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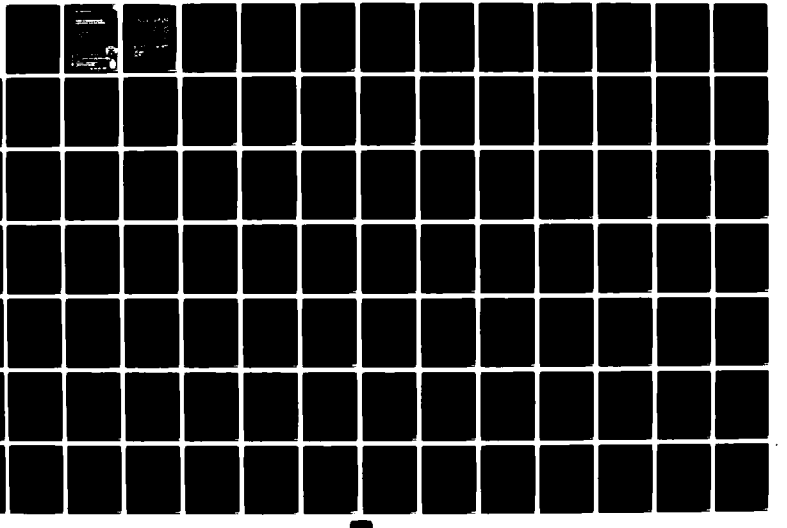

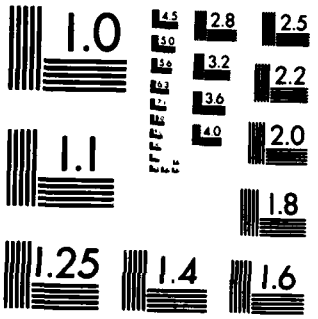

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The primary purpose of this review is to present analyses of research results and other pertinent information on the biological effects of radiofrequency radiation (RFR) to serve as a basis for determining whether the health of people exposed briefly or continuously to the RFR transmitted by proposed or currently operating Air Force RFR-emitting systems is likely to be affected adversely. Representative research results were selected from the large body of literature on the bioeffects of RFR and analyzed. The selection included those most significant scientifically and most pertinent to RFR frequencies and intensities

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20. ABSTRACT (Contd)

likely to be encountered in regions, around such systems, that are accessible occupationally or to the general public.

Discussed first as background information are the increasing use of RFR emitters by the public, private, and governmental sectors; measurements by the Environmental Protection Agency of environmental levels of RFR in selected U.S. cities; problems of risk assessment; and current and proposed exposure standards in various countries. The review of RFR bioeffects proper is in two major parts. In the first, physical effects are discussed, including postulated mechanisms of interaction of continuous-wave and modulated (including pulsed) RFR for both thermal and nonthermal effects. The concept of specific absorption rate is described. Also included are brief discussions of representative exposure systems and RFR instrumentation used for bioeffects research. In the second part, analyses of representative published articles, reports, and abstracts are presented under nine major bioeffects topics. These analyses are followed by sections on several popular misconceptions and unresolved issues regarding RFR bioeffects. More than 400 references are cited.

SUMMARY

The current state of knowledge regarding the biological effects of RFR was examined on a topic-by-topic basis. Representative articles were selected from the large body of scientific literature for review and analysis. The discussions also covered related topics, such as background information on other RFR-emitting devices and equipment in the United States; safety standards in the United States and other countries; problems of risk assessment related to scientific issues, philosophical positions, and range of legal applicability of safety standards; mechanisms of interaction of RFR with biological entities, involving definitions of "thermal" and "nonthermal" and distinctions between interactions of CW and pulsed RFR; uncertainties in epidemiologic studies; and the basic problems of assessing possible hazards to humans of any environmental agent by extrapolating results of experimental research performed on animals.

Collectively, the results of the relatively few epidemiologic studies performed in the United States, the USSR, and other Eastern European countries are not regarded as evidence that environmental levels of RFR are likely to constitute a hazard to the general population.

Most U.S. experiments with animals that yielded recognizable and repeatable effects of exposure to RFR were performed at incident average power densities of more than about 2 mW/cm^2. Such effects are thermal, in the sense that the RFR energy is absorbed by the organism as widely distributed heat that increases the whole-body temperature, or as internally localized heat that is biologically significant even with natural heat-exchange and thermoregulatory mechanisms operating. The existence of threshold average power densities has been experimentally demonstrated for some effects and postulated for the others. Exposure to RFR at average power densities exceeding the threshold for a specific effect for durations of a few minutes to a few hours (depending on the value) may or may not cause irreversible tissue alterations. The heat produced by indefinitely long or chronic exposures at power densities well below the threshold is not accumulated because its rate of production is readily compensated for by heat-exchange processes or thermoregulation. Most investigations involving chronic exposures of mammals yielded either no effects or reversible, noncumulative behavioral or physiological effects for average power densities exceeding 2 mW/cm^2. In the few cases in which irreversible adverse effects of exposure were found, such effects were absent for average power densities below 2 mW/cm^2.

In a relatively small number of investigations, biological effects of RFR were reported at incident average power densities less than about 2 mW/cm^2. Such effects have been called "nonthermal," to distinguish them from those considered above. However, this usage of "nonthermal" is confusing and imprecise because the interaction mechanisms involved in each such effect differ considerably from those for

the other effects, and clear distinctions between "thermal" and "nonthermal" based on precise scientific definitions of these terms are difficult to discern in the interactions.

Alterations of the blood-brain barrier that permit entry of normally blocked substances into brain tissue from its blood vessels have been reported for pulsed and CW RFR at average power densities as low as 0.03 mW/cm^2, but the effects at such low levels appear to be artifactual. Results of a subsequent study at 15 mW/cm^2 indicate that the technique used does not permit discrimination between changes in local cerebral blood flow and small alterations of the blood-brain barrier. Most experimental results indicate that significant localized heating of brain tissue is necessary to produce the effect.

The calcium-efflux phenomenon in brain-tissue preparations exposed to VHF or UHF RFR modulated at sub-ELF frequencies has been ascribed to complex, long-range quantum interactions, and such interactions are basically nonthermal. Most of the experiments to date were performed in vitro. Some of the results indicate that the phenomenon may occur in narrow amplitude "windows" for specific modulation frequencies, which may account in part for apparently contradictory findings. However, very few experiments were performed in vivo thus far.

One pulse power effect known to occur in humans is the detection of individual RFR pulses as apparent sound. This phenomenon has been characterized as nonthermal, primarily on the basis that the average power density would be minuscule if the time intervals between consecutive pulses were large. However, the average power density is not relevant, because the interactions that produce the effect are dependent primarily on the characteristics of individual pulses. For perception, a pulse-power-density threshold of about 300 mW/cm^2 must be exceeded. No ill effects from this phenomenon have been reported, and human volunteers have been exposed to pulse power densities as high as 2,000 mW/cm^2 without apparent ill effects.

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1 INTRODUCTION

1.1 Background

1.1.1 Definition of "RFR"

The generic term "RFR" (radiofrequency radiation) is used herein to include other terms commonly found in the literature, such as electromagnetic radiation (EMR), nonionizing electromagnetic radiation (NIEMR), microwave radiation, radiofrequency electromagnetic (RFEM) fields, electromagnetic fields (EMF), microwave fields, and others. The frequency range of primary interest to the Air Force is from 10 kHz to 300 GHz. However, the term RFR used in this document applies to frequencies from 0 to 300 GHz.

1.1.2 Purpose of this Review

The primary purpose of this review is to present analyses of research results and other pertinent information on the biological effects of RFR to serve as a basis for determining whether the health of people exposed briefly or continuously to the RFR transmitted by proposed or currently operating Air Force radar systems is likely to be affected adversely. Representative research results were selected from the large body of literature on the bioeffects of RFR and analyzed. The selection included those that are most significant scientifically and most pertinent to the RFR frequencies and intensities likely to be encountered around such radars in regions accessible occupationally or to the general public.

This review is an updated version of Appendices C, "Human Exposure to Radiofrequency Radiation," to previously issued Environmental Impact Statements for the PAVE PAWS radar systems at Otis Air National Guard Base, Massachusetts, and Beale Air Force Base, California, and for the OTH-B system in Maine. However, the new version does not contain conclusions regarding possible RFR-bioeffects hazards from any specific system. Instead, it is to serve as a more general reference document that provides the background information from which such system-specific conclusions may be drawn.

1.2 Data Base and Literature Selection

Under sponsorship by the Air Force, a data base of detailed reviews and analyses of research projects on RFR bioeffects published in various scientific journals and reports or presented at recent

seminars and professional-society meetings is being developed on an ongoing basis. Thus far, two reports have been issued (Heynick and Krebs, 1981; Heynick, 1982). Other sources used in acquiring information for this review were bibliographies in previous reviews of the literature and several comprehensive bibliographies prepared by U.S. government personnel or by other organizations under government sponsorship.

Several criteria were used in selecting articles for inclusion in this review. Preference was given to complete papers published in scientific journals or proceedings of scientific symposia. Abstracts of presentations at recent scientific symposia were also selected if they included adequate details of the procedures and findings. Criteria included the date of publication (more recent articles were preferred because of improvements in experimental methodology and in the technology of exposure and dose measurement) and the significance of the findings to human health (e.g., studies of human population to ascertain whether the occurrence of specific effects is statistically higher in population samples exposed to RFR than in similar population samples not exposed, and experiments involving long-term exposure animals). Other criteria included the relevance of an article to others on the same topic and possible relevance to concerns expressed by citizens' groups. We stress that most bioeffects of RFR are frequency-dependent but not frequency-specific per se; rather, the frequencies of the incident RFR (together with its average power density and polarization and the size, shape, and orientation of the biological entity) determine the rate of energy absorption and its internal distribution. For this reason, the selection of articles was not confined to those involving frequencies close to those of specific systems, but was extended to articles involving frequencies over the general range from 0 to 300 GHz as appropriate. The number of articles selected was necessarily limited because of resource constraints. However, we consider the articles selected to be representative of the many documents related to the biological effects of RFR.

1.3 Eastern European Bioeffects Literature

Probably the most controversial aspects of research on the biological effects of RFR are the large discrepancies between results, at low levels of RFR, reported in the Eastern European literature and those obtained in Western countries such as the United States, and the basic differences in philosophy between the two groups of countries in prescribing safety standards or guidelines for the protection of humans against possible hazards from exposure to RFR.

From the end of World War II to about the late 1960s, few of the scientific reports on bioeffects research in the USSR (or other Eastern European countries) were amenable to critical review because they lacked essential information. In the early 1970s, starting essentially with an international conference on the bioeffects of RFR in Warsaw in 1973 under the joint sponsorship of the World Health Organization

(WHO), the U.S. Department of Health, Education, and Welfare (HEW), and the Scientific Council to the Minister of Health and Social Welfare of Poland, international interchanges of information increased materially, and translations of Eastern European articles became easier to obtain. Because most Eastern European documents published before 1973 (and many since then) are merely abstracts that contain no details of the experimental method, number of subjects, or analytical approach used in the study, evaluation of them proved difficult. More recent Eastern European studies contain more detail, and some of them have been included in our analysis.

2 PRESENT CLIMATE AND CONTEXT

2.1 Proliferation of RFR Emitters

Public use of RFR-generating devices and acceptance of their benefits have been growing almost exponentially over a number of years. Public television and radio broadcasting stations, ham radio transmitters, citizens-band radios, ground-level and satellite communication systems, civil and military aircraft navigation systems, airport traffic control systems, medical diathermy units, defense tracking systems, remote garage-door-opening devices, microwave ovens, and a variety of units for industrial heating and processing of materials contribute to the expansion of RFR use in this country.

