under diverse experimental conditions would serve no useful purpose. However, one parameter of RFEM exposure, frequency, is potentially very important because it determines the depth to which the radiation may penetrate below the skin surface (Durney *et al.*, 1978). Maximal penetration at the resonant frequency has the potential for very deep heating of body tissues which may overwhelm the thermoregulatory system.

Lotz (1982b) has begun to investigate this possibility by exposing rhesus monkeys for ~4 hours to 225-MHz (near whole-body resonance) or 1290-MHz (above resonance) fields at $T_{db} = 24$ °C. At the higher frequency, a rise in rectal temperature (ΔT_{re}) of ~0.5 °C occurred at a power density of 28 mW/cm^2 (*SAR*, 3.0 W/kg), whereas, at the near-resonant frequency, the same ΔT_{re} occurred at a much lower power density (2.5 mW/cm^2) and *SAR* (1.2 W/kg). It is not yet clear whether normal mechanisms of heat loss were occurring during the exposures; more data are required before it can be concluded that exposure to a near-resonant-frequency field may easily compromise normal thermoregulation.

15.6.2 *Intense or Prolonged Exposure*

The thermoregulatory consequences of exposure to intense RFEM fields have been explored by Michaelson and his coworkers in experiments that have spanned several years. Unrestricted exposure of dogs to 2880-MHz pulsed fields at 200 mW/cm^2 (SAR, 3.7 W/kg) for 6 h or at 165 mW/cm^2 (SAR, 6.1 W/kg) for 2 to 3 h produced a characteristic triphasic change in internal body temperature (Michaelson *et al.* 1961; Michaelson, 1974). These phases were described as (a) an initial

increase in core temperature, (b) a plateau phase at the hyperthermic level, and (c) thermoregulatory failure. Presumably, the heat-loss mechanisms mobilized by these exposures were able to counterbalance partially the thermalizing energy absorbed by the animal but only temporarily. The strain placed on the thermoregulatory system ultimately exhausted the heat-loss capabilities of the dog and death ensued from hyperpyrexia. Michaelson (1974) also reported that the animals displayed a greater susceptibility to field heating after administration of sodium pentobarbital, morphine sulphate, or chlorpromazine, indicating that the thermoregulatory mechanisms of heat loss had been compromised by the drugs.

Innumerable studies have corroborated the general finding in many species that absorption of RFEM energy on the order of 1 MET will elevate the deep-body temperature of an experimental animal by 1 °C or more. Of special note is the work of de Lorge (1976, 1977) who has correlated the rise in core temperature with work stoppage in animals executing a vigilance task. Because the animals of de Lorge are often tested in restraining devices, it should be possible to monitor individual thermoregulatory responses such as metabolic heat production, vasomotor tonus, and sweating rate in order to derive a more complete assessment of the effects of RFEM radiations on changes in thermoregulatory processes during behavioral tasks.

15.7 Summary and Conclusions

Because only a handful of studies has been devoted to investigation of the response of human subjects to RFEM radiation, and these have dealt in the main with thermal sensations, our knowledge of basic thermal physiology must be used to predict the changes in thermoregulatory responses that might occur in the presence of such radiation. During normal thermoregulation, the metabolic heat produced in the body is balanced by heat lost to the environment through the avenues of radiation, convection, and evaporation such that heat storage is minimal; under such conditions, the body is said to be in thermal balance. In man, the physiological mechanisms of vasodilation and sweating, under the control of specialized thermoregulatory centers in the brain, function to eliminate excess body heat, especially in neutral and warm environments. These responses, together with efficient thermoregulatory behavior, will be activated when thermalizing energy is deposited in the body by exposure to RFEM fields. The situation can be shown to be analogous to that occurring during exercise, rather

than during a febrile episode. Because the thermal characteristics of the human body are reasonably well known, it is possible to develop mathematical models that simulate the human thermoregulatory system and to validate them against experimental data. The deposition of RFEM energy in all or certain parts of the human body is a specific condition that lends itself uniquely to an evaluation through simulation modeling. Results of such procedures indicate that efficient thermal averaging over all body tissues of locally deposited RFEM energy will probably occur through convective heat transfer via blood flow. Human tolerance to such exposure will, of course, be limited by environmental variables such as temperature, vapor pressure, and clothing as well as physiological conditions that include exercise or disease. Although certain general characteristics of the thermoregulatory responses to RFEM irradiation can be derived from animal studies, the need is urgent for psychophysical, behavioral, and physiological investigations of human subjects to evaluate thermal sensations and the impact of exposure to such fields on normal human thermoregulation.

16. Medical Applications

16.1 Shortwave Diathermy—Early Clinical Use

Diathermy played a major role in shaping the early research on RFEM fields and in providing an understanding of their biological effects on human beings. This physical-medical modality, long used to produce therapeutic heating by the conversion of electromagnetic energy into thermal energy, dominated the early literature on the interaction of RFEM fields with biological tissue. Interest in this interaction dates to 1892, when d'Arsonval, the French physicist, physiologist and physician (and also, in current terminology, bioengineer), observed that currents passed through the body at a frequency of 10 kHz and higher can produce a sensation of warmth without the painful muscular contractions or the lethality that can occur during passage of intense currents at lower frequencies (Licht, 1965). This application heralded the use of RFEM energy by physicians for therapeutic heating of diseased tissues. RFEM currents as a modality of heating became popular because high-frequency currents penetrate deeply into the body and can produce heating via ohmic loss. Diathermy often replaced the use of hot packs and infrared radiation, which produce only superficial heating.

By the 1900s, physicians were using high-frequency currents between 0.5 and 3.0 MHz for therapy (Licht, 1965). As early as 1909, de Keating-Hart used intense heating via high-frequency electrical currents in combination with ionizing radiations for the treatment of cancer. Many clinicians and researchers have used these combined modalities in the treatment of cancer in human beings and in laboratory animals over the past seven decades. Work prior to 1920 was summarized by Rohdenburg and Prime (1921), who also reported their own work involving the treatment of spontaneous tumors in mice of the Lathrop strain by x rays alone, by diathermy alone, or by a combination of the two. Their work showed that, compared with controls, tumors treated with diathermy or x radiation alone showed little inhibition or regression of growth as compared with tumors treated by the combined agents.

By 1928, radiations near a frequency of 100 MHz (shortwave diathermy) were being used clinically. Research and clinical applications

of diathermy as an adjunctive treatment of cancer continued with the use of higher-frequency generators. Work during the 1920s and 1930s is well-summarized by Arons and Sokolov (1937). Although Rohdenburg and Prime (1921) contended that combined diathermy and x-ray treatments are required for satisfactory results, Liebesny (1921) was able to eradicate carcinoma in mice by using diathermy alone.

With the introduction of shortwave apparatus, Schereschewsky (1928) was often able to inhibit the growth of transplanted carcinomas in mice, and, in some cases, to completely eradicate tumors by treating mice with shortwaves of 3-m wavelength. Pflomm (1931) was able to inhibit the growth of Jenson-rat sarcoma by shortwave treatments at 4.5-m wavelengths. Some researchers, for example Reiter (1932), after experimenting with shortwaves varying from 3 to 15 m in wavelength, stated that there is a specific biological effect associated with wavelength. He reported that diathermy at 3.5 m was the most efficacious in treatment of tumors. He excluded elevated temperature as a possible factor in his interpretation of specific biologic action.

Roffo (1934) demonstrated that waves ranging from 0.58 to 6.75 m can inhibit the growth of rat sarcoma *in vitro*, but not that of embryonic chicken heart. Hill (1934) showed that exposure to shortwave radiation alone or to radium alone did not retard the growth of Jenson-rat sarcoma, whereas in combination growth was retarded. He stated that the elevation of temperature was insufficient by itself to be tumoricidal, but Mortimer and Osborne (1935) believed that heating alone is responsible for the therapeutic effect of shortwaves. Hasche and Collier (1934) found no evidence that the growth of Ehrlich mouse sarcoma *in vitro* was retarded when exposed to 3.5-m waves. Eidinow (1934) held that there is no specific action of shortwaves of 3- to 4-m wavelengths, and stated that they act the same way as diathermy currents of longer wavelengths simply by heating of tissues.

Schliephake (1935) treated carcinoma of the uterus by a combination of shortwaves and x rays; he observed, after several treatments, a marked disintegration of the carcinomatous tissue but, on suspending treatment for a period of several weeks, malignant growth recurred. Fuchs (1936) reported retardation of tumor growth after low-power shortwave exposures, in which heating was negligible, as an adjunct to x-ray therapy. Arons and Sokolov (1937) conducted a series of experiments based on the premise of athermal properties of shortwave therapy in which the temperature in the region treated was not allowed to rise above 26 to 27 °C. They used shortwaves of 6-m wavelength in combination with x rays to treat 30 cases of human malignancy, including carcinoma of the oral cavity, of the larynx, of the epigastrium, of the uterus, and of the rectum. At the time of their report,

they could not form definite conclusions concerning the radiosensitivity of the tumors treated by the shortwaves. They stated, however, that the method was of value in that there was no aggravation or stimulated growth of neoplastic tissue in any of their cases and that there was a lessening of skin injury caused by the x rays. They also reported other benefits of the treatment: Post-operative suppuration was inhibited, and an analgesic effect was often observed during the course of treatment.

16.2 RFEM Fields and Oncology—Pioneering Studies of Animals

In 1940, H. J. Johnson, using more precise quantitative methods than those employed by earlier investigators, reported on the action of shortwaves on transplanted tumors *in vivo* and *in vitro*. He developed a technique for continuously measuring elevated temperatures in tumors during exposure, studied the thermal sensitivity of the Jensen-rat sarcoma and the Walker-rat Carcinoma-256 over a range of temperatures (43.5 to 47 °C), and then quantified the exposure time necessary for 50-percent regression at various temperatures. Johnson found that the exposure durations required to produce a 50-percent regression of the Walker-rat Carcinoma-256 at 47, 45, and 43.5 °C were, respectively, 45 min, 1.5 h, and 6 hours. Exposure durations for 50-percent regressions of the Jensen-rat sarcoma at the same set of temperatures were 25 min, 1 h, and 3 hours. Johnson measured temperatures with thermocouples embedded in hypodermic needles; he tried to eliminate coupling of high-frequency currents by using a tuning process. Considerable problems were encountered because of wave trapping by thermocouples under certain conditions, but he was able at times to obtain reliable temperature measurements.

Despite the early reports of successful use of shortwaves to control malignancies in the laboratory and in the clinic, the methodology was never widely adopted in practice.

16.3 Thermal-Athermal Controversy

Arguments in support of and against the thesis of athermal effects of RFEM fields developed during the early history of therapeutic applications of RFEM waves. In addition to the claimed frequency-

specific effects in shortwave treatment of tumors, Danilewsky and Worobjew (1935) demonstrated that contractions by frog-nerve-muscle preparations increased in amplitude when high-frequency currents were applied along with minimal faradic stimulation. When the high-frequency currents were removed, the excitability of the nerve rapidly returned to its original level. With increasing current (at 0.5–1.0 MHz), a point was reached at which excitability was depressed. This same phenomenon of altered nerve-muscle excitability was also obtained by irradiating the sciatic nerve of a warm-blooded animal.

Audiat (1932) asserted that, because excitability of the nerve-muscle preparation diminished under the action of RFEM waves, it had to be a "specific" effect, because heating supposedly would have an opposite effect. It was also claimed by Delherm and Fischgold (1934) that high-frequency currents diminished excitability of the nerve-muscle preparation in a manner similar to that produced by the anodic effect of a direct current. Later, it was shown by Weissenberg (1935) that an interrupted, high-frequency current applied to a nerve-muscle preparation of a frog showed stimulating effects similar to those obtained by a pulsating DC current. It was postulated that the nerve rectified a small portion of the applied current. Pflomm (1931) stated that when a frog's heart was placed in a shortwave field, the beat became slower and that contractions lessened with the diastolic beat finally ceasing. But, when the field was switched off, the heart gradually resumed its beating. Hill and Taylor (1936), on the other hand, repeated Pflomm's work, showing that weak, high-frequency currents at wavelengths of 600, 22, and 6 m would increase the excitability of a nerve-muscle preparation, whereas stronger currents produced a depression of excitability. They showed that similar effects could be produced by a hot wire placed near the nerve and concluded that the mode of action of the high-frequency current on the nerve-muscle preparation is thermal. These researchers also demonstrated that the effects observed by Pflomm on the frog's heart were identical to that obtained when the frog's heart was warmed by conventional means.

Between 1931 and 1941, there were many basic problems in the use of shortwaves for effective therapeutic heating of tissues. Most of these problems arose because investigators were not able to quantify the actual rate of energy absorption by tissues during treatment. The results of therapeutic treatment were left to chance, and many quantitatively uncontrolled experiments resulted in contradictory statements in the medical literature. The various shortwave generators produced by different manufacturers operated at widely differing levels of output power. It was implied through advertisements that heating of deeper tissues would be enhanced with greater output power of the

generating equipment. Because the extent of heating of tissues seemed to vary considerably with frequency, even with the same apparent output power of the various devices, many researchers jumped to the conclusion that there are selective therapeutic properties associated with specific wavelengths.

16.4 Clinical Dosimetry

A research team consisting of engineers and physicians (Mittlemann *et al.*, 1941) measured elevations of temperature *in vivo* in tissues as a function of time rates and joule quantities of energy absorption; they presciently recognized that quantities of absorbed energy are superior to the output power of the diathermy applicator and the intensity of the incident field as dosimetric and therapeutic indices. The team instrumented a shortwave diathermy generator such that the quantity of energy absorbed by a limb of a patient under treatment could be measured to levels within 5 percent. As expected, the quantity of absorbed energy was highly correlated with the rate of temperature elevation of tissues. Table 16.1 shows the interrelation between absorbed energy, elevations of temperature, and duration of treatment (i.e., watts per 1000 cm^3 of tissue for an elevation of 0.1 °F per minute).

TABLE 16.1—*Relationship of temperature rise per minute to power absorption*[a]

Subject and thigh volume	No.	Absorbed power	Temperature rise	Specific absorbed power[b]	Deviation[c]
		W	°F min^{-1}	W $(1000\ cm^3)^{-1}$ $(0.1\ °F)^{-1}min^{-1}$	percent
Subject I	1	60	0.275	5.75	−1.0
3800 cm^3	2	72	0.310	6.15	+4.8
	3	74	0.300	6.42	+8.0
	4	85	0.384	5.86	0.0
	5	86	0.390	5.78	+0.7
	6	100	0.460	5.75	+0.7
	7	137	0.652	5.55	+5.2
Subject II	8	88	0.440	6.15	+4.8
3280 cm^3	9	88	0.440	6.15	+4.8
	10	44	0.260	5.20	−13.0
	11	135	0.720	5.75	−0.7
			Average	5.86	

[a] After Mittlemann *et al.* (1941).

[b] Specific absorbed power: watts per 1000 cm^3 thigh volume per 0.1-°F temperature rise per minute.

[c] Deviation of specific absorbed power from average value.

This work made use, for the first time, of partial-body, volume-normalized rates of energy absorption in units of W/1000 cm^3 closely related to the W/kg now widely used to index the RFEM absorbed energy rate, the *SAR*. The results of the energy-absorption measurements agreed closely with theory. The amount of energy absorbed per unit volume that raised the tissue temperature to a certain extent in a given period of time was virtually the same in all of their tests.

Mittlemann *et al.* (1941) conducted another series of measurements in which a patient was exposed to fields of differing wavelengths under differing conditions of exposure. The results (Figure 16.1) indicated that the ΔT per minute was proportional to the quantity of energy absorbed by the patient. The rate of energy absorption necessary to raise the temperature of 1000 cm^3 of tissue by 0.1 °F per minute was computed from the results of Figure 16.1 and is recorded in Table 16.2, a value that is in excellent agreement with the results in Table 16.1. It is significant that deviations from linearity did not take place during a 20-min exposure, unless the whole-volume absorption rate exceeded 100 W (calculated *SAR*, 48 W/kg), or unless the subject had been treated for a short time previously (curves with index 2 in Figure 16.1).

The work by Mittlemann *et al.* (1941) clearly demonstrated that the average level of tissue heating is dependent on rate of energy absorption and not on wavelength of the field for similar ratios of deep-to-

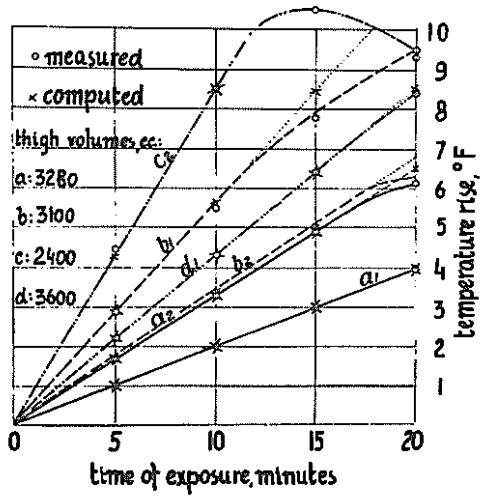


Fig. 16.1. Temperature rise as a function of duration of exposure showing the proportionality between temperature rise and the energy absorbed. See Table 16.2 for identification of curves. (After Mittlemann *et al.*, 1941.)

TABLE 16.2—*Heating results for four different subjects in response to various absorbed powers, techniques and wavelengths*[a]

Thigh volume	Curve no.	Wavelength	Technique	Absorbed power	Specific absorbed power[b]	Deviation[c]
cm^3		m		W	W $(1000\ cm^3)^{-1}$ $(0.1\ °F)^{-1}min^{-1}$	percent
3280	a1	6	Air Spacing	35	5.35	9.0
3280	a2	6	Air Spacing	63	5.83	0.0
3100	b1	12	Air Spacing	110	6.25	6.2
3100	b2	12	Air Spacing	70	6.60	11.0
2400	c2	12	Pancake Coil	115	5.68	3.0
3600	d1	8	Double Cuffs	80	5.35	9.0
				Average	5.83	

[a] After Mittlemann *et al.* (1941).

[b] Specific absorbed power: watts per 1000 cm^3 thigh volume per 0.1-°F temperature rise per minute.

[c] Deviation of specific absorbed power from average value.

superficial heating. It is also significant that there is a marked difference in the character of the temperature-time curves at high and low levels of power. At levels of power below 100 W (calculated *SAR*, 33 to 42 W/kg), temperature in the deep tissue was noted to rise along a straight line until the termination of the 20-min exposure period. When the *SAR* exceeded 42 W/kg, the final temperature was lower than the earlier peak temperature because of vasodilation and consequent rapid cooling of the volume of exposed tissue by circulatory convection.

During the first 10 years of development and use of shortwave diathermy, most research consisted of measuring the temperatures of superficial and deep tissues of both animal and human subjects exposed to capacitive- and inductive-type applicators, the generator wavelengths of which varied from 6 to 24 meters. The only dosimetric index at this earlier time was the power level of a source or a temperature measurement in tissues. A number of researchers, as a result of their observations of varying temperatures in exposed tissues in association with different wavelengths, concluded that absorption characteristics are wavelength specific. Others, however, such as Osborne and Coulter (1941), concluded that the variations were more dependent on electrode configuration and spacing and on the geometry of the tissue being treated than on frequency. These early researchers also observed that it was difficult to produce therapeutic elevations to 42 to 45 °C in deeper tissues, such as muscle and bone marrow, without adversely affecting the skin and other, more superficial, tissues.

16.5 Microwave Diathermy and Hemodynamic Effects

During the late 1930s and early 1940s, there was growing interest in the use of even shorter wavelengths of RFEM fields for therapeutic purposes. Williams (1937) reported that waves of a few centimeters could be focused, and Southworth (1937) pointed out that such waves can be directed through hollow conductors (waveguides). The proposal to use microwaves for therapeutic purposes originated in Germany when Hollman (1938) discussed the possibility of therapeutic applications of 25-cm waves; he predicted that the waves could be focused to produce heating of the deep tissues without excessive heating of the skin. Similar predictions were made shortly afterward by Hemingway and Stenstrom (1939) in the United States. The lack of hardware during the late 1930s prevented development and clinical application of these concepts, and diathermy continued to be applied at frequencies below 100 MHz.

At the end of World War II, when security restrictions were lifted on magnetrons as sources, the first microwave-diathermy apparatus was developed and operated at a frequency of 3000 MHz. With the new equipment, therapeutic application of microwaves began at the Mayo Clinic in 1946 (Krusen *et al.*, 1947; Leden *et al.*, 1947). This application involved exposure of laboratory animals to 3000-MHz fields at an output power of 65 W. Temperature distributions in thighs of experimental dogs were measured by thermocouples before and after irradiation. In this work (thermocouples were removed during periods of irradiation), it was demonstrated that deep tissues could be heated, resulting in a number of physiological responses, including an increased blood flow to the treated area. But, as in the case of shortwave diathermy, it was noted that the average elevation of temperature under microwave diathermy was greater in the skin and subcutaneous fat than it was in deeper muscular tissues, although the final temperature in the muscle tissue was higher than that obtained with sources in earlier use.

Worden *et al.* (1948) found that a monopole antenna with a hemispheric reflector, which was energized at 30 W and at 2450-MHz, resulted in maximal heating of thighs of dogs after an exposure period of 20 min when the antenna was located 2.5 cm from the surface of the thigh. If the period of exposure was extended to 30 min, the temperature dropped below the peak value as a result of a sharp increase in blood flow. This finding was consistent with that found earlier by Mittlemann *et al.* (1941). Worden *et al.* also carried out comparative studies on the effects of exposing ischemic tissue and tissue with normal circulation to the same amount of microwave energy

delivered over a period of 15 to 20 minutes. They reported serious damage in ischemic areas even though the recorded temperatures were not observed to be higher than those of tissues with normal circulation.

Siems *et al.* (1948) performed comparative studies of the effect of shortwave and microwave diathermy on blood flow. Their experiments clearly demonstrated that shortwave and microwave diathermy were equally effective in producing increased blood flow in the extremities of normal dogs. A number of such experiments were carried out, sometimes with conflicting reports on elevations of temperatures. To resolve the conflict, Richardson *et al.* (1950) carried out research on the relation between deep-tissue temperature and blood flow during irradiation of the gastrocnemius muscles of dogs by shortwave and microwave diathermy. They found, with both modalities, that blood flow in a volume of tissue depended largely on the ΔT. It was necessary to increase temperatures at the 1-cm depth in an extremity of the dog to a level of 42 to 43 °C before a consistent increase in blood flow occurred in the femoral artery. The increase in blood flow was sufficient to diminish the temperature by 3 °C after once reaching a critical temperature. These results are consistent with the findings of Mittlemann *et al.* (1941) and they have been observed subsequently by many researchers and clinicians.

16.6 Clinical Application of RFEM Fields in Cancer Therapy

After 1950 and until 1965, research on the use of microwave diathermy in physical medicine expanded significantly. Clinical and experimental studies were much more predominant than any quantitative work on dosimetry. Gessler *et al.* (1950) appear to be the first group of physicians to use RFEM energy at microwave frequencies in the experimental treatment of cancer. They were able to eradicate spontaneous mammary carcinoma in C3H/HeJ mice solely by irradiation at 150 to 200 MHz and at 2450 MHz. Five years later, Allen (1955) eradicated Crocker sarcoma 39 in rats by combined exposure to x rays (1500 to 2000 R) and to 12.5-cm fields; the animals were exposed to the fields for 10 to 20 min, and a peak temperature of 42 °C was recorded in the tumors.

Crile (1962) reported that growth of tumors in dogs and human beings was controlled by 2450-MHz microwave diathermy and x irradiation in combination. Crile noted that prolonged elevation of temperature in certain cancers at levels between 42 and 50 °C selectively

destroyed tumors without damaging normal tissues. He concluded that it was a secondary inflammatory reaction rather than a primary elevation of temperature that destroyed the tumors. Two years later, Cater *et al.* (1964) reported that combined therapy of 2620-R (220-kV x rays) and subsequent 10-cm-microwave irradiations of the tumor (47 °C for 8 to 10 min) cured some rats of hepatoma 223 transplanted to the leg. The investigators noted that there were no long-term survivors treated by x rays alone or by diathermy alone; tumors were smaller and survival times were significantly longer in rats treated by the combined therapy. In the same year, Moressi (1964) reported that mortality patterns were essentially identical in mouse sarcoma-180 cells exposed to 2450-MHz fields and in conventionally heated cells held at the same temperatures over a range of 43 to 48 °C. He found that the malignant-cell decay was highly temperature-dependent, as indicated by the "spontaneous" destruction of cellular material. His investigation also showed that temperature deviations no greater than 1 °C, if undetected, can lead to erroneous interpretations:

> "One may critically question the role of unrecognized temperature discrepancies in many of the previously reported studies in which gross results seemed to indicate the presence of a non-thermal factor. Temperature regulation is thus a major concern in investigations concerned with the effects of high frequency electromagnetic irradiation on biological systems, especially when some form of cellular destruction is involved." (Moressi, 1964, page 250.)