All of these devices are regulated by the federal government, mainly the Federal Communications Commission (FCC), and all are restricted to specific frequency bands. The power levels that most devices may emit are also restricted. Still, as the number of such devices increases, the background level of RFR in this country, particularly in urban and industrial centers, is bound to increase as well. It is therefore appropriate to ask whether this increasing level of RFR will be deleterious to human health.

Various agencies of the federal government have established programs to deal with the question of RFR effects on human health. The U.S. Air Force has taken an active role for more than 10 years to advance the state of knowledge of RFR bioeffects in the interest of personnel safety. The Environmental Protection Agency (EPA) is conducting a study of environmental levels of RFR. The Bureau of Radiological Health (BRH) has promulgated a performance standard for permissible microwave oven leakage (21 CFR 1010, "Performance Standards for Electronic Products"). The National Institute for Occupational Safety and Health (NIOSH) is investigating the use of industrial microwave devices. The Air Force, together with the Army, Navy, and other government agencies, maintains research programs on the biological effects of RFR, with the objective of assessing effects on human health. The results of these programs indicate that the biological effects of RFR are largely confined to average power densities exceeding about 1 mW/cm^2. Further, present maximum environmental levels in cities are generally in the range of 0.00001 to 0.005 mW/cm^2, with the occasional exception of regions in the immediate vicinity of broadcast towers, where environmental levels may range from less than 0.01 to more than 0.2 mW/cm^2 (see Section 2.2).

In summary, the benefits of RFR devices for communications, radar, personal and home use, and industrial processes are widely accepted. On the other hand, many people are concerned that the proliferation of the use of RFR devices, including various military radar and communications systems, may be associated with some as-yet-undefined hazardous biological effects. The purpose of the present review is to address such concerns.

2.2 Measurements of Environmental Levels of RFR in Selected U.S. Cities

EPA has measured the environmental field intensities at selected locations in various U.S. cities. [illegible]ll and Mantiply (1980) and Janes (1979) discuss the results for the 15 cities (a total of 486 sites) studied so far. The sites in each city were selected to permit estimations of cumulative fractions of the total population being exposed at or below various average power densities, based on the population figures for the 1970 census enumeration districts.

Field intensity measurements were made at 6.4 m (20 ft) above ground at each site in the following frequency ranges (Janes et al., 1977): 0.5-1.6 MHz (the standard AM-radio broadcast band), 54-88 MHz and 174-216 MHz (the VHF-TV bands), 88-108 MHz (the standard FM-radio broadcast band), about 150 and 450 MHz (land-mobile bands), and 470-890 MHz (the UHF-TV bands). The signals in each band were received with separate antennas designed specifically for each band. However, the measurements in the standard AM-radio broadcast band were not included in the analyses because this band is below the 10-MHz lower frequency limit of the 1974 U.S. radiation protection guideline (ANSI, 1974).

The measured field strengths at each site were integrated over the frequency bands (54 to 890 MHz) included in the analyses and converted into equivalent average power densities. The site values in each city were then used with the population figures in the various census enumeration districts in a statistical model designed to estimate the population-weighted median exposure value for that city and to calculate other statistics of interest.

The population-weighted median value for a city is defined as the average power density at or below which half the populatic[illegible] of the city is being exposed. The estimates are based on the assumption of continuous exposure of people at their place of residence; they do not take into account population changes since the 1970 census, population mobility, exposure at heights greater than 6.4 m (20 ft), attenuation of signals by buildings, or periods of time when any of the contributing RFR sources are not transmitting. These median values range from 0.000002 mW/cm^2 (for Chicago and San Francisco) to 0.000020 mW/cm^2 (for Portland, Oregon). The population-weighted median for all 15 cities is 0.0000048 mW/cm^2. Also, the percentage of the population of each city exposed to less than 0.001 mW/cm^2 ranges from 97.2% (for Washington, D.C.) to 99.99% (for Houston, Texas), with a mean value for all 15 cities of 99.4%. The major contributions to these exposure values are from the FM-radio and TV broadcast stations.

EPA also measured RFR levels at sites close to single or multiple RFR emitters, e.g., at the bases of transmitter towers and at the upper stories (including the roof) of tall buildings or hospital complexes close to transmitter towers. At the base of an FM tower on Mt.

Wilson, California, for example, the fields ranged from 1 to 7 mW/cm^2 (Tell and O'Brien, 1977), but such values are believed to be uncommon. Most measurements in tall buildings close to FM and TV transmitters yielded values well below 0.01 mW/cm^2, but a few values were close to or slightly exceeded 0.2 mW/cm^2 (e.g., 0.23 mW/cm^2 on the roof of the Sears Building, Chicago).

Janes (1979) also discussed the field intensities near ground-based transmitters of satellite communications systems, radars used for air-route surveillance and other activities, microwave radio relay transmitters, microwave ovens, and personal radios (CBs). He also mentioned other emitters such as those used for medical (diathermy, electrosurgery) and industrial (heating, drying, and sealing) applications.

2.3 Problems of Risk Assessment

Assessing risk to human health and setting standards to protect health are extremely complex problems. In addition to purely technical and scientific questions, there are problems of philosophy, law, administration, and feasibility of programs that are still only vaguely recognized. It is clearly beyond the scope of this document to deal with those subjects in detail, but it is important that they be mentioned. Three aspects of risk assessment need to be considered: the scope of biological effects evaluated in setting standards, the overall approach to setting standards, and standards of protection from overexposure to RFR in the United States, the USSR, and other countries.

Alternative approaches to determining the acceptable degree of risk or undesirable effect can be illustrated by comparing occupational air pollution standards that prevailed until recently in the USSR and the United States (Zielhuis, 1974). In the USSR, maximum allowable concentrations (MACs) for airborne noxious agents are set at a value that will not produce any deviation from normal in physiological parameters, or any disease in anyone exposed to the agent (occupational or general population). In the United States, threshold limit values (TLVs) for airborne noxious agents are set to ensure that nearly all workers can be exposed regularly during the working day without adverse effect. The differences stand out clearly: in the USSR, all biological effects are considered without regard to their medical significance or the possibility of human adaptation, and the values of MAC selected must, in principle, protect the most susceptible member of the population. In the United States, only harmful effects are considered, and protection is not extended to the most susceptible workers, except that a safety factor is generally included in the TLV such that an adverse reaction in an individual can be detected before serious medical consequences ensue.

Both approaches are predicated on the existence of a threshold concentration; that is, on a concentration below which no biological effect will occur. In the absence of a true threshold, one can only weigh the extent of protection to give to the population against the

cost and technical feasibility of providing that protection. Making such choices is the function of risk/benefit analysis in the assessment of environmental hazard.

The subject of the existence or nonexistence of thresholds has been debated at length, but much of the debate has been based on opinion rather than evidence. As a practical scientific matter, thresholds for noxious or deleterious effects must exist for at least some substances, because many naturally occurring substances are essential to life at one concentration and highly toxic at higher concentrations (Horne, 1972). In this document, the possible existence of threshold levels for RFR effects is considered on a case-by-case basis, with due regard for the physiological mechanisms of effect.

2.4 Exposure Standards

The term "exposure standards" is generally applied to specifications or guidelines for permissible occupational and/or nonoccupational exposure of humans to electromagnetic fields. The standards are expressed as maximum power densities or field intensities in specific frequency ranges and for indicated exposure durations.

The American National Standards Institute Subcommittee C95.4 has adopted a frequency-dependent standard (ANSI, 1982) for both occupational and general-public exposure to RFR, to replace the ANSI Radiation Protection Guide, published in 1974, of 10 mW/cm^2 or equivalent electric and magnetic field strengths for the frequency range from 10 MHz to 100 GHz (ANSI, 1974). The newer limits, like the older ones, are not to be exceeded for exposures averaged over any 0.1-hr period. The older standard was promulgated by the (Federal) Occupational Safety and Health Administration (OSHA) for occupational exposure and was also adopted by several other organizations, including the Department of Defense.

The older 10-mW/cm^2 value originated from the physiological consideration that whole-body exposure of a human to levels of about 100 mW/cm^2 or more would produce a mild to severe (depending on the level) increase in thermal load. A safety factor of 10 was then applied to the lower limit of this power density range. The principle underlying this guide was the belief, based on the then-available scientific evidence, that nearly all workers could be exposed to RFR at such levels during the normal series of working days without adverse effects. Adoption of the guide gave recognition that electromagnetic fields at the maximum allowable levels might cause biological effects that have no medical consequences, or that workers could readily accommodate to such effects.

The new ANSI standard, shown in Table 2-1 and graphically in Figure 2-1, was derived from analyses of a large number of representative recent experimental and theoretical results selected by a subcommittee of ANSI C95.4. It covers the frequency range from 300 kHz to 100 GHz and is based on a mean whole-body specific-absorption-rate

Table 2-1

NEW ANSI RADIOFREQUENCY RADIATION PROTECTION GUIDES

(1) Frequency Range (MHz)	(2) E^2 (V^2/m^2)	(3) H^2 (A^2/m^2)	(4) Power Density (mW/cm^2)
0.3 - 3	400,000	2.5	100
3 - 30	4,000 ($900/f^2$)	0.25 ($900/f^2$)	$900/f^2$
30 - 300	4,000	0.025	1.0
300 - 1,500	4,000 (f/300)	0.025 (f/300)	f/300
1,500 - 100,000	20,000	0.125	5.0

Note: f is the frequency in MHz.