Although the use of microwaves in therapeutic heating gained in popularity in the 1950s and early 1960s, interest in the use of shortwaves also continued. Birkner and Wachsmann (1949) reported regressions and cures in skin carcinoma of patients exposed to shortwaves and x rays in combination. Exposure of each of 82 patients for a period of 2.5 h to 6-m shortwaves (tumor temperatures of 42 to 44 °C) alone produced regressions but not cures. When shortwave exposures were combined with x irradiation, however, some cures were observed. Fuchs (1952) reported good clinical results when 6-m-shortwave exposures of 10 to 20 min duration were followed by x irradiation. He claimed that the good clinical results arose from increased radiosensitivity incident to hyperemia and to acceleration of metabolism.

In addition to the use of combined RFEM-field and x-ray therapy, interest developed in the use of microwaves in selective heating of tumors to provide more effective therapy in conjunction with injected radioactive materials and chemotherapy. Copeland and Michaelson (1970) reported that the heating of Walker carcinoma 256 by focused radiation (2800-MHz fields at 260 mW/cm^2 for 5 min) induced a

substantial increase in the amount of intravenously-injected ^{131}I fibrinogen that was localized in the tumor. They pointed out that this tumor-heating technique could effectively increase the therapeutic tumor-irradiation dose delivered by ^{131}I fibrinogen by 400 percent.

Zimmer *et al.* (1971) reported the use of selective RFEM heating of tumors of animals in deep hypothermia to enhance the action of chemotherapy. They treated spontaneous mammary tumors in C3H mice and induced mammary tumors in Sprague-Dawley rats. In 20 control mice, there were no spontaneous regressions of tumors, and, in 20 mice treated with chemotherapy only, two animals showed regression of tumors with a regression time of 10 days. In the group treated by differential, 9.05-GHz, field-induced hyperthermia (a colonic temperature of 4 to 8 °C and a tumor temperature of 30 to 42 °C) without chemotherapy, only one tumor regressed, this after 7 days. In the group of 20 mice treated by differential hyperthermia and by chemotherapy in combination, 17 animals exhibited regression of tumors after 55 ± 25 days. Similar results were obtained in the study of rats; all 10 animals exposed to 2450-MHz fields exhibited regression of tumors; the average regression time was 22 days.

Overgaard and Overgaard (1972a) provided an excellent review and reported on extensive and well-conducted experiments on 1200 mice in their laboratory, where mice with transplanted tumors were permanently cured without damage to normal tissues by treatment with 27.12-MHz shortwaves. They used a special, field-nonperturbing thermocouple that could be embedded in a tumor to provide automatic regulation of the shortwave output. Thus, it was possible to maintain a desired tumor temperature continuously with a variation of about ± 0.1 °C. With carefully controlled elevations of temperature in the range of 41.5 to 43.5 °C, they were able to work out a quantitative relation between temperature and exposure time for eradicating the transplanted tumors.

In their analysis, Overgaard and Overgaard showed that the thermalizing treatments induced histological changes in tumor cells without damaging stomal and vascular cells in the tumor or in the surrounding normal tissue. Immediately after treatment, definite changes were observed in the mitochondria and lysosomes in the tumor cells. The magnitude of these changes was directly related to the elevation of temperature, and became more pronounced within hours or days. The authors noted changes in the nuclei of the tumor cells and in the chromosomal and nucleolar chromatin within the first few hours after exposure. They observed severe injury in all tumor cells 24 h after exposure to a curative dose. Through histological and biochemical observations, the authors obtained clues that allowed them to assume

that the direct effect of heating was a selective activation of the acid hydrolases localized in the lysosomes of the tumor cells.

In later work with diathermy, Overgaard and Overgaard (1972b) found that the addition of a small dose of localized x radiation produced a highly significant intensification of the tumor-eradicating effect. They found that successive application of x rays and diathermic heating, both at levels substantially smaller than those required in isolation to produce cures, produced a larger number of total cures. They also noted that intervals as long as 24 h between applications did not appreciably alter the curative effect.

From the mid-1970s on, interest in use of RFEM fields, either alone or in combination with x rays, increased substantially; a larger number of favorable reports on the use of combined therapy has appeared in symposia proceedings and publications. Among these are the Proceedings of the *First* and *Second International Symposia on Cancer Therapy by Hyperthermia and Irradiation* (ACR, 1975; Streffer *et al.*, 1978); a special issue of *IEEE Transactions on Microwave Theory and Techniques* on microwaves and medicine, with accent on the application of RFEM energy to cancer treatment (IEEE, 1978); a special *Radiation and Environmental Biophysics* issue on hyperthermia in cancer therapy (1980); *The Third International Symposium on Cancer Therapy by Hyperthermia, Drugs, and Radiation* (Dethlefsen and Dewey, 1982); a special issue of *The Journal of Microwave Power* on *Electromagnetic Hyperthermia* (JMP, 1981); and *The Annals of the New York Academy of Science* on *Thermal Characteristics of Tumors: Applications in Detection and Treatments* (Jain and Gullino, 1980). In addition, new textbooks, Lehmann (1982), Storm (1982), Hahn (1982), and Gautherie and Albert (1982) cover the subject in great detail.

Some examples of more recent applications of RFEM fields are in the reports of von Ardenne (1978), Overgaard (1978), Kim *et al.* (1978), LeVeen *et al.* (1976), Storm *et al.* (1981), Kim *et al.* (1981) and Gibbs (1981). Continuing success is reported in the use of microwave hyperthermia as an adjunct in the treatment of tumors. Szmigielski *et al.* (1978) reported prolonged survival of mice bearing Sarcoma-180 tumors after irradiation by 3000-MHz fields that elevated rectal temperature by 3 to 4 °C. The inhibitory effects of microwave hyperthermia were enhanced by simultaneous treatment of the mice with interferon and interferon inducers. Mendecki *et al.* (1978) completely eradicated transplanted mammary adenocarcinoma in C3H mice and, in several clinical cases, obtained favorable results in the treatment of basal-cell carcinoma, malignant melanoma, and skin metastases of carcinoma of the breast by both 2450-MHz and 915-MHz fields. In

these studies, the tumors were raised to a temperature between 42.5 and 43 °C. Nelson and Holt (1978) and Harnback *et al.* (1977, 1979) successfully treated cancers in patients by combined therapy with 433-MHz fields and ionizing radiation.

More recent clinical successes with microwave hyperthermia have been reported by Gibbs (1981) and Perez (1981). Interstitial application of low-frequency energy (500 kHz) has also been successfully used in the treatment of tumors (Conner, 1980).

16.7 Biophysical Characterization of Diathermy

Significant research to quantify various biological effects of RFEM fields was done by Schwan (1954, 1955, 1957, 1958, 1959) at the University of Pennsylvania. Schwan's work on dielectric properties of biological tissues and on the influence of tissue geometries on scattering deserves special attention. He demonstrated theoretically that irradiation at a frequency of 2450 MHz is often not therapeutically advantageous because of several major deficiencies including: (1) excessive heating of subcutaneous fat by standing waves, (2) poor penetration into muscle tissue, and (3) poor control of the distribution of energy absorption in the patient because of large variations in electrical thickness of tissues (compared with wavelength in subcutaneous tissues). He recommended that frequencies be reduced to 900 MHz and lower.

Lehmann *et al.* (1962a, b; 1965a, b; 1970a) and Guy (1966) experimentally verified Schwan's earlier theoretical prediction that irradiation at 900 MHz or below can produce more determinate therapeutic patterns than those obtained with 2450-MHz fields. Since 1966, Lehmann *et al.* (1970a), deLateur (1970), and Guy (1971a, b) have developed and clinically tested direct-contact applicators that operate at 915 MHz, which have proven to be therapeutically more effective and safer in terms of leakage radiation than extant 2450-MHz equipment.

Recently, there have been considerable advances in the design, efficacy, and safety of both shortwave- and microwave-hyperthermia applicators and systems (Christensen and Durney, 1981; Kantor, 1981; Cheung *et al.* 1981; Samaras *et al.* 1981; and Salcman, 1981). Schwan's pioneering work in the characterization of biophysical properties of normal tissues under RFEM irradiation is being extended to include neoplastic tissue by Foster and Schepps (1981), Burdette *et al.* (1982, abstract), and Stuchly *et al.* (1981).

16.8 Mode of Action of Diathermy and Therapeutic Indications

In physical medicine, the effects of RFEM fields are believed to arise from simple volume heating. When local elevations of temperature are induced in living tissues, many physiological responses occur that are due, in part, to direct thermalization of tissues and, in part, to reflexive changes initiated distally by heating of local nerve receptors. One response is an increase in blood flow via vasodilatation. This response is accompanied by increases in capillary pressure, in cellular-membrane permeability, and in metabolic rate. The latter increase can also produce a further increase in tissue temperature.

Millard (1961) measured effects of shortwave irradiation on local blood circulation through the use of radioactive sodium in accord with the method of Kety (1949). He showed that the quantity of radioactive sodium remaining at the site of injection decreased along a straight line when plotted semilogarithmically against time, the slope of which he called the clearance constant. He found that the clearance constant of the blood flow in the skin increased approximately 150 percent after exposure. The average ΔT over the injection site was 5.3 °C. Clearance constants in muscle, on the other hand, were found to increase by 36 percent when the corresponding ΔT was 5.2 °C. In about one-third of his subjects, there was little overall change in the muscle-clearance constant, and in one-third there was a decrease followed by an increase.

Harris (1963) was able to quantify the effects of shortwave diathermy on local circulation in knees of normal and rheumatic patients by using the same radiosodium method. The results in Figure 16.2 indicate that in the normal knee, the increase in circulation averages 100 percent when the knee is exposed via condenser electrodes to fields that are adjusted for maximal skin tolerance to heating. In osteoarthritic knees or rheumatoid knees with minor involvement, the shortwaves produced an increase in circulation averaging 40 to 60 percent. In contrast, rheumatoid knees with active involvement subjected to shortwaves exhibited the same clearance constant as the other exposed knees, but this value represented a decrease of 25 percent in circulation. Thus, assuming the rate of sodium clearance is related to the degree of hyperthermia, the author stated that the results indicate that it would be logical to heat only active rheumatoid joints with shortwave diathermy as regional therapy in rheumatoid arthritis.

McNiven and Wyper (1976) measured the increase in blood flow in the vastis lateralis muscle of five men under treatment by 2450-MHz diathermy when output power was adjusted to produce maximally

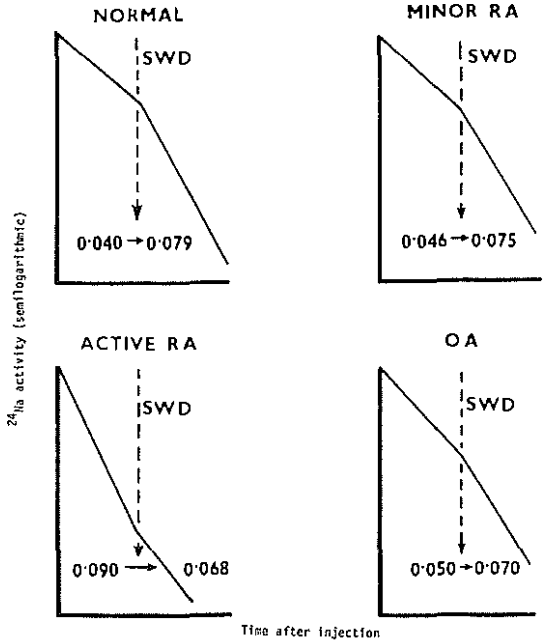


Fig. 16.2. Effect of short-wave diathermy on clearance from normal, rheumatoid arthritic (RA) (minor and major activity), and osteoarthritic (OA) knee joints. The numbers in the figures are the slopes of the curves, i.e., the clearance constants (min^{-1}), before and after application of the shortwave diathermy (SWD). (After Harris, 1963.)

comfortable heating. Blood flow in the muscle was measured by the ^{133}Xe-clearance technique by which 200 μCi of inert, diffusable radioactive tracer ^{133}Xe is dissolved in 0.1 ml of sterile isotonic saline and injected into the muscle. A scintillation counter monitors the count rate of gamma rays emitted by the ^{133}Xe as a function of time after injection, thus enabling the rate of clearance of xenon, and therefore of the blood flow, to be determined. After a single injection, blood flow in the muscle was measured at rest, during application of microwaves, and during static exercise. Under steady-state conditions, the count rate of ^{133}Xe, when plotted as a function of time, produces a straight line on a semilogarithmic plot, as shown in Figure 16.3. Muscle blood flow, F, can then be obtained by the equation $F = 48.5/T_{1/2}$, where $T_{1/2}$ is the half life for clearance as determined from the slope of the plot. If $T_{1/2}$ is in minutes, then the units of F are in milliliters per 100 grams per minute. Figure 16.3 indicates that after 8 min of irradiation, the slope of the clearance curve was observed to increase, which corresponded to a rise in the blood flow rate in the muscle. When the flow reached a steady-state value, the apparatus was switched off. It was

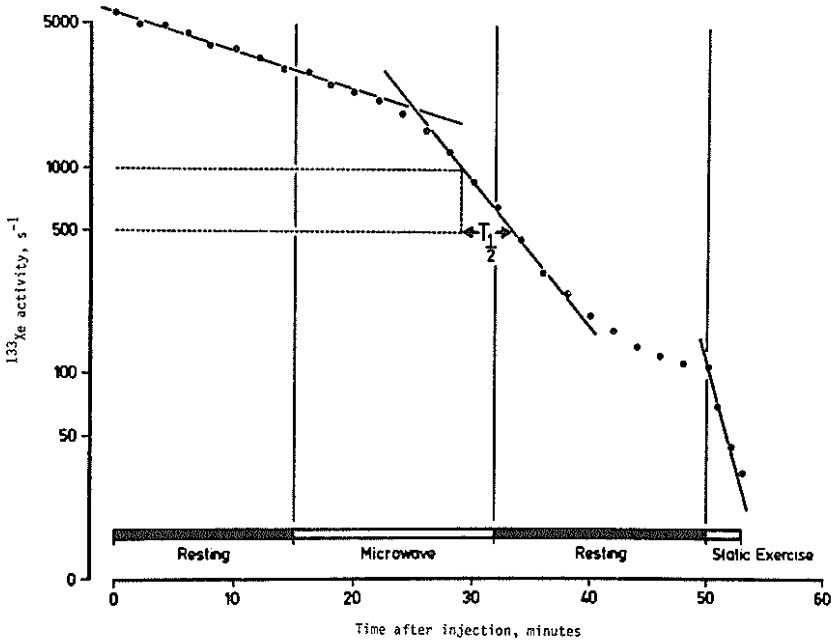


Fig. 16.3. Clearance curve of ^{133}Xe obtained from a single intramuscular injection. The values obtained for clearance half lives are 16.7 min for the initial resting period, 4.2 min at the end of the microwave application, and 1.6 min during static exercise. The corresponding muscle blood-flow values are 2.9, 11.5 and 30.3 ml (100 g)$^{-1}$ min^{-1}, respectively. (After McNiven and Wyper, 1976.)

then noted that the flow was maintained at the higher level for about 5 min before gradually decreasing. The results based on all five subjects (Figure 16.4) show mean values of 2.9 ml (100 g)$^{-1}$ min^{-1} at rest, rising to 11.4 mL (100 g)$^{-1}$ min^{-1} at the conclusion of irradiation. It was also observed that blood flow increased to 30.0 ml (100 g)$^{-1}$ min^{-1} during static exercise. In contrast to the 150-percent increase in blood flow reported by Millard (1961) for shortwave diathermy, microwave diathermy produced an increase of 400 percent.

Guy *et al.* (1974a) estimated that increases in blood flow in thighs of normal human subjects exposed to shortwave diathermy were as high as 13.7 ml (100 g)$^{-1}$ min^{-1}. This rate was obtained by observing the time dependence of the temperature in the muscle that was exposed to the shortwave fields. The time-dependent change in the slope of the temperature curve during shortwave exposure, both before and after flow of blood was occluded by a tourniquet, provides the quantitative information necessary to predict the increase in blood flow. This method was later used by Lehmann *et al.* (1978) to determine

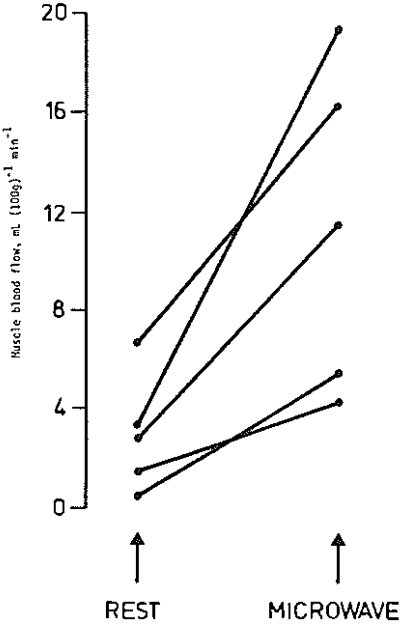


Fig. 16.4. Muscle blood-flow values during the initial resting period and at the end of microwave therapy in 5 subjects as determined by the ^{133}Xe-clearance method. (From McNiven and Wyper, 1976.)

blood flow in deep muscle exposed to 915-MHz fields during simultaneous cooling of the skin's surface by air convection. Calculated blood flow of 29 ml (100 g)$^{-1}$ min^{-1} was obtained when the *SAR* in the muscle was 112 W/kg, a value that produced a maximal elevation of temperature deep in the muscle to a level between 43 and 45 °C. Similar results, a calculated maximal blood flow of 32 ml (100 g)$^{-1}$ min^{-1}, were obtained by Sekins *et al.* (1980) by the ^{133}Xe-clearance method in evaluating the same 915-MHz diathermy applicator under the same experimental conditions.

Many physicians believe that enhanced circulation can increase the rate of healing of diseased or damaged tissue by increasing the transfer of metabolites across cell membranes, thereby providing for greater concentration of white cells and antibodies and for an increased transport rate of toxins, engulfed bacteria, and debris away from the treated areas (Schliephake, 1958). Heating can promote relaxation in muscles, reduce pain, and provide relief of muscle "spasms" (Fischer and Solomon, 1965; Lehmann, 1971). Heating can also produce changes in the properties of collagenous tissues, as found in tendon, joint capsule, and scarred synovium. As the collagenous tissue is heated

to therapeutic levels, the property of viscous flow becomes predominant and tension is reduced (Lehmann *et al.*, 1970b). If a physical therapy program of stretching is used in conjunction with heating, for example in patients with limited hip and shoulder movement, one can take advantage of the increase in extensibility and produce significant increases in range of motion (Lehmann, 1971; Lehmann *et al.*, 1954, 1961). Joint stiffness can also be relieved by heating. Backlung and Tiselius (1967) have measured the joint stiffness of rheumatoid patients and have shown a decrease in the hysteresis loop after heating of the joint.

16.9 Thermal Considerations

The temperature of tissues is probably the most important factor in determining the extent of the physiologic response to heat. Lehmann (1971) has shown, in studies of experimental animals, the relation between hyperemia (increase in blood volume) and temperature (Figure 16.5). The results indicate that tissue temperature must be elevated above 41 °C to produce significant therapeutic action, and a focal temperature near 45 °C is needed for a maximal reaction. The body's metabolic rate will also increase initially with increased temperature. The factor of increase is approximately $(1.1)^{\Delta T}$ within physiological limits (Brown and Brengelmann, 1965). For example, if initial tissue temperature is 34 °C, an elevation of temperature to 40 °C will produce

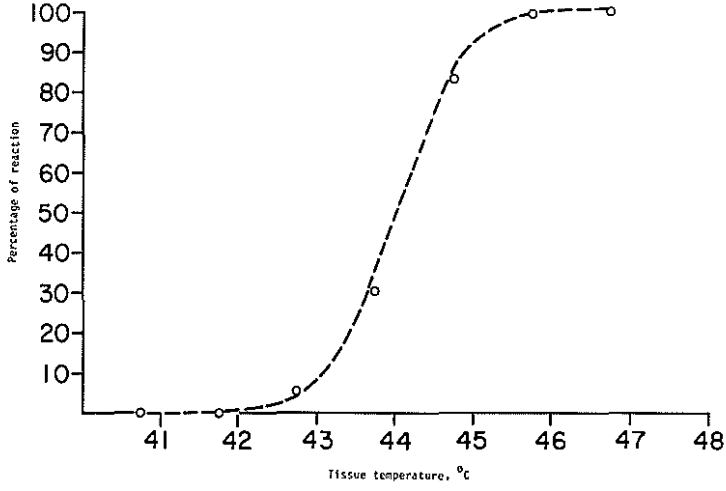


Fig. 16.5. Dependence (relative to maximal value) of hyperemia on tissue temperature. (From Lehmann, 1971.)

a 77-percent increase in metabolic rate. If it is assumed that the metabolic increase in a specific tissue is comparable to the general increase of metabolic rate associated with a net increase in body temperature, a focal temperature of 45 °C is probably the safe upper limit; a further increase would sharply retard or block local metabolism (Lehmann and Vorshuty, 1950; Lehmann and Hohlfeld, 1952).

The threshold of thermal pain corresponds to a skin temperature of 45 °C, and the intensity of pain will increase to a maximum at approximately 65 °C. The threshold for irreversible damage of skin tissue is 44 to 45 °C if the temperature is maintained for a sufficiently long period of time (Hardy, 1965). For short periods of elevated temperature, the skin can tolerate higher temperatures without irreversible damage. For example, 65 °C can be tolerated for 1 s, 50 °C can be tolerated for 1 min, and 46 °C can be tolerated for 1 hour. For many other tissues, 39 °C appears to be the maximal temperature that is tolerated without damage during prolonged elevations (Kottke, 1965). Certain tissues appear to have a lower tolerance, however. For example, the testicles, which are normally at lower temperatures than other organs, can be affected adversely at temperatures near normal (37 to 37.5 °C) body temperatures (Imig *et al.*, 1948). The lens of the eye is especially vulnerable to radiant heating, and irreversible damage can occur at elevated temperature because of a lack of blood circulation and poor tissue-repair capabilities (Carpenter and Van Ummersen, 1968).

Figure 16.5 illustrates that the range of therapeutic temperatures is not only narrow, but is very close to damaging levels.

Lehmann (1971) has shown that the duration of elevated temperatures in tissues is important in determining the extent of biological actions (Figure 16.6). This figure indicates that a minimal effective duration of elevation is 3 to 5 min, whereas maximal therapeutic effects may be obtained after a 30-min application. It is clear that the elevation of temperature plays an important role in determining the extent of the biological response because, during the total period of application, only the period in which the effective temperature level is reached is therapeutically beneficial. Also, the physiological responses of nervous-system temperature receptors seem to be more pronounced when the rate of temperature elevation is rapid (Lehmann *et al.*, 1958; Dodt and Zotterman, 1952).

When the skin is superficially heated, its temperature will elevate and it will exhibit the reactions described above. Although beneficial in treatment of pathologic lesions at or near the skin's surface, superficial heating is ineffective in treating deeper lesions. The subcutaneous fat acts as a thermal barrier that, in combination with

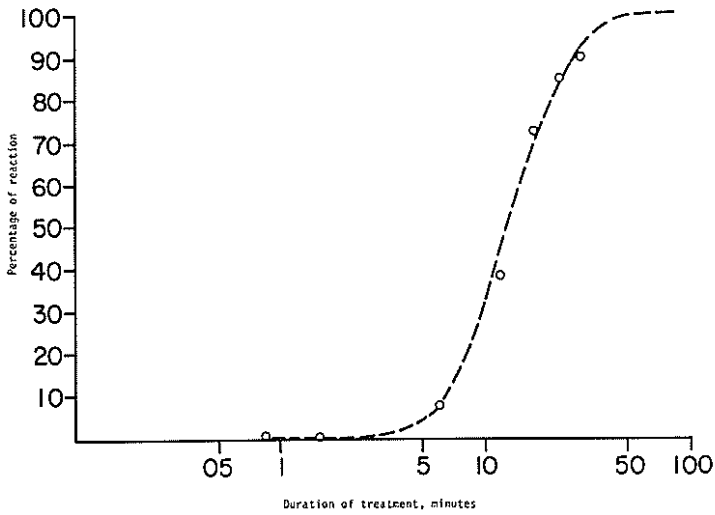


Fig. 16.6. Dependence (relative to maximal value) of hyperemia on duration of treatment. (From Lehmann, 1971.)

increased surface vasodilation, will prevent flow of thermal energy into the deeper musculature. No increase in the flow of blood to deeper tissues will result, and there may even be vasoconstriction to compensate for the increased flow of blood near the body's surface.