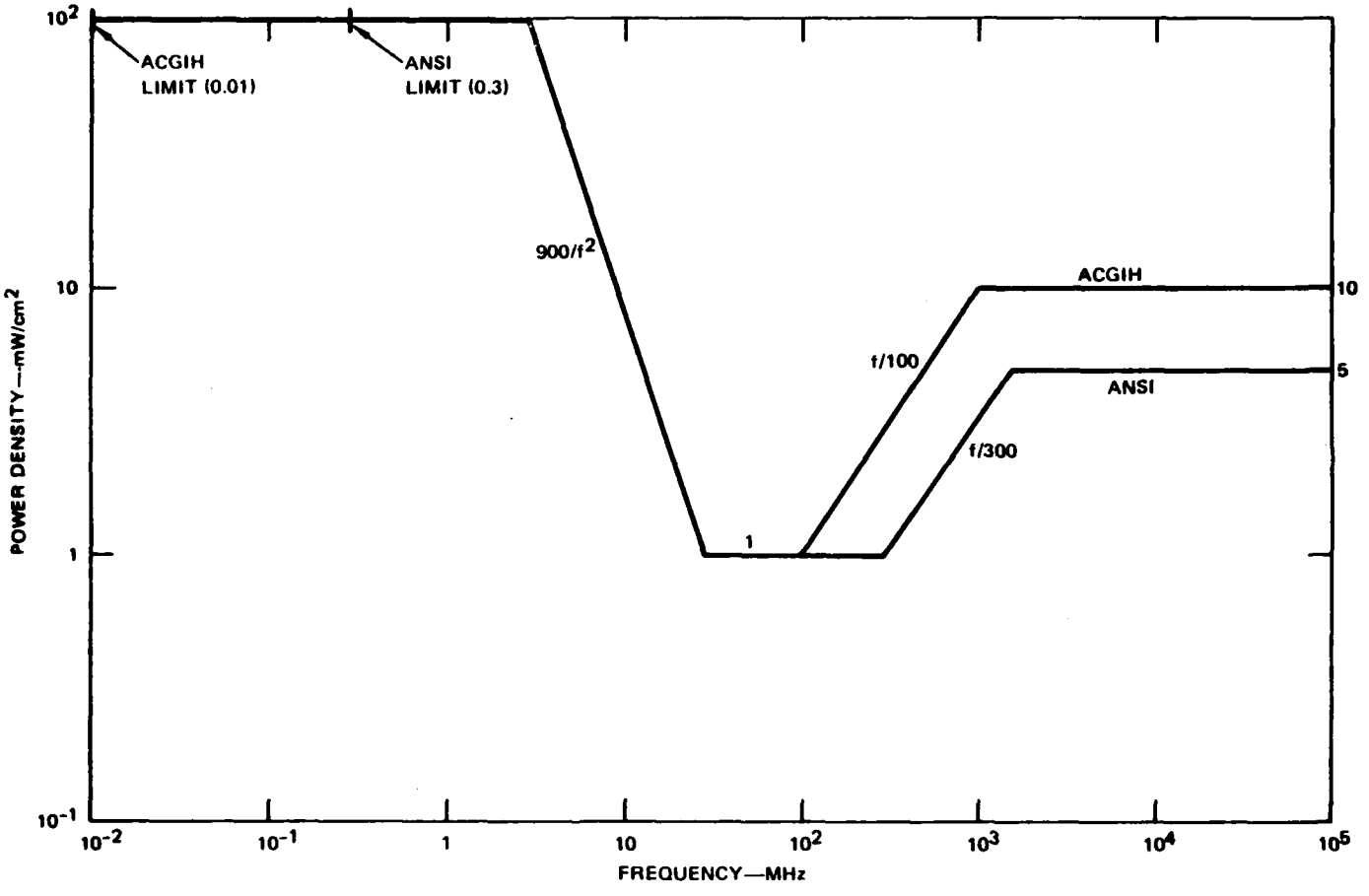
(SAR) limit of 0.4 W/kg instead of a constant incident power density. SAR is defined as the rate at which radiofrequency electromagnetic energy is imparted to an element of mass of a biological body (see Section 5.1.2 for a more detailed discussion of SAR). The lowest limit, 1 mW/cm^2, is for the range from 30 to 300 MHz, within which RFR absorption by the human body as a resonant entity is highest. As with the previous standard, the value 0.4 W/kg includes a safety factor of 10, and the specified limits are not to be exceeded for exposures averaged over any 0.1-hr period.

In the far field of an RFR source, the governing maximum values are the power densities shown in column 4 of Table 2-1, and the corresponding squares of the electric- and magnetic-field amplitudes (E^2 and H^2) in columns 2 and 3 are approximate "free-space" equivalents, defined as follows for 1 mW/cm^2 (10 W/m^2):

$$E^2 = (Z_0) \times 10\ W/m^2 \quad (1)$$

$$H^2 = (1/Z_0) \times 10\ W/m^2 \quad (2)$$

where Z_0 represents the impedance or value of E/H for free space, but rounded off from 377 ohms to 400 ohms to yield limit values to one significant figure.



*Based on average SAR limit of 0.40 W/kg in exposed tissue.

FIGURE 2-1 ANSI AND ACGIH SAFETY GUIDES FOR WHOLE-BODY EXPOSURE OF HUMANS*

In the near field of an RFR source, the governing maxima are the values of E^2 and H^2. In such exposure situations, E^2 and H^2 can be expressed in terms of corresponding power densities by using equations 1 and 2, but primarily for convenience in expressing the entire standard in terms of one unit (power density), as is done in Figure 2-1.

The American Conference of Governmental Industrial Hygienists (ACGIH) has proposed (in a notice of intent) a new standard also based on 0.4 W/kg, but for occupational exposures only. The ACGIH threshold limit values are displayed graphically in Figure 2-1 for comparison with the ANSI values. The major difference is that the 1-mW/cm^2 value extends only from 30 to 100 MHz and rises from the latter with a slope f/100 to 10 mW/cm^2 at 1 GHz. This difference is based on the premise that children, who have higher whole-body resonant frequencies than adults (see Section 5.1.2), are not likely to be occupationally exposed to RFR. Another difference is that the free-space equivalent field intensities for 1 mW/cm^2 are given by equations 1 and 2 but with Z_0 = 377 ohms instead of 400 ohms. Lastly, the lower frequency limit for the ACGIH standard is at 10 kHz instead of 300 kHz.

The currently applicable Air Force permissible exposure limits (PELs) are given in AFOSH Standard 161-9. For exposures averaged over any 0.1-hr period to frequencies between 10 MHz and 300 GHz, the PEL is 10 mW/cm^2, and from 10 MHz down to 10 kHz, the PEL is 50 mW/cm^2. For exposure during any 0.1-hr period, the product of the power density and the exposure duration shall not exceed 3,600 $mW\text{-}s/cm^2$ for frequencies between 10 MHz and 300 GHz, or 18,000 $mW\text{-}s/cm^2$ for frequencies between 10 kHz and 10 MHz. This standard is being revised: Currently proposed PELs for exposure, during any 0.1-hr period, of adults of normal size (55 in. or more in height) are the new ACGIH values, and the PELs for exposure of humans of small size (less than 55 in. tall) are the new ANSI values, but extended down to the ACGIH lower frequency limit of 10 kHz.

Both Multnomah County in Oregon, and the City of Portland, located in Multnomah County, have separately promulgated ordinances regulating general population exposure to RFR. More stringent than the Portland standard, the Multnomah County standard specifies maximum exposures of one-fifth of the recently adopted ANSI standard, e.g., it permits up to 0.2 mW/cm^2 average power density over any 0.1-hr period in the 30-300 MHz band.

The Massachusetts Department of Public Health (MDPH) is preparing regulations governing human exposure to RFR. The proposed limits for occupational exposure are the same as the new ANSI limits. However, the limits for general public exposure are one-fifth those for occupational exposure (based on a whole-body SAR of 0.08 W/kg) and are to be averaged over any 0.5-hr (instead of 0.1-hr) period. Other states are contemplating similar regulations.

Action to develop local RFR exposure standards is under way in the City of New York and the town of Onondaga, New York.

An exposure standard for the general (nonoccupational) population is also under consideration by the EPA. It has issued an Advance Notice of Proposed Recommendations (EPA, 1982).

The Canadian federal government has revised its exposure standard, which was essentially the same as the ANSI 1974 guideline, along the lines shown in Table 2-2 (Stuchly and Repacholi, 1978). The maximum permissible general (nonoccupational) level for continuous exposure is 1 mW/cm^2, applicable to frequencies in the band from 10 MHz to 300 GHz. For occupational exposure, the maximum levels are frequency- and duration-dependent. For example, for the frequency range from 10 MHz to 1 GHz, the new standard permits exposure to 1 mW/cm^2 for a maximum of 8 hr/day, up to 10 mW/cm^2 for 6 min or less, and up to 25 mW/cm^2 for 2.4 min or less.

Table 2-2

NEW CANADIAN
MAXIMUM PERMISSIBLE EXPOSURE LEVELS

Exposure Group	Frequency (GHz)	Duration	Maximum Level
General public	0.01 to 300	24 hr	1 mW/cm^2
Occupational group	0.01 to 1	8 hr	60 V/m 0.16 A/m 1 mW/cm^2
		t(min) = 60/P	1 to 25 mW/cm^2
	1 to 300	8 hr	5 mW/cm^2
		t(min) = 300/P	1 to 10 mW/cm^2
		t(min) = 60/P	10 to 25 mW/cm^2

Note: P = power density

The Swedish standard, which used to be essentially the same as the ANSI 1974 guideline, was revised in 1976 as shown in Table 2-3 (Stuchly and Repacholi, 1978). Again, the new maximum occupational exposure levels are about tenfold lower than they were. The new standard is assumed to apply to the general (nonoccupational) population as well as to RFR workers.

Table 2-3

SWEDISH OCCUPATIONAL STANDARD OF
MAXIMUM PERMISSIBLE EXPOSURE LEVELS

Frequency (GHz)	Exposure Duration (hr)	Maximum Power Density (mW/cm^2)	Remarks
0.01 to 0.3	8	5	Averaged over 6 min
0.3 to 300	8	1	Averaged over 6 min
0.01 to 300		25	Averaged over 1 s

Exposure limits in the USSR are considerably lower than those of Western countries, especially the limits for general-population exposure, presumably because of differences in philosophy and processes for setting standards. In the United States, only harmful effects are considered, but safety factors are usually applied to values at which medically significant effects are observed. In the USSR, the principle of "no effect" on any person (Zielhuis, 1974; Baranski, 1976) appears to be the basis for standard setting. More recently, Trakhtenberg (quoted in Goldmann, 1982) has defined significant changes as "characterized by the deviation of the factors studied beyond the limits of annual or seasonal fluctuations by more than two standard deviations away from the norm." Whatever the basis, until recently the maximum level for 24-hr exposure of the general population was 0.005 mW/cm^2 (Shandala, 1978; McRee, 1979), and the occupational standard was as summarized in Table 2-4 (Stuchly and Repacholi, 1978; McRee, 1979). Table 2-4 specifies higher maximum levels than those for the general population. For example, in the frequency range from 300 MHz to 300 GHz, it permits exposure from rotating antennas of 0.1 mW/cm^2 for a full working day and 1 mW/cm^2 for 2 hr. (Phased array antennas are analogous to rotating antennas.) The Soviet military services and establishments were specifically exempted from such standards.

Recent U.S. visitors to the USSR have reported pending and/or adopted revisions to the standards above (Microwave News, November 1982). For 24-hr exposure of the general population, the maximum level has been increased from 0.005 to 0.010 mW/cm^2 (Barnes, 1982). Also, the USSR appears to be developing standards for specific types of RFR emitters. As examples, for a specific radar that emits 1-microsecond pulses of 10-cm (3-GHz) RFR at 3 pulses/s, the exposure limit is 0.015 mW/cm^2 (average power density), and for microwave ovens, the maximum value at a distance of 50 cm is 0.010 mW/cm^2 (Barnes, 1982). Regarding occupational exposure, for the frequency range from 0.3 to 30 GHz and exposures of 0.2 hr or longer, the product of the average power density and the exposure duration should

Table 2-4

USSR MAXIMUM PERMISSIBLE LEVELS FOR OCCUPATIONAL EXPOSURE

Frequency (GHz)	Exposure Duration	Exposure Limit	Remarks
0.01 to 0.03	Working day	20 V/m	--
0.03 to 0.05	Working day	10 V/m 0.3 A/m	--
0.05 to 0.3	Working day	5 V/m 0.15 A/m	--
0.3 to 300	Working day	0.01 mW/cm^2	Stationary antennas
	Working day	0.1 mW/cm^2	Rotating antennas
	2 hr	0.1 mW/cm^2	Stationary antennas
	2 hr	1 mW/cm^2	Rotating antennas
	20 min	1 mW/cm^2	Stationary antennas

not exceed 0.2 $mW\text{-}hr/cm^2$. Thus, the exposure limit for an 8-hr working day has been increased from 0.010 to 0.025 mW/cm^2, the limit for 2-hr exposure is 0.1 mW/cm^2 (no change), and the 1-mW/cm^2 limit is for exposures of less than 12 (instead of 20) min (McRee, 1982; Swicord, 1982). Though not stated, by implication these changes are applicable to RFR from stationary antennas; no information regarding rotating antennas was obtained. The limits for the frequency ranges 0.03 to 0.05 GHz and 0.05 to 0.3 GHz are unchanged (Swicord, 1982).

The exposure limits in Poland and Czechoslovakia are higher than those of the USSR but lower than those of the Western countries.