Nervous reflexes arising from surface heating of one part of the body can lead to temperature increases in other parts of the body, e.g., in an opposite extremity, but these ΔTs are less pronounced than the primary increases (Fischer and Solomon, 1965). Relaxation of striated skeletal muscles may occur, and muscle spasms may be resolved by surface heating because of reflexive nervous reactions from surface-temperature receptors. Thus, in general, surface heating provides only mild physiologic and therapeutic reactions, and any effects of the deeper pathologic conditions are only reflexively mediated.

Effective therapeutic heating of tissues below the skin, e.g., in the subcutaneous layer of fat, by RFEM fields requires proper selection of frequency, applicator, and input power so that the temperatures of the deeper tissue can be raised to the optimal level of 44 to 45 °C within a 5- to 15-min period. The duration of the maximal temperature can be controlled by adjusting the input power level. Just before or when the temperature reaches the maximal level, vasodilatation will produce a marked increase in blood flow that will limit the ΔT in tissues with good vascularity, which will be followed by a decrease in temperatures from the peak value by several degrees Celsius. An exposure period of 20 to 30 min is generally required to produce optimal therapeutic benefits.

17. Exposure Criteria and Rationale

17.1 Background

In the early to middle 1950s, tentative efforts were made to establish exposure criteria for RFEM fields to provide a margin of safety for industrial populations. The data base needed to establish exposure criteria and limits was almost non-existent from a biological point of view, and only the preliminary, pioneering studies of energy absorption and transfer processes by Schwan and students had been reported (*cf.*, e.g., Schwan and Piersol, 1954, 1955; Schwan and Li, 1953, 1956). Because the evidence at that time supported the position that hazards would arise only from heating of tissues by absorption of RFEM energy, the general approach was to establish an exposure criterion based on tolerable thermal loading. Participants in the first Tri-Service Conference on the Biological Hazards of Microwave Radiation (Pattishell, 1975) formally accepted for the first time a limit on occupational exposure: a maximal power density of 10 mW/cm^2, which was applicable to military personnel at all "microwave frequencies." Several private corporations also established working limits on exposure as operating guidelines, but it was not until 1966 that Committee C95.1 of the American National Standards Institute (ANSI) established a working subcommittee (Subcommittee C95-IV) to develop exposure criteria. The limit proposed by this subcommittee was the same as that prepared by the Tri-Service Committee in 1957 (a power density of 10 mW/cm^2 at frequencies from 10 MHz to 100 GHz). In 1974, this standard was retained unchanged, except for minor revision, by the C95.1 committee. In 1982, ANSI promulgated a new revision that incorporated recognition of substantial frequency-dependent variations in rates of energy transfer to the human body from an RFEM field (ANSI C95.1-1982). The limits of the new standard, which are summarized in Table 17.1, explicitly account for these variations.

ANSI standards are advisory only. The Occupational Safety and Health Administration adopted the 1966 ANSI-C95.1 standard as an exposure guide in the workplace (OSHA, 1971). However, in the application of the OSHA regulations, two rulings by the OSHA Review Commission, an independent agency, (1) that standards based on

TABLE 17.1—*ANSI C95.1-1982 protection guides: radiofrequency electromagnetic radiation*[a,b]

Frequency (f) range	Equivalent power density[c]	(Electric field)^2	(Magnetic field)^2
MHz	mW/cm^2	V^2/m^2	A^2/m^2
0.3–3	100	4×10^5	2.5
3.0–30	$900/f^2$	4×10^3 $(900/f^2)$	$0.025(900/f^2)$
30–300	1.0	4×10^3	0.025
300–1500	$f/300$	4×10^3 $(f/300)$	$0.025(f/300)$
1500–100,000	5.0	2×10^4	0.125

[a] From ANSI (1982).

[b] measured 5 cm or greater from any object in the field and averaged for any 0.1 h (6 min).

[c] (Electric Field)$^2/1200\pi$ or 12π(magnetic field)^2, whichever is greater.

"*should*" statements, which the regulations are, are not enforceable because they are advisory, and (2) that a hazard addressed by an advisory standard cannot be the subject of a general duty citation, as attempted by OSHA to counteract the effect of the first ruling, resulted in the inability of OSHA to implement and enforce its non-ionizing regulations. In a 1982 Field Directive, OSHA affirmed, among other matters, that these decisions of the OSHA Review Commission are its current policy.

In 1975, the United States Air Force published a two-step frequency-dependent standard, AFR 161-42, that specified permissible exposure levels of 50 mW/cm^2 at frequencies between 10 kHz and 10 MHz, and 10 mW/cm^2 at frequencies between 10 MHz and 300 GHz (USAF, 1975).

It is beyond the scope of this report to provide a complete coverage of proposed and current exposure criteria for countries other than the United States. As in other Western nations, these values range from limits quite close to those recommended in the ANSI-1974 standard (e.g., 10 mW/cm^2 in the Federal Republic of Germany, in the United Kingdom, and in the Netherlands), to values similar to the more recent Swedish and Canadian standards (~1 mW/cm^2). Among the Eastern European countries, the working levels for occupational exposure are significantly lower than those of any ANSI standard. These standards are reviewed in a document published by the World Health Organisation (WHO, 1981). In summary, this document classifies Eastern European standards in two groups. Group I is represented by the standard of the Union of Soviet Socialist Republics, which specifies a working-day limit of 10 μW/cm^2, which can be increased to 1 mW/cm^2 for periods not exceeding a few minutes. The WHO Group-

II standards include those of the German Democratic Republic, Poland, and Czechoslovakia. These countries have general-population, continuous-exposure guides ranging from 10 to 100 $\mu W/cm^2$.

Clearly, varied opinion and philosophy underlies these widely ranging standards for exposure to RFEM fields. It is also clear that, until the promulgation of the ANSI-1982 standard, little consideration had been given by standard setting bodies in the United States to the role of the carrier frequency of the radiating source in relation to the deposition of energy within the body, and, hence, to a more accurate assessment of biological effectiveness of the radiation.

17.2 Measurement and Units for RFEM Fields

The transfer of energy from the radiation field of an RFEM source to a biological system, and the ultimate fate of that transferred energy in terms of biological change in living tissue, is an extremely complex problem. The details of field-body interactions have been presented at length in a publication by NCRP Scientific Committee 39, Report No. 67, which is entitled *Radiofrequency Electromagnetic Fields: Properties, Quantities and Units, Biophysical Interaction and Measurements* (NCRP, 1981). Report No. 67 is a primary source on which the present report is based with respect to determination of exposure guidance. Indeed, it was also the basis upon which the ANSI standard was developed.

17.2.1 *Power Density and Field Strengths*

NCRP Report No. 67 reviews the various means of measuring RFEM fields and emphasizes that there is little possibility of directly measuring the absorption of energy by biological bodies at the cellular level. It is necessary to measure some characteristic of the incident field, and from this to impute an energy deposition rate in the tissue of interest. From the earlier portions of this section, it is evident that all previous exposure criteria have characterized the field in units of the power density of an equivalent far-field plane wave (in, e.g., mW/cm^2 or W/m^2). In some cases, measurements of the electric-field strength in V/m and/or of the magnetic-field strength in A/m have also been used as exposure criteria (see Table 17.1). Because nearly all devices available to measure radiation fields fundamentally measure the strength of the electric or the magnetic field, there is much to be said for specifying exposure limits in these terms. The relation between

the power density of a far-field plane wave and the strength of its fields is simple:

$$S = E^2/1200\pi = 12\pi H^2, \tag{17.1}$$

where power density, S, is expressed in mW/cm^2, electric field strength, E, is expressed in V/m, and magnetic field strength, H, is expressed in A/m.

17.2.2 *Dosimetry*

Although the frequency-dependent rate of RFEM energy absorption by a biological body was not formally incorporated into exposure guidelines until the advent of ANSI-1982 standard, this dependency was discovered in the early 1960s by a Soviet scientist, V. A. Franke (*cf.* Franke, 1961; Presman, 1970), who exposed models of human beings to fields that simulated longwave, shortwave, and microwave irradiation in the far field. These experiments were later confirmed and extended by Gandhi and colleagues (*cf.*, e.g., Gandhi, 1974, 1975b, 1980b; Gandhi *et al.*, 1977; Durney *et al.*, 1978; Gandhi *et al.*, 1979), who performed analytical and experimental studies on models of human beings in conjunction with experimental studies of small animals. The primary factors that control rate of energy absorption were found to be the wavelength of the incident field in relation to the dimensions and geometry of the irradiated organism, the orientation of the organism in relation to the polarity of field vectors, the presence of reflecting surfaces, and whether conductive contact is made by the organism with a ground plane. The maximal rate of energy absorption from a plane wave by the isolated, ungrounded mammal was found to occur when its long axis is parallel to the vector of the electric field and its axial length approximates four tenths of the wavelength of the incident field. Under these conditions, the organism exhibits *resonance*, and its electromagnetic capture surface is larger by 2- to 3-fold than is the area of its geometric cross section. The biological body, therefore, conforms to predictions of antenna theory (Gandhi, 1974). In addition, if the resonant target is electrically grounded—which roughly halves the resonant frequency—or if other reflective surfaces or objects are in proximity, the rate of energy absorption can increase to even higher levels.

In the wake of the pioneering investigations of Franke and Gandhi, it came as no surprise when a sizeable number of studies of murine and primate animals revealed that rates of energy absorption are more reliable predictors of biological effects than are power densities of the

incident field (see, e.g., Section 12). That measures of absorbed energy are a prerequisite to valid scaling of strengths of incident fields at different frequencies for predicting biological responses was recognized early by the clinicians (Mittlemann *et al.*, 1941; see also Section 16), but it was not until the late 1960s that a dosimetric approach to control of RFEM radiations, comparable to that used in the fields of clinical pharmacology and ionizing radiation, was introduced (Justesen and King, 1970; Justesen *et al.*, 1971; King *et al.*, 1971; Johnson, 1975; Justesen, 1975; NCRP, 1981; Guy, 1983). The mass-normalized time rate of energy absorption (dose rate) and its time integral (energy dose), as respectively specified in SI units of W/kg and J/kg, were adopted by the NCRP, and are described in detail in NCRP Report No. 67 (NCRP, 1981). The RFEM-energy dose was labeled *Specific Absorption* (*SA*), and the dose rate was labeled *Specific Absorption Rate* (*SAR*). This nomenclature, which is specifically applicable to dosimetric measures of RFEM fields, was devised by NCRP as a more suitable terminology than the generic terms of *dose* and *dose rate*, which carry for many individuals connotations of ionizing radiation.

The *SAR* is defined as the time (t) derivative of incremental energy (dW) absorbed by an incremental mass (dm) contained in a volume element (dV) of a given density (ρ):

$$SAR = \frac{d}{dt}\left(\frac{dW}{dm}\right) = \frac{d}{dt}\left(\frac{dW}{\rho dV}\right) . \tag{17.2}$$

The *SA* is the time integral of the *SAR*. NCRP Report No. 67 discusses the *SAR* in detail and presents a comprehensive review of the physical theory that underlies it.

17.2.2.1 *Whole-Body Dosimetry.* The *SAR*, as utilized in the ANSI-1982 standard and in the present report is based, unless otherwise noted, on the whole-body mass of the irradiated organism. The *SA* values are similarly based and are implied, if not made explicit, by the 6-min period that is adopted for averaging the limiting *SAR* for exposed workers. Thus, the limiting whole-body-averaged *SA* for any 6-min period of exposure is 144 J/kg for the *SAR* limit of 0.4 W/kg (Sections 17.3 and 17.4.1).

17.2.2.2 *Distributive Dosimetry.* The *SA* and *SAR* are as applicable to the mass of individual body parts as they are to the total mass of the organism, and, indeed, because rates of absorption of RFEM energy can differ radically within the volume of an organism, there is both clinical and experimental utility in determining *SA*s and *SAR*s in discrete organs or tissues of interest. Distributive dosimetry was pioneered by A. W. Guy (Guy, 1971b; Guy *et al.*, 1968, 1974), who used the thermographic camera in studies of biologically simulating models

("phantoms") and of cadavers of laboratory animals. This work revealed that the distribution of *SAR*s is a highly complex function of many variables: carrier frequency; zone of irradiation; field polarization; electrical properties of tissues; and mass, geometry, and momentary orientation of the biological target.