3 ASSESSMENT OF SCIENTIFIC INFORMATION

In an assessment of the potential biological effects of RFR from a specific system, certain quantitative relationships must be considered among (1) the physical parameters of the RFR such as frequency, power density, and polarization; (2) the mechanisms of absorption and distribution of energy within the biological organism; and (3) the resulting biological effects as measured by some functional or anatomic alteration. Like all scientific theory, the body of biophysical theory that links these three factors has been synthesized from a variety of experimental evidence. The theory is subject to refinement or revision as valid new evidence accumulates that is inconsistent with the theory. Nevertheless, it furnishes the context in which new experimental evidence is considered.

Experimental evidence comes from the observation of experimental animals and, sometimes, humans who have been exposed to RFR. The physical characteristics of the radiation, the mechanisms of interaction, and the biological response are known in some cases, at least qualitatively. The most directly applicable experimental evidence concerning possible bioeffects of any specific system would come from experiments in which humans were exposed to its specific frequency range and likely power density values. Furthermore, the best evidence would come from quantitative evaluation of many biological endpoints. Such data, however, do not exist. The available information is indirect because it is derived primarily from experiments with animals and requires at least some extrapolation of species, field characteristics, duration of exposure, and biological effects.

Epidemiologic studies elucidate the distribution of a disease or physiological condition in human populations and describe the factors influencing this distribution (Lilienfeld and Lilienfeld, 1980). Although such studies deal with human subjects and thus might furnish direct evidence from a species standpoint, epidemiologic evidence for effects of exposure to RFR is considered to be indirect, for two reasons. First, numerical values of the exposure parameters for most epidemiologic studies are not known in detail. Second, the extent to which the unexposed control group of people selected for comparison differs from the exposed population (other than in exposure to RFR) is a critical matter in assessing the validity of the conclusions.

Regardless of the particular line of evidence being considered, certain concepts and constraints affect the interpretation. In particular, scientists disagree over whether an effect, especially one that is reversible or can be compensated, constitutes a hazard. Furthermore, only rarely is any particular study subjected to confirmation by the performance of an identical experiment by another investigator. More often, an analogous--but not identical--experiment is conducted with the objective of clarifying or expanding the results of the initial experiment. The second experiment ideally provides a better

means of incorporating the findings into the theory that underlies the body of knowledge in a particular field of investigation, but it does not necessarily confirm the results of the first investigation.

Still another consideration is also important: scientific findings are probabilistic in nature, in that facts are known only to some level of probability for a given population; the applicability of those facts to a particular individual may be constrained. For example, the term "median effective dose" for a certain agent refers to the dose that will elicit the response characteristic of that agent in one-half of the exposed individuals. Before the dose is administered, however, one cannot predict whether any specific individual will respond, although the prediction that an individual will have a 50% chance of showing the response is valid. In effect, the probabilistic nature of scientific evidence means that no amount of scientific data can guarantee the absolute safety of any agent for any individual or group of individuals. Analysts disagree over whether the conventional scientific approach, whereby an investigator finds or fails to find a statistically significant (very low probability of chance occurrence) difference between experimental and control groups, is appropriate to considering potential hazards to humans. The scientist's statement that no statistically significant differences between the groups are discernible is not equivalent to the absolute statement that there is no difference between the groups.

Conceivably, agents may have effects that are biologically real but so small in magnitude that the difference in mean response between experimental and control populations may not be discernible within the scattering of values for both populations if the sample sizes are small. Biological studies to detect such small differences and to show that they are statistically significant (to a prespecified probability that they are not due to chance) would require the use of large numbers of animals and, in some cases, long exposure times. The expenditures in time and money necessary to perform such studies may be so large that sponsoring institutions with limited budgets often decide that such studies are not cost-effective in terms of the sponsor's overall objectives. A frequent alternative is to predict effects at very low levels by extrapolation from findings at higher levels, on the basis of assumptions about the mathematical relationship between the level (or dose) of the agent and the degree of the effect. Such assumptions are open to challenge, however, and this approach may lead to disagreement over the possible existence of a threshold dose or dose rate below which the agent has no effects.

It must also be remembered that scientists have personal values, goals, and attitudes. It has been said that there is no such thing as an unbiased expert because becoming an accepted authority involves a personal commitment over a period of time that leads to emphasis of certain viewpoints. Thus, like probabilistic scientific findings, objectivity may well be characteristic of scientists as a group without necessarily being characteristic of any individual scientist. Personal bias can consciously or unconsciously affect how the experiment

is designed, how the data are interpreted, and particularly, how the results are applied to decision making. The last is especially important when the decision to be made is in an area outside the scientist's field of expertise.

Finally, scientific experiments are usually restricted to the evaluation of only one factor. In the real world, however, interactions are far more complex. The effect of combinations of factors is illustrated in the incidence of lung cancer in uranium miners, which is higher than in the general population, presumably as a result of the inhalation of radioactive material. The extent of the increased incidence in nonsmoking miners is marginal, but miners who smoke cigarettes have a much higher incidence of lung cancer than either nonsmoking miners or the general population. Thus, scientific evidence can only supply probabilistic information that is relatively narrow in its application to the real world.

4 OTHER REVIEWS

This section contains descriptions of representative general reviews of the literature on the bioeffects of RFR, including two by Eastern European authors (Baranski and Czerski, 1976; Sudakov and Antimoniy, 1973) and two of Eastern European research by an American (McKee, 1979, 1980). The bibliographies in these reviews served as additional sources of possibly relevant literature citations, thereby ensuring adequate coverage of the literature. The conclusions and opinions of the authors of these reviews were carefully examined.

Papers describing progress in research being conducted by all contractual and in-house investigators sponsored by the U.S. Air Force School of Aerospace Medicine (USAFSAM/RZP) are contained in J. C. Mitchell (1981). Although this compendium is not a general review of the entire RFR-bioeffects field, it does include important recent results pertaining to specific frequency ranges used in such Air Force radar systems as PAVE PAWS and OTH-B.

Two useful recent compendia are the issue of the Bulletin of the New York Academy of Medicine (1979) that covers the "Symposium on Health Aspects of Nonionizing Radiation" held at the Academy in April 1979 and the Proceedings of the IEEE, Special Issue on Biological Effects and Medical Applications of Electromagnetic Energy (1980). Both publications contain reviews of specific RFR bioeffects topics, as well as reviews of the entire field. The presentations in the Bulletin are directed primarily toward informing physicians about the status of the field, whereas those in the Proceedings are primarily for the nonspecialist in RFR bioeffects. The Proceedings also contains first publication of some recent research results. Only the general review articles in these issues and those selected from earlier publications are considered in this section.

In the Proceedings, Michaelson (1980) presents an overview that includes brief discussions of principles of biological experimentation and interpretation of results, the necessity for and the problems associated with scaling and extrapolating results with animals to effects on humans, and some basic physiological considerations involved in exposure to RFR. He then summarizes the current state of research on all the major bioeffects. He concludes that most of the experimental data indicate that the reported effects of RFR exposure are primarily due to temperature increases or internal changes in temperature gradients, but he recommends further research to resolve substantial uncertainties in certain areas, particularly the effects of chronic exposure to low levels of RFR. Michaelson cites 99 references. An earlier review by Michaelson (1978) covers much of the same subject matter and provides 209 reference citations.

In both the Bulletin and the Proceedings, McRee (1979, 1980) reviews the difficulties in assessing the Eastern European literature on bioeffects of RFR before about 1972, and he discusses the inception of the cooperative agreements between the USSR and the United States. He also indicates that the initial stages of the cooperative program primarily involved exchanges of information (and interchange visits). It became evident that most of the USSR research involved chronic exposures to average power densities of about 0.5 mW/cm^2 or less, whereas the U.S. research involved relatively short exposures to about 5 mW/cm^2 or more. This situation led to an agreement to perform duplicate experiments in the two countries.

In the duplicate experiment that McRee describes, rats were exposed at 0.5 mW/cm^2 for 7 hr/day, 7 days/week for 3 months, and specific behavioral and biochemical tests were performed. The U.S. study found a decrease in sulfhydryl activity and blood cholinesterase, as did the USSR study; blood chemical analyses at the end of the 3-month exposure period showed aldosteronism in the exposed animals, relative to controls, due to vacuolation and hypertrophy in the zona glomerulosa of the adrenal glands. Also, the results showed significant differences in the same direction as those found in the USSR in all behavioral parameters studied (increased threshold in footshock detection, decreased activity in an open field, and poor retention of an avoidance response).

In both reviews, McRee summarizes effects on humans and animals reported by Soviet, Polish, and Czechoslovakian scientists, and in the Bulletin, he discusses safety standards in these and Western countries. McRee cites 33 references in the Proceedings and 5 in the Bulletin.

In the Bulletin, Cleary (1979) presents a brief overview of research, with emphasis on reported effects of exposure at low average power densities. He indicates the difficulties in making quantitative comparisons of results and extrapolating from data on animals to effects on humans. He cites 22 references.

In a more comprehensive, earlier review, Cleary (1977) analyzes the results of 12 studies on various aspects of RFR bioeffects and includes references to 100 other articles. He discusses the physical characteristics of RFR, the mechanisms of RFR interaction with biological systems, and whole-body dose rates and dose-rate distributions within actual and model biological systems. He also reviews the major physiological and behavioral effects of RFR.

Assenheim et al. (1979) provide a report intended for people without scientific backgrounds. It includes discussion of the physical principles involved in the mechanisms of interaction between RFR and biological tissues, applications of RFR (including a brief discussion of OTH radars), treatments of the various RFR-bioeffects topics, comparisons of the exposure standards of various countries, appendices related to specific subjects, 299 references, and a glossary of terms and abbreviations used.

Two reviews, one covering RFR biophysics and the other discussing biological and pathophysiological effects of exposure to RFR, are presented in the transactions of a short course held in Ottawa, Canada, in June 1978. Lin (1978b) presents an assessment of the current knowledge about RFR interactions with biological systems, with emphasis on the dielectric properties of tissue materials, propagation and absorption of RFR in tissues, and basic physical mechanisms of interaction. He cites 76 references.

Stuchly (1977) reviews potentially hazardous RFR emitters, citing 38 references. The review discusses those emitters judged to have potential for producing hazardous levels of RFR under normal operating conditions and under possible malfunction, and considers satellite communication systems and microwave-power devices for generating heat.

Carpenter (1977) gives a critical, comprehensive review of RFR and its effects, emphasizing RFR as an environmental agent. There are sections on physical characteristics and properties of RFR; effects on tissue; "thermal" and "nonthermal" effects; exposure levels; biological effects of RFR on human beings and experimental animals; RFR effects on the eye, the testes, and the nervous system; and RFR effects on development. Carpenter cites 110 references.

Dodge and Glaser (1977) assess international trends in research, development, and occupational health and safety, concentrating on events since 1975. They discuss exposure standards, research on bioeffects, effects of RFR on humans, and U.S. federal RFR health and safety programs, citing 25 references.

The 234-page book by Baranski and Czerski (1976), published in English (translation by Czerski), is a comprenensive Eastern European presentation of the then-current literature and research results through 1975. The book contains references to 614 articles; Western, as well as Eastern European, investigations are well represented. The seven chapter headings are:

- Introduction
- Physical Characteristics of Microwaves
- Interaction of Microwaves with Living Systems
- Biological Effects of Microwaves. Experimental Data
- Health Status of Personnel Occupationally Exposed to Microwaves, Symptoms of Microwave Overexposure
- Safe Exposure Limits and Prevention of Health Hazards
- Final Comments.

Sudakov and Antimoniy (1973) provide an extensive review (224 references) of the neurophysiology and behavior of animals and humans. They appear to accept as uncontestable the premise that RFR has direct effects (denoted by them as "nonthermal") on the nervous system of animals. The review is in two main sections. The first concerns biological aspects of the effects of RFR on the central nervous system (CNS) of animals and humans. It contains subsections on natural RFR

as a factor in evolution; the sensing of RFR by living organisms; and the effects of natural RFR on animals and humans, on the activity of the CNS, and on the behavior and conditioned activity of animals and humans. The second main section concerns neurophysiological mechanisms of the action of RFR, with subsections on bioelectrical activity of the brain during exposure to RFR, morphological and functional changes in the CNS from RFR exposure, and selective action of RFR on structures of the CNS.

5 PRESENT STATE OF KNOWLEDGE REGARDING PHYSICAL EFFECTS

5.1 Interactions of RFR with Biological Entities

Interactions of electromagnetic fields with biological entities are often loosely characterized in the bioeffects literature as "thermal" or "nonthermal," a usage that has led to confusion and controversy. Therefore, it is appropriate at this point to introduce working definitions of these terms, with the recognition that the boundary between these types of interaction is not sharp.

The interaction of an agent (e.g., RFR) with an entity (biological or nonbiological) can be characterized as thermal if the energy absorbed by the entity is transformed at the absorption site into heat. Heat absorption, in turn, is defined in classical thermodynamics as either an increase in the mean random speed (or kinetic energy) of the molecules at the site (a local increase in temperature), or as an increase in the disorder or randomness of the molecular motion without an increase in mean random speed (a first-order phase change, such as the process involved in ice melting at 0 deg C), or both.

An entity can also absorb energy at specific discrete frequencies in the form of energy packets or quanta, each of which has an energy proportional to one of the discrete frequencies. Although large numbers of molecules can be involved, quantum absorption is essentially a microscopic phenomenon in that the constituents and configurations of the various molecular species comprising the entity determine the specific frequencies or characteristic spectra at which such absorption can occur. The kinds of interactions involved are numerous and of varying degrees of complexity. They include alterations of molecular orientations and configurations that do not change the basic identities of the molecules, disruption of intermolecular or intramolecular bonds, and excitation of atoms or molecules to higher electron states (including ionization). Such interactions can be characterized as "short-range" processes.

It is theorized that cooperative interactions also occur among subunits of molecules within biological cells, in cell membranes, and in extracellular fluids. Cooperative interactions are often characterized as "long-range" because absorption of energy at one specific site in a structure (e.g., in a membrane or in a biological macromolecule) can affect a process elsewhere in the structure, or a function of the structure as a whole can be triggered by the release of energy stored in the structure, thereby producing biological amplification.

Conceptually, all such quantum interactions can be characterized as "nonthermal." However, if most of the energy thus absorbed is subsequently transformed locally into heat (as defined above), the distinction between nonthermal and thermal is blurred. Pragmatically,

therefore, to characterize an interaction of RFR with a biological entity as nonthermal requires that the interaction give rise to a frequency-specific effect that is experimentally distinguishable from heating effects caused by thermalization of the absorbed RFR energy.

5.1.1 Thermal Interactions

Consider now the incidence of continuous-wave (CW) RFR on a human or an animal. The relative magnetic permeability of most organic constituents is about unity. Therefore, thermal interactions (as defined previously) can be described in terms of the dielectric, electrical conductivity, and thermal properties of the body organs, tissues, fluids, and so forth, as well as the characteristics of the RFR (frequency, power density, polarization). Measurements of these properties were made some years ago for various mammalian tissues, blood, cellular suspensions, protein molecules, and bacteria over the spectral region from about 10 Hz to 20 GHz by Cook (1951, 1952) and by Schwan and coworkers (Schwan and Li, 1953; Schwan and Piersol, 1955; Schwan, 1957; 1963). In general, the dielectric constants were found to vary inversely with frequency in a separate characteristic manner for each of three parts of that frequency range (the "alpha," "beta," and "gamma" dispersion regions), as shown for muscle tissue in Figure 5-1. These dispersion regions are ascribed to different predominant relaxation mechanisms, each characterized by specific time constants (Schwan, 1957). In the low and intermediate frequency ranges (about 10 Hz to about 100 MHz), which encompass the alpha- and beta-dispersion regions, the properties of cell membranes, which have large specific capacitances (about 1 microfarad/cm^2), predominate. In the range above about 10 GHz (the gamma-dispersion region), membrane impedances are negligible, and the behavior of the water and electrolyte content are most predominant. As an example of the large numerical variation of dielectric constant, the values for muscular tissue decrease by five orders of magnitude, from about 3×10^6 at 10 Hz to 30 at 20 GHz.

In the frequency range from 3 to 30 MHz, the dielectric constant of muscle varies from about 360 to about 110. The values for skin, blood, and other tissues with high water contents are comparable. The values for fat, bone, and other tissues with low water contents are about an order of magnitude smaller and are sensitive to the amount of water the tissues contain. From about 300 MHz to about 10 GHz, the dielectric constants of skin, muscle, and blood vary little with frequency because the transition between the beta- and gamma-dispersions occurs in this range. The mean dielectric constants for these three constituents are about 40, 50, and 60, respectively; the differences in values are largely ascribable to the proportion of water in each constituent, water having a dielectric constant of about 80. A graph of dielectric constant versus frequency for muscle tissue is displayed in Figure 5-2.