Because the distributions of absorbed energy across species, frequencies, and exposure environments are so highly variable, the whole-body-averaged *SAR*s and *SA*s have been adopted on practical grounds as the dosimetric measures of choice in regulatory practice and standard setting. Moreover, because ethical considerations dictate that whole-body dosimetric values must be estimated or extrapolated for living human beings, the primary guides in limiting human exposures to RFEM fields must be specified in electric and magnetic field strengths (or in power densities in the case of exposure in the far field of a plane wave). As such, the role of *SA*s and *SAR*s is that of *deriving* permissible field strengths or power densities of incident fields of differing carrier frequency. In those cases in which it has been established that there are highly intense, focal concentrations of absorbed RFEM energy in the body (i.e., electromagnetic "hot spots"), this knowledge should supersede the whole-body value and lead to a corresponding reduction in the permissible level of exposure.

17.2.2.3 *Caveats on Interpretation of Dosimetric Measures.* Neither the strength of the incident field nor the quantity of energy absorbed from it by an organism has any *a-priori* warrant in the interpretation of causal mechanisms. There has been an unfortunate proclivity by some investigators to assume that the *SAR* and the rate of tissue heating are physical identities. Although the consequence of the Second Law of Thermodynamics is that the *ultimate* fate of absorbed RFEM energy is thermalization of tissues, transient field-specific effects have also been observed. A response by an organism to RFEM radiation may have a thermal basis, an athermal basis, or a combined basis. Determination of which of these three classes of causation is operative in a given context rests upon appropriate experimentation and inference, not on presumption.

The *SAR* is a practical tool by which one can make allowances for the complex absorbing and scattering properties of organisms as exemplified by the large frequency-dependent variations in quantities of energy absorbed from a field at a constant power density. Figure 17.1 (composite from Gandhi, 1979; Guy *et al.*, 1978, 1983, abstract; Lin *et al.*, 1977; Chou and Guy, 1982) shows frequency-dependent *SAR* curves of several prolate spheroids at a power density of 10 mW/cm^2 in the far field of a plane wave. These curves also demonstrate the

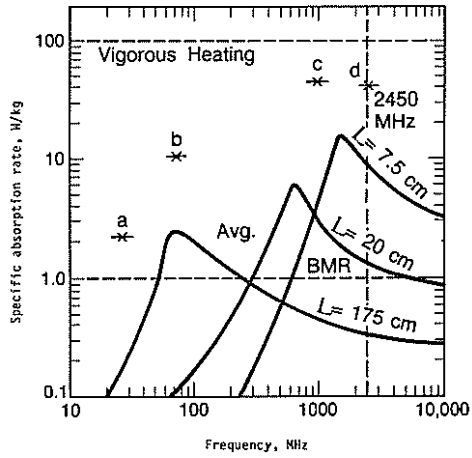


Fig. 17.1. Average *SAR* measured in prolate spheroids of various lengths, L, for an exposure to a power density at 10 mW/cm^2 at various frequencies. These models are used to simulate exposure of various experimental subjects in RFEM fields (after Gandhi, 1979). The points identified by the letters a, b, c and d indicate maximal localized *SAR* levels based on measurements as follows: a and b, in models of human beings (Guy *et al.*, 1978, 1983); c, in rats (Lin *et al.*, 1977); and d, in mice (Chou and Guy, 1982.) The average basal metabolic rate (BMR) is shown by the lower dashed horizontal line.

extreme differences in "worst-case" whole-body-averaged rates of energy deposition as a function of body dimensions. Given a length of 7.5 cm for the prolate spheroidal model of a 25-g mouse, the maximal *SAR* (~12 W/kg) occurs near 1500 MHz. For the model of standard man, a 175-cm prolate spheroid, the maximal *SAR* (~2 W/kg) occurs at approximately 70 MHz.

For the purpose of establishing exposure criteria in the following sections, the *SAR* is a fundamental quantity. There is, however, no intent to define exposure criteria solely in terms of *SAR*. Consideration is also given to other factors where appropriate. These factors include the possibility of severe deviation from uniformity of energy deposition, especially at the spectral extremes of frequency, as well as possible modulation- and carrier-frequency-specific biological responses.

17.3 Development of the SAR Exposure Criterion

As discussed earlier in this section, the absorption and distribution of RFEM energy result in an extremely complex phenomenology that is dependent on a body's mass and shape, its orientation with respect

to field vectors, its electrical properties, and the electrical properties of the exposure environment. Because of the multiplicity of interacting factors, exposure criteria must be established in a manner such that allowance is made for maximal amplification of biological effects as a result of field-object interactions. Furthermore, the criteria should take into account possible effects arising from unusual circumstances in either the external environment of the individual (e.g., ambient temperature and humidity) or the internal environment of the individual (e.g., hyperthermia, debility and disease).

The approach used by ANSI, in establishing exposure criteria that account for the frequency dependence of the *SAR*, has been chosen as appropriate to follow, with particular emphasis on examination of the domain of resonant frequencies of human beings from small infant to large adult. Special attention is therefore paid to the biological effects reported in the resonant-frequency region (30 to 300 MHz).

The body of scientific knowledge of biological effects of RFEM irradiation, although containing several thousands of archival reports, is fragmented: it is preponderantly based on acute exposures at relatively few frequencies. Ideally, exposure-control guidelines would also be based on a well-documented literature that reflects effects of chronic irradiation of a variety of species across a wide spectrum of frequencies. In spite of the shortcomings of the data, it is necessary to proceed prudently with the process of exposure control through the setting of standards, while exercising appropriate caution and fully informing the worker and the public of the limits of knowledge.

It would be inappropriate to repeat here an *in-extenso* review of data on RFEM radiations that have induced harmful effects in experimental animals, because the preceding sections have dealt with this subject exhaustively. It is essential, however, to summarize information on key end points that are useful in establishing exposure criteria.

The most important and directly useful data for the establishment of criteria for limiting exposure to any noxious environment are, of course, measurements and findings based directly on human beings. Unfortunately, data of this type, which are epidemiological or clinical in nature, are relatively few in number. The data that do exist have been reviewed in Sections 14 and 16.

In the absence of human data, it is necessary to turn to data on subhuman species in full realization that body dimensions and mass have an enormous controlling influence on the *SAR* at a given frequency. It is also necessary to realize that direct extrapolation of subhuman data to man is also fraught with problems because of specific anatomical, physiological, and biochemical differences among species.

In the frequency range of primary interest, i.e., 30 to 300 MHz, and also at higher frequencies in the microwave bands, a review of the

data of the previous sections indicates that behavioral disruption (Section 12) appears to be the most statistically significant end point that occurs at the lowest observed *SAR*.

The carrier frequencies associated with behavioral disruption range from 400 MHz to 5.8 GHz. These studies were performed on species ranging from laboratory rats to rhesus monkeys, and involved near-field, far-field, multipath, and plane-wave fields, both CW and modulated. In spite of marked differences in field parameters, thresholds of behavioral impairment were found within a relatively narrow range of whole-body-averaged *SAR*s ranging from ~3 to ~9 W/kg. In contrast, the corresponding range of power densities is 8 to 140 mW/cm^2.

Thresholds of disruption of primate behavior were invariably above 3 to 4 W/kg, the latter of which has been taken in this report, as well as by ANSI, as the working threshold for untoward effects in human beings in the frequency range from 3 MHz to 100 GHz. It is clear that the laboratory-animal to human-being generalization over this wide spectrum should be modified in light of any evidence of increased susceptibility in specific frequency domains. (These specific domains are noted in Section 11 and are accounted for later in this section.) Having accepted a threshold of effect in terms of the whole-body-averaged *SAR*, one must apply an appropriate margin of safety. This safety margin has been taken as a factor of 10 for occupational populations, and the fundamental *SAR* exposure criterion of 0.4 W/kg is established for frequencies from 3 MHz to 100 GHz. The fundamental criterion arrived at in this report, a whole-body-averaged *SAR* of 0.4 W/kg averaged over any 6-min exposure period, does not differ from that chosen by ANSI. Here, however, this value is proposed as a limit only for occupationally exposed individuals, and new lower levels of averaged exposure are proposed for members of the general population.

17.4 Implementation of Exposure Criteria

17.4.1 *Occupational Exposure Criteria*

Because measurements of incident fields in the working environment will necessarily be made in terms of field strengths or in the more familiar units of power density, it is necessary to provide exposure criteria in these units. Furthermore, restatement of the exposure guidelines in terms of plane-wave-equivalent power densities allows a clear expression of the frequency dependence of the average *SAR*. For occupational exposures, this report proposes the adoption of a schedule of frequency-dependent power densities as shown in Figure 17.2. These do not differ from the schedule given by the ANSI protection guides in Table 17.1.

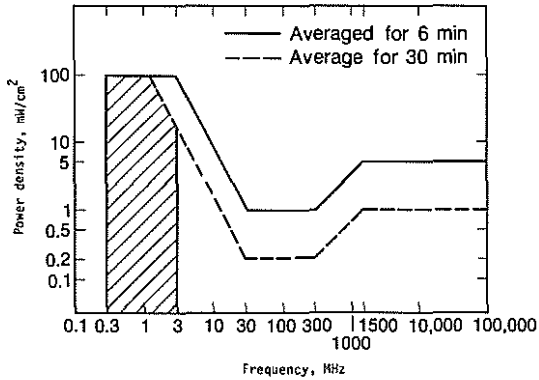


Fig. 17.2. Criteria for exposure to RFEM fields. Exposure, expressed in equivalent far-field power density (mW/cm^2) for a whole-body averaged *SAR* of 0.4 W/kg, is shown in the solid line, taken to be the occupational exposure criterion. The dashed line, one-fifth that of the occupational criterion, is the criterion for the general population. Note the time-averaging period allowed for each criterion. The cross-hatched area represents a frequency range in which whole-body *SAR* has limited significance (see Section 17.4). The overall frequency range for the criteria is 0.3 MHz to 100 GHz. Depending on the circumstances, use of these criteria is constrained by a number of conditions (Sections 17.4.1 to 17.4.9) and the criteria cannot be applied without reference to these conditions.

At frequencies from 30 to 300 MHz, which is taken as the resonant-frequency domain for human beings from smallest child to tallest man, under both grounded and ungrounded conditions, the criteria are related to an equivalent far-field power density of 1 mW/cm^2, a value that limits the maximum whole-body averaged *SAR* to a level below 0.4 W/kg.

To limit the maximal whole-body averaged *SAR* to 0.4 W/kg beyond this range of frequencies (Figure 17.2), conversions are necessary, as follows:

1. At frequencies above 300 MHz, a transitional region is defined between 300 and 1500 MHz where the limiting power density for exposure is taken as the quotient of frequency in MHz divided by 300 ($f/300$). The resulting quotient expresses the power density in units of mW/cm^2.
2. At frequencies from 1500 MHz to 100 GHz, the power-density limit is 5 mW/cm^2.
3. At frequencies below 30 MHz and above 3 MHz, a transitional region is defined where the limiting power density for exposure is taken as the quotient of 900 divided by the square of the frequency in MHz ($900/f^2$). Again, the result of this calculation is expressed in units of mW/cm^2.

4. Below 3 MHz and above 0.3 MHz, the exposure criterion expressed in terms of power density is taken as 100 mW/cm^2, for reasons that are discussed later.

The rationale for the stated recommendations is that the resulting power density at any given frequency is roughly descriptive of the inverse of the resonance curve in Figure 17.1. At the two extremes of frequency, other considerations become important.

At frequencies below 3 MHz, energy deposition in the body decreases directly with the square of frequency (Figure 17.1), and the power density required to achieve a whole-body averaged *SAR* of 0.4 W/kg is very large indeed. At these frequencies, the physical and physiological effects of the ambient electric field will dominate. Because the effects of highly intense, low-frequency electric fields are associated with surface interactions, the average *SAR* at potentially harmful levels will fall to levels considerably below 0.4 W/kg. Figure 17.2 shows a cross-hatched area for frequencies below 3 MHz where the strength of the electric field is the limiting condition.