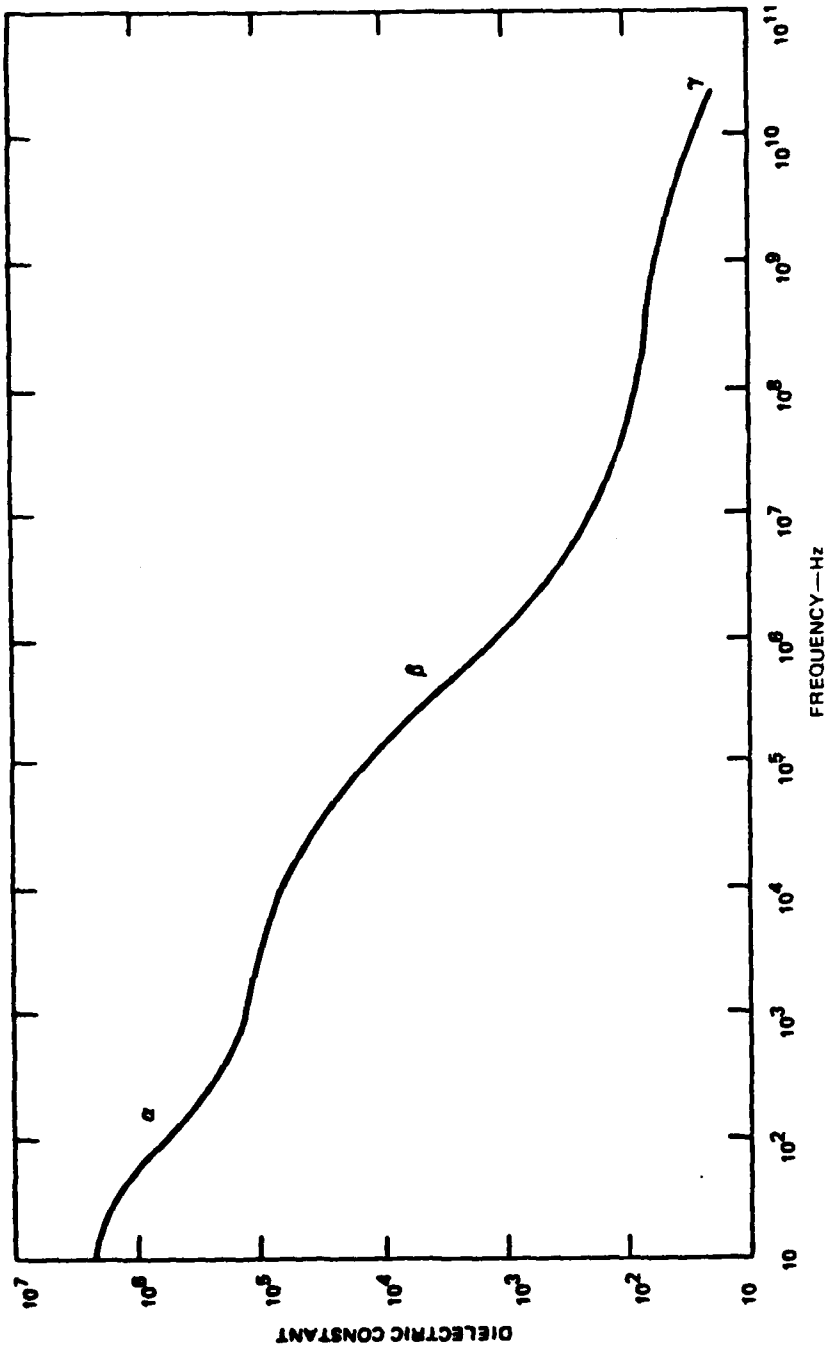


FIGURE 5-1 DIELECTRIC DISPERSION FOR MUSCLE TISSUE

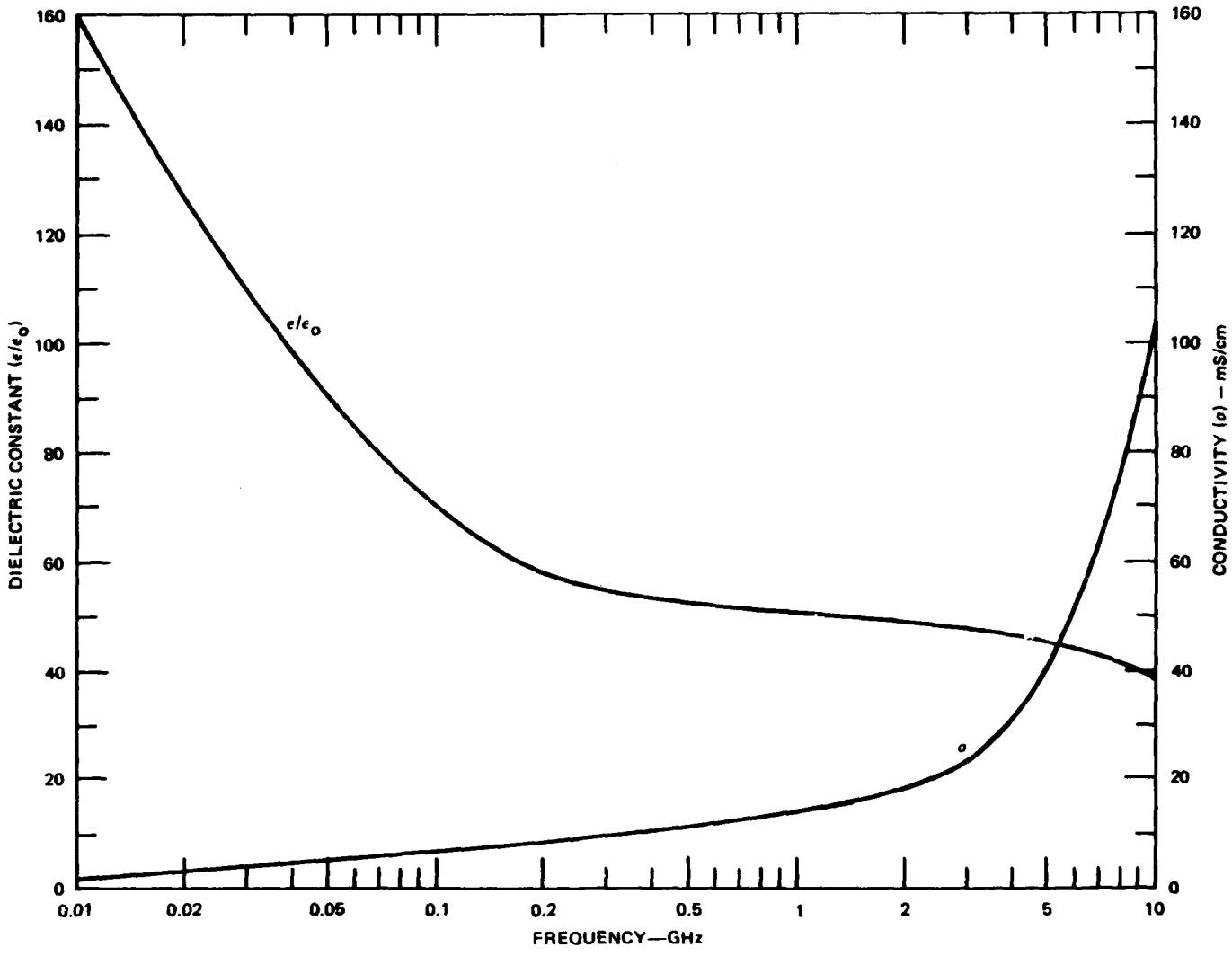


FIGURE 5-2 VARIATION OF DIELECTRIC CONSTANT AND ELECTRICAL CONDUCTIVITY WITH FREQUENCY FOR MUSCLE TISSUE

Subsequent *in vitro* measurements were performed with more advanced techniques and instrumentation as they became available. Such studies include those of Lin (1975), Bianco et al. (1979), Schwan and Foster (1980), Foster and Schepps (1981), and Foster et al. (1982). In addition, the dielectric properties of various animal tissues were measured *in vivo* at frequencies up to 10 GHz by Burdette et al. (1980) and by Stuchly et al. (1981). Some differences in dielectric constant and electrical conductivity were found between *in vivo* and *in vitro* measurements of similar tissues, ascribed primarily to differences in water content. Stuchly and Stuchly (1980) tabulated data for the 10 kHz-10 GHz range.

Because the index of refraction of any material is related to its dielectric constant, electromagnetic fields are reflected and refracted at the air-surface interface and at internal boundaries between constituents of widely different dielectric properties (e.g., at interfaces between connective and fatty tissues or between a body cavity and adjacent tissues), thereby affecting the internal field distributions. Figure 5-3 displays plots of the power transmission factor at air-muscle, fat-muscle, and air-fat interfaces over the frequency range from 100 MHz to 10 GHz. At an air-muscle interface, for example, only about 22% of the incident power density of 100-MHz RFR is transmitted (the remainder being reflected), and similarly, about 41% and 46% are transmitted for 1-GHz and 10-GHz RFR, respectively. The corresponding values for the air-skin interface are approximately the same.

At an air-surface interface, the fraction of the incident energy that is not reflected enters the body and suffers partial or complete absorption. The attenuation constant (rate of energy absorption with distance) of any material is proportional to the square root of its electrical conductivity. The electrical conductivities of skin, muscle, blood, and other constituents of the body increase slowly with frequency up to about 1 GHz and rapidly from that frequency upward, as illustrated in Figure 5-2 for muscle tissue. The concept of "penetration depth" (the inverse of attenuation constant) is often used. For homogeneous planar specimens, the penetration depth is defined as the distance at which the electric-field amplitude is 1/e (37%) of its value or the power density is $1/e^2$ of its value just within the surface. Figure 5-4 displays plots of penetration depth versus frequency for muscle, blood, and fat. At 1 GHz, for example, the penetration depth for muscle is about 2.4 cm, whereas at about 10 GHz and higher, field penetration is confined to the skin. Thus, in the latter frequency range, RFR is much like sunlight with regard to absorption.

5.1.2 Dose-Rate Considerations

In the literature on RFR bioeffects, thermal energy absorption from an electromagnetic field is usually characterized by the specific absorption rate (SAR), which is defined as the rate of energy absorption per unit volume in a small volume at any locale within an entity, divided by the mean density of the constituents in that volume. SAR is expressed in terms of W/kg or mW/g (1 mW/g = 1 W/kg). The numeri-

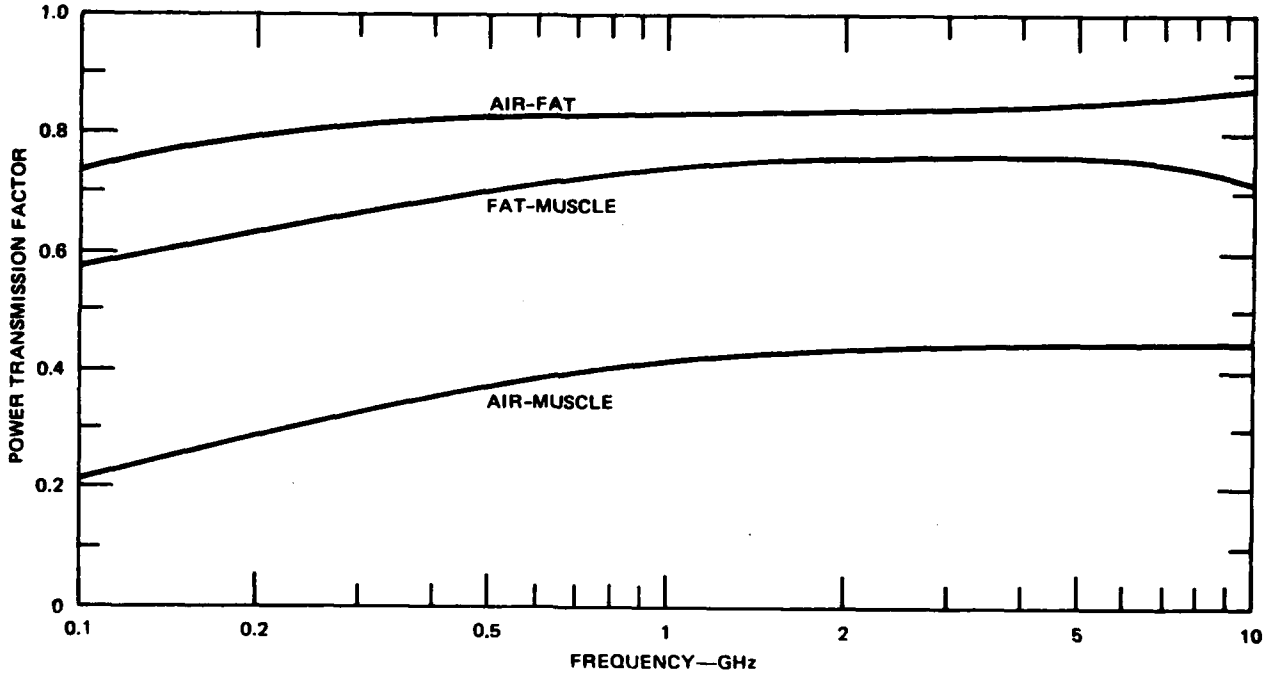


FIGURE 5-3 POWER TRANSMISSION FACTORS VERSUS FREQUENCY FOR AIR-FAT, FAT-MUSCLE, AND AIR-MUSCLE INTERFACES

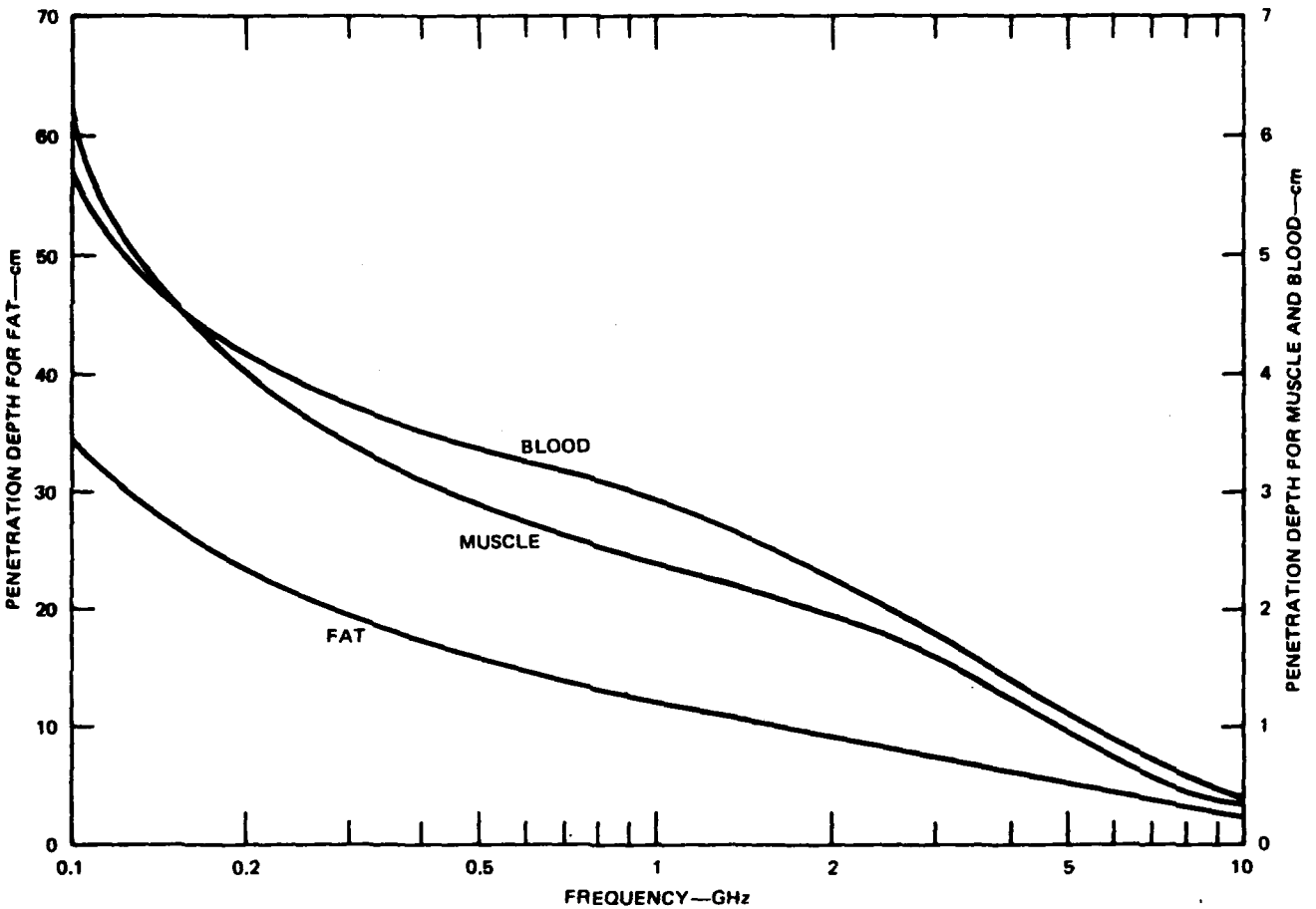
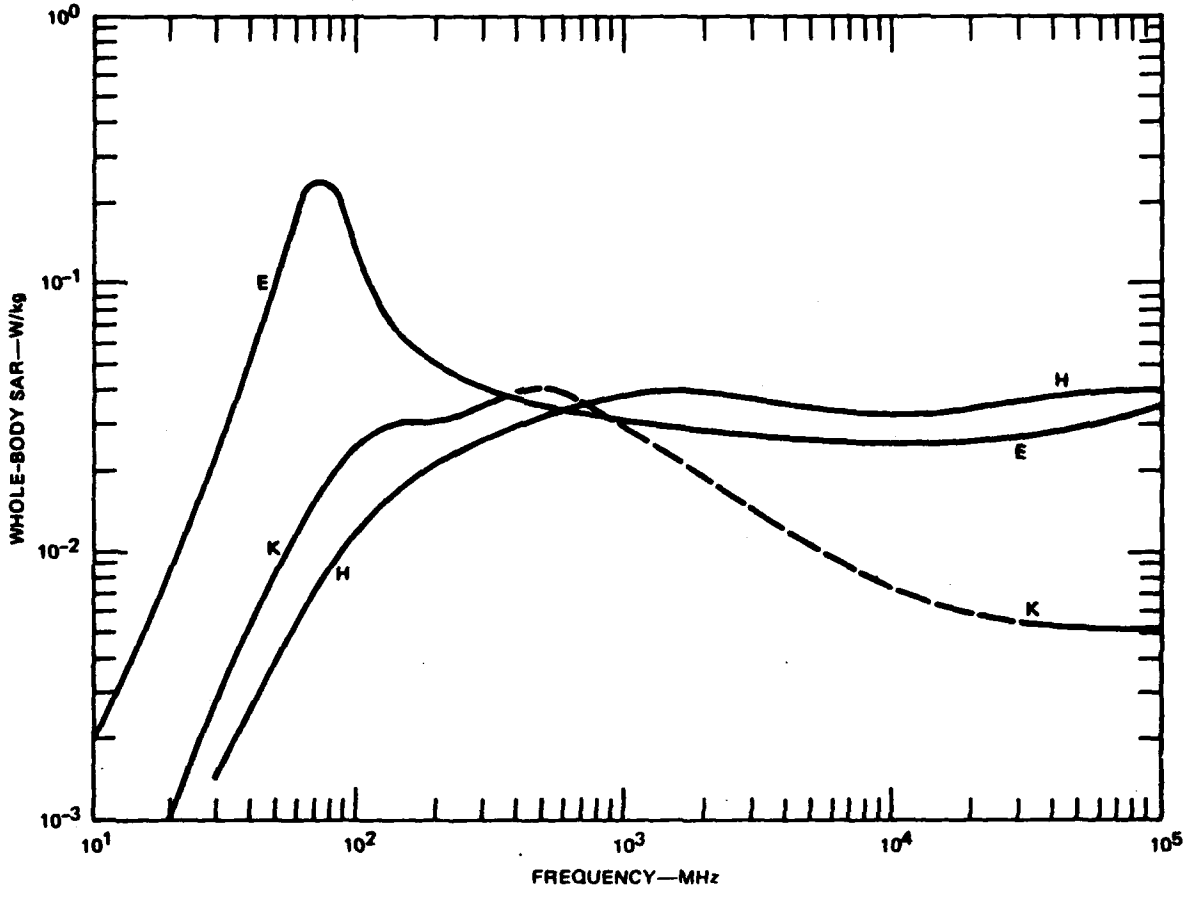


FIGURE 5-4 PENETRATION DEPTH VERSUS FREQUENCY FOR MUSCLE, BLOOD, AND FAT

cal value of SAR in any small region within a biological entity depends on the characteristics of the incident field (power density, frequency, polarization), as well as on the properties of the entity and the location of the region. For biological entities that have complex shapes and internal distributions of constituents, spatial distributions of local SAR are difficult to determine by experiment or by calculation. Thus, the concept of "whole-body SAR," which represents the spatial average value for the body per unit of incident power density, is useful because it is a quantity that can be measured experimentally--e.g., by calorimetry--without information on the internal SAR distribution.

Many investigators have studied relatively simple geometric models (including homogeneous and multilayered spheroids, ellipsoids, and cylinders) that have weights and dimensions approximately representative of various species, including humans. For studies pertaining to the far fields of RFR sources, such models were actually, or were assumed to be, irradiated with linearly polarized plane waves to determine the dependence of whole-body SAR on frequency and orientation relative to the polarization direction of the RFR. Many of the significant data have been included in a series of handbooks (Johnson et al.; 1976; Durney et al., 1978, 1980) that are useful for very approximate frequency-scaling and interspecies comparisons of whole-body SAR values. An important result of this work is that the largest value of whole-body SAR is obtained when the longest dimension of each kind of model is parallel to the electric component of the field and when the wavelength of the incident RFR is about 2.5 times the longest dimension. The adjective "resonant" is often applied to the frequency corresponding to this wavelength. The resonant value of whole-body SAR for each model is also inversely dependent on the dimension perpendicular to the polarization direction (and propagation direction) of the field; i.e., the model has characteristics somewhat similar to those of a lossy dipole antenna in free space. Resonances would also occur for circularly polarized RFR. Such RFR can be resolved into two mutually perpendicular components, each having half the total power density. Therefore, an entity exposed to circularly polarized RFR would have lower resonant SAR values than it would have if exposed to linearly polarized RFR of the same total power density.

Figure 5-5 shows plots of whole-body SAR versus frequency for a prolate-spheroidal homogeneous model of an "average" or "standard" man, approximately 5 ft 9 in. (1.75 m) tall and weighing about 154 lb (70 kg), exposed to 1 mW/cm^2 of plane-polarized RFR in three orientations relative to the polarization direction. A relatively sharp peak is obtained at resonance for the "E" orientation in which the long axis of the prolate spheroid is parallel to the polarization direction (electric vector) and perpendicular to the magnetic vector and propagation direction. In the "H" orientation, the long axis is parallel to the magnetic vector and perpendicular to the electric vector and propagation direction; in the "K" orientation, the long axis is parallel to the propagation direction. For this model of man, the resonant frequency (in the E orientation) is about 70 MHz; at this



NOTE: The dashed segment represents estimated values.

FIGURE 5-5 *WHOLE-BODY SAR FOR PROLATE-SPHEROIDAL HOMOGENEOUS MODEL OF "AVERAGE" MAN EXPOSED TO 1-mW/cm^2 RFR IN THE "E," "H," AND "K" ORIENTATIONS*

frequency, the SAR is about 0.2 W/kg for 1 mW/cm^2 incident power density, or about 1/6 of his resting metabolic rate or about 1/21 to 1/90 of his metabolic rate when performing exercise ranging from walking to sprinting (Ruch and Patton, 1973).

In Figure 5-6, whole-body-SAR curves are presented for prolate-spheroidal multilayered models of the "average" man, woman, and 10-year-old child exposed to 1 mW/cm^2 of plane-polarized RFR in the E orientation. The average woman is assumed to be approximately 5 ft 3 in. (1.61 m) tall and to weigh about 135 lb (61.14 kg). The corresponding values for the child are about 4 ft 6 in. (1.38 m) and 71 lb (32.2 kg). The resonant frequency for the woman is about 80 MHz and her whole-body maximum SAR is about the same as for the man. The resonant frequency for the child is still higher, about 95 MHz; and the whole-body maximum SAR is about 0.3 W/kg, somewhat larger than for the adults. It should be noted that all three maximum SARs are smaller than the 0.4 W/kg value used as the basis for the new ANSI standard. Moreover, the data from which Figure 5-6 was derived can be used to calculate, by simple proportion, the incident power densities necessary to produce an SAR of 0.4 W/kg. Plots of power density versus frequency derived in this manner will lie above the limits of the new ANSI standard, an indication that the limits are somewhat more stringent than such data.

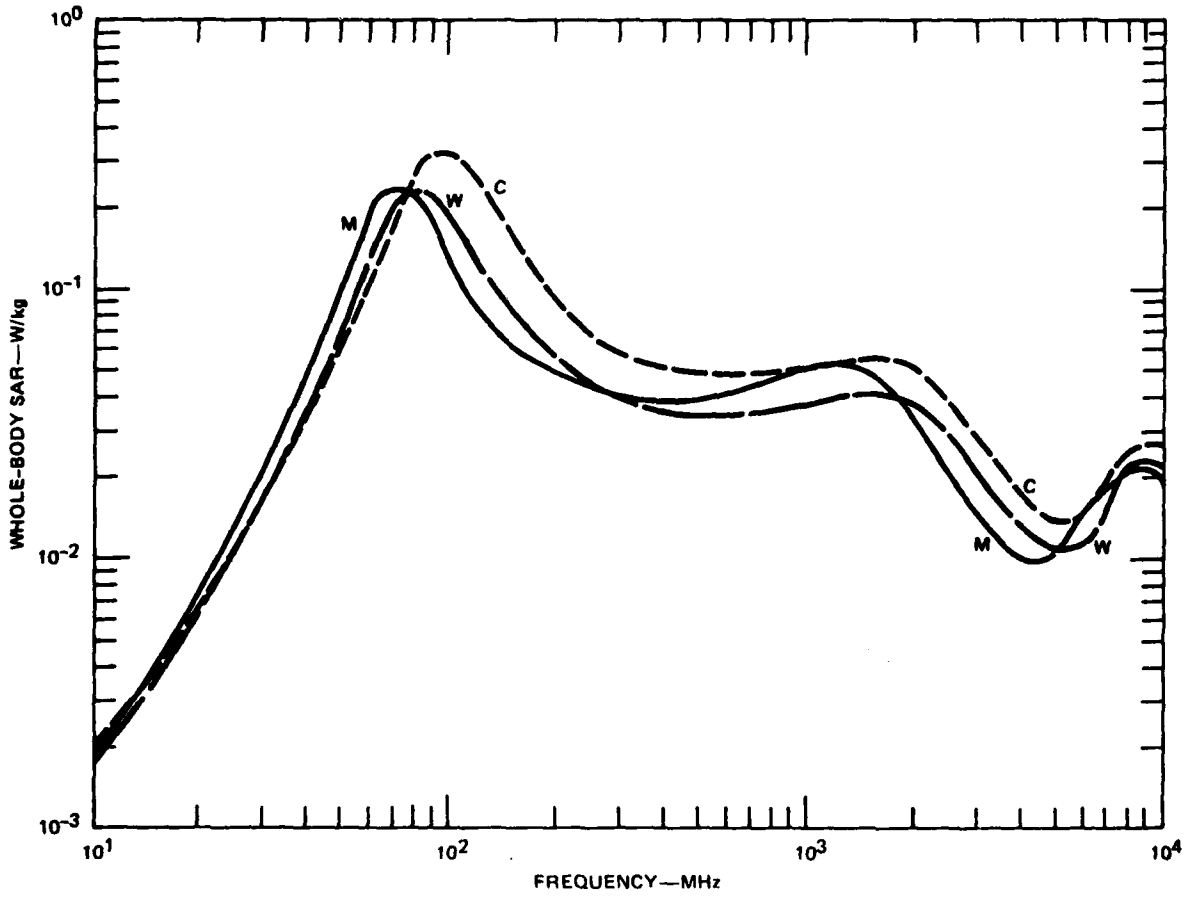
In general, the whole-body SAR below resonance in the E orientation is approximately proportional to f^2; above resonance the SAR is approximately proportional to 1/f for about one decade of frequency and exhibits secondary resonances (smaller relative maxima) at higher frequencies, as exemplified by the curves in Figure 5-6.

The foregoing discussion of whole-body SAR also largely applies to modulated RFR (including pulsed RFR) at corresponding carrier frequencies and time-averaged incident power densities.

To see how the concept of whole-body SAR could be interpreted, consider the standard model man. Absorption of energy as heat by exposure of such a model man at his resonant frequency (70 MHz) in the E orientation to an average power density of 1 mW/cm^2 (SAR of 0.2 W/kg) for 1 hr would produce a mean body temperature rise of only about 0.2 deg C if no heat removal mechanisms were present and if no first-order phase changes were involved.