The recommended limits of exposure below 30 MHz, and perhaps at frequencies somewhat higher, apply to free-space exposure conditions, i.e., to conditions under which a person is not in contact with any object including the ground. In fact, the limits are also based on a person standing barefoot on the ground, this person having an unrealistic average conductance of a homogenized body. For other conditions, such as standing on the ground with insulation (e.g., shoes or wooden floor) and being grounded by contact of the hand with a grounded object (e.g., metal fence or pipe) or being grounded and touching an insulated metallic object (e.g., truck or crane), these limits should be lowered. For the first two conditions, the exposure limits must be determined with the use of three criteria: (1) whole-body average *SAR* (0.4 W/kg), (2) maximal local *SAR* (8 W/kg) (see Section 17.4.5), and (3) RF burns at point of contact (200 mA). Limits for the case of being grounded and touching an insulated metallic object can be determined with the use of the same three criteria but only on a case-by-case basis because the degree of hazard depends on the size of the object. (See Section 17.6 for possible future considerations influencing the criteria.)

17.4.1.1 *Pulsed or Continuous-Wave (CW) Exposure, Time Averaging for the Occupationally Exposed.*

The biological data available for development of criteria were collected from a wide variety of radiation sources. In addition to varying

frequency, the duty cycle of the generators also varied widely from CW to pulsed waves with large and small duty cycles. Because limited data are available to establish the relation between the biological effects of CW and pulsed sources, the decision has been made to continue the traditional usage of health-protection practices in controlling exposures to RFEM fields. This practice has been to average the power density over a period of 0.1 h (6 min), which serves to limit the mass-normalized quantity of energy imparted to the body to an *SA* of 144 J/kg. The same time-averaging period is recommended in the ANSI-1982 standard.

17.4.2 *General-Population Exposure Criteria*

Previous efforts to establish national and international exposure criteria have generally led to the publication of exposure guidelines that are designed for application to individuals who are occupationally exposed in a typical career pattern, i.e., 40 h per week and 50 weeks per year. The ANSI-1982 standard recommends the same limits of averaged exposure for the work place and for the general environment. Such a uniform approach is not traditional and, in keeping with NCRP's practice of differentiating between occupational and general populations, another set of criteria is recommended for the general public.

The reasons for a twofold set of criteria can be stated as follows. First, individuals exposed in the work place should be relatively well informed of the potential hazards associated with their occupation. Furthermore, these workers may have the opportunity to make personal decisions in regard to their exposure, based on the relative risk as they perceive it. Individuals subjected to RFEM radiation outside the work place are generally unaware of their exposure, and furthermore, if they are aware, they rarely have the option to reduce their level of exposure. Second, the population at large, some members of which could be exposed continuously to RFEM fields, contains subpopulations of debilitated or otherwise potentially vulnerable individuals for whom there is presently inadequate knowledge to set firm standards. For example, the sensitivity of aged individuals, of pregnant females and their concepti, of young infants, or of chronically ill persons is not known. Third, because the general population is much larger than the occupational population, there are more persons at risk, and, hence, the proportionate number of persons susceptible to potential harm can be greater unless exposure of the general population is kept at a lower level.

For the reasons given above, it is recommended that there be an averaged exposure criterion for the general public that is set at a level equal to one-fifth of that of occupationally exposed individuals. Therefore, the whole-body averaged *SAR* for the general public for continuous exposure should not exceed 0.08 W/kg. The rationale for the reduction by a factor of 5 is based on the exposure periods of the two populations, rounded off to one digit (40 work hours per week/168 hours per week = ~0.2). Implementation of this *SAR* in terms of power density is shown in Figure 17.2 as a dashed line. For reasons of prudence, considering the lack of knowledge of biological effects at low frequencies, it is recommended that, for frequencies below 3 MHz, the population exposure limit should continue to rise as shown, following the $900/f^2$ relationship. However, the line of this relationship intrudes into the frequency domain in which it is expected that hazards are associated with surface-acting electric fields and other factors may control the limits of exposure as described in Section 17.4.1.

17.4.3 *Time Averaging for the General Population*

The time base by which to average the limiting *SAR* for occupational exposure is 0.1 h (6 minutes). For exposure of the general population, an averaging period of 0.5 h (30 min) is recommended. The increased stringency of the general-population limit allows this liberalization with no significant additional risk because the population limit, along with the 30-min time-averaging period, restricts the maximal *SA* to the population during the 30-min period to a value of no larger than that experienced during the 6-min time-averaging period of occupational exposure. Overall, the *SA* for the population remains at one-fifth that of the occupational value. At the same time, the 30-min time-averaging period is responsive to some special circumstances for the public at large. Examples are transient passage by the individual past high-powered RFEM sources, and brief exposure to civil telecommunications systems.

17.4.4 *Special Circumstances for Population Exposure*

It is recognized that there are special circumstances in which the exposure limits for the general population may unnecessarily inhibit activities that are brief and non-repetitive. For example, the presence nearby of a number of emergency vehicles engaged in telecommunications might cause a brief exposure to fields at strengths above the

general-population limit. Because only small groups of the population would be exposed under these conditions, and almost certainly not on a repeated basis, the occupational exposure levels are permitted for such cases.

17.4.5 *Localized Exposure Criteria*

Exposure limits for RFEM radiation for the human population are based to a great extent on data obtained from exposures of small animals to plane waves. Under such conditions, it is relatively easy to quantify the maximal rate of energy absorption by analytical or experimental means.

Although it is not practical to quantify distributions of absorbed energy, except for a few cases where special theoretical or laboratory techniques can be employed, it has been demonstrated frequently that the maximal localized *SAR* typically reaches levels as high as 10 to 20 times the whole-body averaged *SAR*. It has also been found in analyses of *SAR* distributions in models of human beings exposed to plane waves that maximal *SAR* levels, as is the case in exposure of the small animal, can reach 10 to 20 times the average value. It must then be recognized that, for exposure criteria based on whole-body-averaged *SAR*, such as those set out in this section, the maximal *SAR* in small regions of the body may be as much as 10 to 20 times higher (Figure 17.1).

The only practical way to cope with localized and non-uniform field exposures is to rely on the data base used to develop whole-body exposure limits. Then the bases for the criteria become quite simply that the general provisions for limiting exposure to a plane-wave field should not be violated: The occupational whole-body-averaged rate of energy absorption during localized exposure or exposure to non-uniform fields should not exceed 0.4 W/kg, and anatomically localized rates should not exceed those that are expected from a whole-body exposure to a plane wave that results in an average *SAR* of 0.4 W/kg.

The plane-wave exposure levels allowed by the limit for occupational exposure can be exceeded for a particular RFEM source, provided it can be shown that, for any individual that might be exposed to emissions from that source, the whole-body-averaged *SAR* does not exceed 0.4 W/kg and the local average *SAR* does not exceed 20 times the average, or 8 W/kg as averaged over a finite mass (one gram) of tissue over any period of 0.1 hour.

By the same argument, the criterion for general-population, localized exposure should allow no more than one-fifth the levels of *SAR* allowed for occupational exposures. However, in the case of individuals

in the general population who use radio emitters of various kinds (e.g., hand-held transceivers, remote control devices, etc.), the exposures of these individuals may be greater than the values recommended for the general population. Use of such devices is permitted, as a personal decision by the individual, provided that the devices are designed and used as designed so that the exposure of the individual does not exceed the recommended occupational guidelines and provided that, in using the devices, the individual does not expose other persons above the population guidelines.

It should be recognized that determination of whether a particular RFEM source will meet these criteria poses technical difficulties, and can be done only by a qualified person, a laboratory, or a scientific body for a general class of equipment. It is not possible to determine conformity to the special criterion by means of a power-density measurement alone.

17.4.6 *Mixed-Frequency Fields*

Simultaneous exposure of a person to several sources of RFEM radiation (e.g., from commercial AM, FM, TV broadcasts) is the rule, each source radiating at a different frequency. Because the *SAR* indexes the exposure limit (Figure 17.2 expresses equivalent far-field power densities for a constant *SAR*), appropriately weighted power densities are needed to reflect a complex radiation environment. The combined power density that meets the criteria for mixed-frequency fields is recommended to be the sum of the power densities at each frequency:

$$S_T = S_1 + S_2 + S_3 + ... S_n, \tag{17.3}$$

where S_T is the combined power density, and S_1, S_2, S_3, and S_n are the power densities at the frequencies, f_i (i = 1,2,3,. . . n), of each RFEM source, with the condition that

$$\sum_{i=1}^{n} \frac{S_i}{L_i} = \frac{S_1}{L_1} + \frac{S_2}{L_2} + \frac{S_3}{L_3} + ... \frac{S_n}{L_n} \leq 1, \tag{17.4}$$

where the *L*s are the exposure limits at the respective frequencies.

17.4.7 *Modulation*

Elsewhere in this report (Section 11), effects of RFEM fields under low-frequency modulation on *in-vitro* and *in-vivo* preparations have been discussed in detail. It is not known whether these effects pose a

risk to health, but their reliability and their independent confirmation in avian and mammalian species dictate the need for caution. Therefore, a special circumstance exposure criterion has been provided as follows: If the carrier frequency is modulated at a depth of 50 percent or greater at frequencies between 3 and 100 Hz, the exposure criteria for the general population shall also apply to occupational exposures.

17.4.8 *Power-Density Peaks*

The time averaging of and the limits on power densities and *SARs* as provided in the criteria in this report preclude circumstances in which excessive instantaneous peak-power levels can occur. There is, therefore, no need to specify a limit on peak power, as such.

17.4.9 *Medical Use of RFEM Radiations*

The proposed exposure criteria are not applicable to medical applications of RFEM fields insofar as the patient is concerned, but are applicable to medical and technical staff that use RFEM sources in diagnostic and therapeutic procedures.

17.5 Measurements of RFEM Fields

Some exposure standards (e.g., ANSI-1982) specify that measurements of field strengths should be made at distances of 5 cm or more from any object to avoid errors incumbent with scattering properties of absorbing and reflecting objects in the RFEM field, and with practical limitations of measuring instruments. For example, objects immersed in an RFEM field at power densities below those specified in the beginning of Sections 17.4.1 and in Section 17.4.3 can produce a scattered field of apparent intensity greatly exceeding that of the primary source. Valid measurements of such scattered fields in proximity to an object are difficult or are not possible because of the finite size of the field sensor and because of the interaction of the field with the object. In addition, the quantity of RFEM energy that can be coupled from a scattered field to an exposed human being is small compared with that from a primary source. Although it is beyond the scope of this report to specify the measurement methodology needed to apply the exposure criteria and, until more detailed guidelines are available, it is recommended that measurements be made at a distance of 5 cm or more from any object in the field.

17.6 Considerations Possibly Influencing the Criteria in the Future

This document is based on literature references published up through the year of 1982. There are two new findings in the literature published after this date that could result in future changes in the RFEM criteria. One finding concerns the possibility of RF burns or excessively high, localized *SAR* occurring in the hands, wrists, or ankles of persons coming in contact with grounded metallic objects, and the other finding concerns a possible link between RFEM exposures and the increased incidence of malignant tumors. Details are discussed below.

17.6.1 *RF Burns and High Localized SAR*

Recent research on identifying hazards in the 10-kHz to 3-MHz frequency range based on measurements of body impedance and induced current in exposed, volunteer human subjects predicts that potentially hazardous levels of body current and localized *SAR* may occur for exposures within the recommended guidelines of this report at frequencies of 1 MHz or greater (Guy and Chou, 1982; Gandhi *et al.*, 1985; Guy and Chou, 1985). The threshold current for RF burns occurring on the finger due to contact with a conducting surface is 200 mA (Rogers, 1981), and the threshold *SAR* for vigorous and possibly damaging local heating based on diathermy treatments is 50 to 120 W/kg (Guy *et al.*, 1984). If the recommended standards based on the 10-kHz to 3-MHz studies are extrapolated to 30 MHz as shown in Figure 17.3, a maximum exposure level of 0.13 mW/cm^2 would have to be imposed to prevent RF burns and to prevent the maximal *SAR* from exceeding 8 W/kg for contact of the hand with any grounded conductor during exposure in an extended field. Because the quasi-static analysis used for the 10-kHz to 3-MHz range will become invalid with increasing frequency in the range 3 to 30 MHz and as the whole-body resonant frequency is approached, prediction of maximum permissible levels above 30 MHz would require more sophisticated models for grounded contact exposures than now available.

17.6.2 *RFEM Fields and Malignant Tumors*

A report (Kunz *et al.*, 1985) that was widely publicized in the news media as linking RFEM fields with cancer, indicated that 18 out of 100 Sprague-Dawley rats exposed for life under specific-pathogen-free

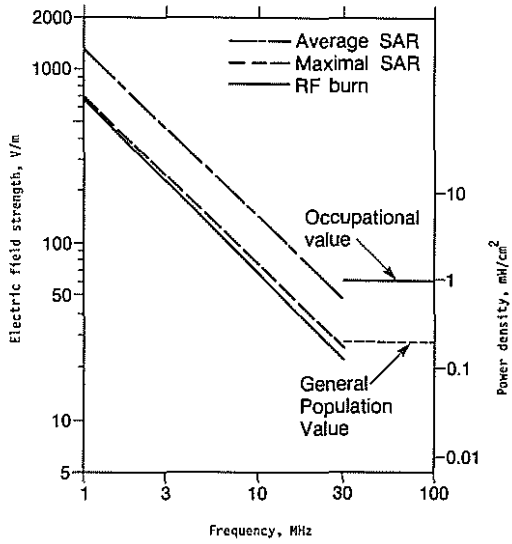


Fig. 17.3. Example of the exposure criteria in terms of electric field strength and power density based on not exceeding the average-*SAR* (0.4 W/kg), maximal-*SAR* (8 W/kg) and RF-burn (200 mA) criteria for whole-body exposure in an extended RFEM field of a person insulated from the ground (by the material on which the person is standing) but with a hand touching a grounded object (e.g., a metal fence). The extrapolation on the analysis of the data, obtained in the range between 10 kHz and 3 MHz, has been made up to 30 MHz, but it is not appropriate because present theory is not adequate to describe the interactions with the field as the frequency increases above 3 MHz and approaches the whole-body resonant frequency. In this example, the RF-burn condition becomes the limiting criterion and, at 30 MHz, it extrapolates to ~22 V/m or ~0.13 mW/cm^2. (Note that the two *SAR* curves are not parallel to the RF-burn curve because of the effect of increasing conductivity with frequency on the *SAR*.) (After Guy and Chou, 1982, 1985.)

(SPF) conditions to 2.45-GHz pulsed fields at *SAR* levels of 0.2 to 0.4 W/kg suffered from malignant neoplastic lesions. Only 5 out of 100 rats sham exposed under identical conditions suffered from the same lesions. The Mantel-Haenszel (M-H) analysis of the relative risk was 4.46 and the Chi-square test was 8.0 ($p = 0.005$, $df = 1$). The incidence of neoplastic lesions in either group is within the range of incidences reported for this strain of rat; only three tumors were present in rats younger than 12 months (all in the sham exposed), and the incidence rapidly increased after 18 months of age. The endocrine system has the highest incidence of neoplasia in the aging rats, as is to be expected in this experimental animal.

However, the authors state in the report: "The low incidence of neoplasia with no increase in any specific organ or tissue required the data to be collapsed and statistically evaluated with respect only to

occurrence of the neoplasm, with no attention given to the area of occurrence. This analysis indicated that neither group has an excess of benign lesions. There is statistical evidence that the mean number of primary malignancies was higher in the exposed animals than in the sham exposed, but the biological significance of this difference is reduced by several factors. First, detection of this difference required the collapsing of sparse data without regard for the specific type of malignancy or tissue of origin. Also, when the incidence of the specific primary malignancies in the exposed animals is compared with the specific tumor incidence reported in the literature, our exposed animals had an incidence similar to that of untreated control rats of the same strain, maintained under similar SPF conditions (Anver, Cohen, Lattuada and Foster, 1982). It is important to note that no single type of primary malignancy was enhanced in the exposed animals. From the standpoint of carcinogenesis, benign neoplasms have considerable significance under the assumption that the initiation process is similar for both benign and malignant tumors. The fact that treatment groups showed no difference in benign tumor incidence is an important element in defining the promotion and induction potential of microwave radiation for carcinogenesis. The collapsing of sparse data without regard for tissue origin is useful in detecting possible statistical trends, and the finding here of excess primary malignancies in the exposed animals is provocative; however, when this single finding is considered in the light of other parameters evaluated, it is questionable if the statistical difference reflects a true biological activity (Ward, 1983)."

The information in this subsection emphasizes that additional work in these important areas is required.

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The NCRP

The National Council on Radiation Protection and Measurements is a nonprofit corporation chartered by Congress in 1964 to:

1. Collect, analyze, develop, and disseminate in the public interest information and recommendations about (a) protection against radiation and (b) radiation measurements, quantities, and units, particularly those concerned with radiation protection;
2. Provide a means by which organizations concerned with the scientific and related aspects of radiation protection and of radiation quantities, units, and measurements may cooperate for effective utilization of their combined resources, and to stimulate the work of such organizations;
3. Develop basic concepts about radiation quantities, units, and measurements, about the application of these concepts, and about radiation protection;
4. Cooperate with the International Commission on Radiological Protection, the International Commission on Radiation Units and Measurements, and other national and international organizations, governmental and private, concerned with radiation quantities, units, and measurements and with radiation protection.

The Council is the successor to the unincorporated association of scientists known as the National Committee on Radiation Protection and Measurements and was formed to carry on the work begun by the Committee.

The Council is made up of the members and the participants who serve on the eighty-two scientific committees of the Council. The scientific committees, composed of experts having detailed knowledge and competence in the particular area of the committee's interest, draft proposed recommendations. These are then submitted to the full membership of the Council for careful review and approval before being published.

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Currently, the following subgroups are actively engaged in formulating recommendations:

SC-1:	Basic Radiation Protection Criteria
SC-3:	Medical X-Ray, Electron Beam and Gamma-Ray Protection for Energies Up to 50 MeV (Equipment Performance and Use)
SC-16:	X-Ray Protection in Dental Offices
SC-18:	Standards and Measurements of Radioactivity for Radiological Use
SC-28:	Radiation Exposure from Consumer Products
SC-38:	Waste Disposal
	Task Group on Krypton-85
	Task Group on Disposal of Accident Generated Waste Water
	Task Group on Disposal of Low-Level Waste
	Task Group on the Actinides
	Task Group on Xenon
	Task Group on Definitions of Radioactive Waste Levels
SC-40:	Biological Aspects of Radiation Protection Criteria
	Task Group on Atomic Bomb Survivor Dosimetry
	Subgroup on Biological Aspects of Dosimetry of Atomic Bomb Survivors
SC-43:	Natural Background Radiation
SC-44:	Radiation Associated with Medical Examinations
SC-45:	Radiation Received by Radiation Employees
SC-46:	Operational Radiation Safety
	Task Group 1 on Warning and Access Control Systems
	Task Group 2 on Uranium Mining and Milling—Radiation Safety Programs
	Task Group 3 on ALARA for Occupationally Exposed Individuals in Clinical Radiology
	Task Group 4 on Calibration of Instrumentation
	Task Group 5 on Maintaining Radiation Protection Records
	Task Group 6 on Radiation Protection for Allied Health Personnel
	Task Group 7 on Emergency Planning
SC-47:	Instrumentation for the Determination of Dose Equivalent
SC-48:	Assessment of Exposure of the Population
SC-52:	Conceptual Basis of Calculations of Dose Distributions
SC-53:	Biological Effects and Exposure Criteria for Radiofrequency Electromagnetic Radiation
SC-54:	Bioassay for Assessment of Control of Intake of Radionuclides
SC-57:	Internal Emitter Standards
	Task Group 2 on Respiratory Tract Model
	Task Group 5 on Gastrointestinal Tract Models
	Task Group 6 on Bone Problems
	Task Group 8 on Leukemia Risk
	Task Group 9 on Lung Cancer Risk
	Task Group 10 on Liver Cancer Risk
	Task Group 11 on Genetic Risk
	Task Group 12 on Strontium
	Task Group 13 on Neptunium

Task Group 14 on Placental Transfer
Task Group 15 on Uranium
SC-59: Human Radiation Exposure Experience
SC-61: Radon Measurements
SC-63: Radiation Exposure Control in a Nuclear Emergency
SC-64: Radionuclides in the Environment
Task Group 5 on Public Exposure from Nuclear Power
Task Group 6 on Screening Models
Task Group 7 on Contaminated Soil as a Source of Radiation Exposure
Task Group 8 on Ocean Dumping
SC-65: Quality Assurance and Accuracy in Radiation Protection Measurements
SC-66: Biological Effects and Exposure Criteria for Ultrasound
SC-67: Biological Effects of Magnetic Fields
SC-68: Microprocessors in Dosimetry
SC-69: Efficacy of Radiographic Procedures
SC-70: Quality Assurance and Measurement in Diagnostic Radiology
SC-71: Radiation Exposure and Potentially Related Injury
SC-74: Radiation Received in the Decontamination of Nuclear Facilities
SC-75: Guidance on Radiation Received in Space Activities
SC-76: Effects of Radiation on the Embryo-Fetus
SC-77: Guidance on Occupational and Public Exposure Resulting from Diagnostic Nuclear Medicine Procedures
SC-78: Practical Guidance on the Evaluation of Human Exposures to Radiofrequency Radiation
SC-79: Extremely Low-Frequency Electric and Magnetic Fields
SC-80: Radiation Biology of the Skin (Beta-Ray Dosimetry)
SC-81: Assessment of Exposure from Therapy
SC-82: Control of Indoor Radon

Committee on Public Education
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Ad Hoc Group on Medical Evaluation of Radiation Workers
Ad Hoc Group on Video Display Terminals
Task Force on Occupational Exposure Levels

In recognition of its responsibility to facilitate and stimulate cooperation among organizations concerned with the scientific and related aspects of radiation protection and measurement, the Council has created a category of NCRP Collaborating Organizations. Organizations or groups of organizations that are national or international in scope and are concerned with scientific problems involving radiation quantities, units, measurements, and effects, or radiation protection may be admitted to collaborating status by the Council. The present

Collaborating Organizations with which the NCRP maintains liaison are as follows:

American Academy of Dermatology
American Association of Physicists in Medicine
American College of Nuclear Physicians
American College of Radiology
American Dental Association
American Industrial Hygiene Association
American Institute of Ultrasound in Medicine
American Insurance Association
American Medical Association
American Nuclear Society
American Occupational Medical Association
American Podiatric Medical Association
American Public Health Association
American Radium Society
American Roentgen Ray Society
American Society of Radiologic Technologists
American Society for Therapeutic Radiology and Oncology
Association of University Radiologists
Atomic Industrial Forum
Bioelectromagnetics Society
College of American Pathologists
Federal Communications Commission
Federal Emergency Management Agency
Genetics Society of America
Health Physics Society
National Bureau of Standards
National Electrical Manufacturers Association
Radiation Research Society
Radiological Society of North America
Society of Nuclear Medicine
United States Air Force
United States Army
United States Department of Energy
United States Department of Housing and Urban Development
United States Department of Labor
United States Environmental Protection Agency
United States Navy
United States Nuclear Regulatory Commission
United States Public Health Service

The NCRP has found its relationships with these organizations to be extremely valuable to continued progress in its program.

Another aspect of the cooperative efforts of the NCRP relates to the special liaison relationships established with various governmental organizations that have an interest in radiation protection and meas-

urements. This liaison relationship provides: (1) an opportunity for participating organizations to designate an individual to provide liaison between the organization and the NCRP; (2) that the individual designated will receive copies of draft NCRP reports (at the time that these are submitted to the members of the Council) with an invitation to comment, but not vote; and (3) that new NCRP efforts might be discussed with liaison individuals as appropriate, so that they might have an opportunity to make suggestions on new studies and related matters. The following organizations participate in the special liaison program:

Commission of the European Communities
Commisariat a l'Energie Atomique (France)
Defense Nuclear Agency
Federal Emergency Management Agency
Japan Radiation Council
National Buerau of Standards
National Radiological Protection Board (United Kingdom)
National Research Council (Canada)
Office of Science and Technology Policy
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United States Air Force
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United States Coast Guard
United States Department of Energy
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United States Department of Labor
United States Department of Transportation
United States Environmental Protection Agency
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The NCRP values highly the participation of these organizations in the liaison program.

The Council's activities are made possible by the voluntary contribution of time and effort by its members and participants and the generous support of the following organizations:

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American Industrial Hygiene Association
American Insurance Association
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American Occupational Medical Association
American Osteopathic College of Radiology
American Podiatric Medical Association
American Public Health Association
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American Society for Therapeutic Radiology and Oncology
American Veterinary Medical Association
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X-Ray Protection Standards for Home Television Receivers, Interim Statement of the National Council on Radiation Protection and Measurements (National Council on Radiation Protection and Measurements, Washington, 1968)

Specification of Units of Natural Uranium and Natural Thorium (National Council on Radiation Protection and Measurements, Washington, 1973)

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