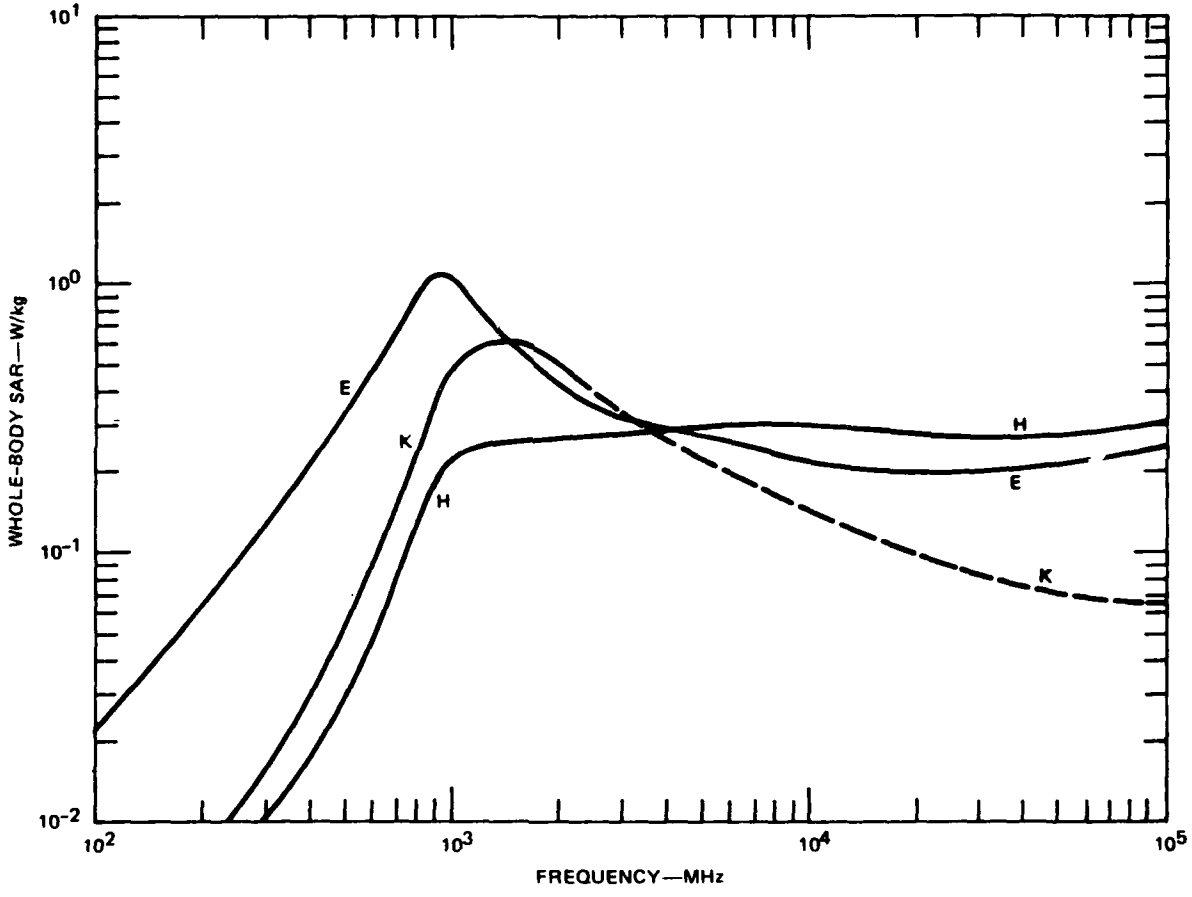
Figure 5-7 presents similar data for a prolate-spheroidal homogeneous model of a "small" rat (0.14 m long and weighing 0.11 kg). Not only is the resonant frequency in the E orientation (approximately 900 MHz) higher than any of the values for humans, but the resonant SAR is also larger (about 1.1 W/kg for the rat, compared with about 0.2 W/kg for the adult human, per mW/cm^2 of incident power density). Therefore, scaling of data from experimental animals to humans must consider such differences of whole-body SAR as well as frequency.

The presence of a ground plane or other reflecting surfaces shifts the resonant frequencies downward and can produce higher values



NOTE: The dashed segment represents estimated values.

FIGURE 5-6 WHOLE-BODY SAR FOR PROLATE-SPHEROIDAL MULTILAYER MODELS OF "AVERAGE" MAN(M), WOMAN(W), AND 10-YEAR-OLD CHILD(C) EXPOSED TO 1-mW/cm^2 RFR IN THE "E" ORIENTATION



NOTE: The dashed segment represents estimated values.

FIGURE 5-7 WHOLE-BODY SAR FOR PROLATE-SPHEROIDAL HOMOGENEOUS MODEL OF A SMALL RAT EXPOSED TO 1-mW/cm^{2}RFR IN THE "E," "H," AND "K" ORIENTATIONS

of whole-body SAR at the lower resonant frequencies (Hagmann and Gandhi, 1979; Gandhi et al., 1977; Gandhi, 1975). Hagmann and Gandhi (1979) showed that for a homogeneous block model of the "standard" man in electrical contact with an infinite, perfectly conducting ground plane, the whole-body resonant frequency (in the E orientation) is shifted from the free-space value of 77 MHz to 47 MHz. Moreover, the whole-body SAR at 47 MHz is 32.5% higher than at 77 MHz. However, they also noted that such ground-plane effects are largely eliminated if conductive contact with the ground is removed.

Numerical calculations of internal spatial distributions of SAR have been performed on "block" models, in which the shape of the body is approximated by an appropriate arrangement of many rectangular cells of various sizes. Each cell is assumed to be biologically homogeneous and to have constant internal field over its volume when the model is exposed to RFR. However, the biological properties ascribed to each cell are selected to approximate those of tissues in corresponding locations of the body (Chen and Guru, 1977; Hagmann et al., 1979a, 1981; Chatterjee et al., 1980). More accurate values of whole-body SAR have been obtained with such models than from simpler ones.

Block models, as well as homogeneous and multilayered spheroidal and cylindrical models having appropriate electromagnetic and thermal characteristics, have also been used to represent various parts of the body, such as the head and limbs (Joines and Spiegel, 1974; Weil, 1975; Lin, 1975; Kritikos and Schwan, 1975, 1976; Neuder et al., 1976; Wu and Lin, 1977; Rukspollmuang and Chen, 1979; Massoudi et al., 1979; Hagmann et al., 1979a, 1979b, 1981; Janna et al., 1980; Spiegel et al., 1980; Kritikos et al., 1981).

An early, very significant finding for spherical models of the isolated head assumed to be exposed to plane-wave RFR was the discovery of local regions of relative maximum SAR values. The locations of such regions depend on the size of the head, the electromagnetic characteristics of its layers, and the wavelength of the incident field. These regions have been conveniently dubbed "hot spots," even for combinations of incident power density and exposure duration that would produce biologically insignificant temperature increases at such spots. An analysis of a homogeneous lossy spherical head model (Kritikos and Schwan, 1975) indicates that there are hot spots inside spheres having radii between 0.1 and 8 cm, and in the frequency range from about 300 MHz to 12 GHz; for larger radii and other frequencies, there are internal hot spots, but the hottest spots are at the front surface (facing the RFR source). Similar results were obtained for multilayered spherical models (Weil, 1975; Kritikos and Schwan, 1976). Specifically, Kritikos and Schwan (1976) analyzed two such models, one with a radius of 5 cm and the other, 10 cm. For the 5-cm head, the hot spots are internal over the frequency range from about 400 MHz to 3 GHz. The highest relative maximum SAR occurs near the center of the head at a frequency of about 1 GHz, and has a value of about 9 W/kg for an incident power density of 1 mW/cm^2. (Of course,

the whole-head SARs are considerably lower.) By contrast, for the head of 10-cm radius (about that for an adult human head), no deep internal hot spots are produced at any frequency; the hot spots are always at or just beneath the front surface.

Rukspollmuang and Chen (1979), starting with a block model of a multilayered isolated spherical head, found qualitatively similar results. They then studied, at 918 MHz and 2.45 GHz, a block model having a shape and internal structure more closely approximating that of the human head (including eyes, nose, skull bone, and brain), and found that much of the energy within the head would be absorbed by the skull. Specifically, for frontal exposure of this model at 918 MHz, the maximum SAR for the brain region is about one-third that for the brain region of a 7-cm-radius multilayered spherical model. Also, for frontal exposure of the more accurate model to 2.45 GHz, the induced field is concentrated primarily near the proximal surface, and therefore energy dissipation within the brain would be relatively low.

Hagmann et al. (1979b) calculated SAR distributions in the attached head of a block model of the human and derived whole-head as well as whole-body SARs for three orientations of the model relative to the RFR source. For front-to-back propagation with the long axis of the body parallel to the electric vector, they found a rather broad head resonance at about 350 MHz with a whole-head SAR of 0.12 W/kg per mW/cm^2; the corresponding whole-body SAR is about 0.05 W/kg. A sharper head resonance at 375 MHz was obtained for head-to-toe propagation, with whole-head and whole-body SARs of 0.22 and about 0.07 W/kg per mW/cm^2, respectively.

Results of theoretical analyses of SARs have been verified experimentally. Physical models of simple geometry or in human- or animal-figurine shape were constructed from synthetic biological materials that have approximately the same electromagnetic characteristics as their corresponding biological constituents. The models were then exposed to sufficient power densities to obtain readily measurable temperature increases, which were measured immediately after irradiation. To use available sources of RFR that provide only specific frequencies and to avoid the problems of exposing large full-scale models, smaller models are often chosen by the use of scaling relationships so that results of exposing such smaller models at the available frequencies can be extrapolated to obtain results on full-size models at other frequencies of interest. Guy et al. (1976) took this approach. They exposed homogeneous human figurines having lengths of 37.6 and 26.5 cm (as well as spheres and ellipsoids) at approximately 143 MHz to simulate exposures of full-size figurines (1.74 m in length) at 31.0 and 24.1 MHz. In their study of head resonances, Hagmann et al. (1979b) exposed human figurines with lengths of 20.3, 25.4, 33.0, and 40.6 cm at 2.45 GHz, to correspond with full-size figurines exposed at scaled frequencies of 284.5, 355.6, 462.3, and 569.0 MHz, respectively.

A technique widely used to determine SAR distributions in physical models or actual animal carcasses is to embed the objects in Styrofoam, section the experimental object along parting planes of interest, then reassemble the object and expose it to RFR. The spatial distribution over each parting plane is measured with scanning infrared thermography immediately after exposure. However, such spatial temperature distributions should not be regarded as corresponding with in vivo internal temperature distributions, because the heat transfer characteristics of such carcasses and physical models are significantly different from those of live animals and do not have the thermoregulatory mechanisms of the latter. Instead, such measured temperature distributions represent approximations to the internal field or SAR distributions.

Among the interesting results obtained by Guy et al. (1976, 1977) was that exposure of a full-size human figurine to an electric field parallel to its length at frequencies in the HF band yields relatively high SARs in regions of the body where the cross section perpendicular to current flow is relatively small, such as the neck, knees, and ankles. Also, exposure of the figurine to a magnetic field perpendicular to the frontal plane in the same frequency range produces eddy currents that yield relatively high SARs where such currents are forced through relatively small cross-sectional areas or are diverted by sharp angular changes, such as in the groin and along the sides of the body near the ribs. These results are especially pertinent to near-field exposure situations, for which it is necessary to measure the spatial variations of the electric and magnetic fields separately because their amplitude ratio may vary from point to point, and they may not be perpendicular to each other and to the propagation direction.

Whole-body (and detached whole-head) SARs, as well as (attached) part-body SARs, were measured by calorimetry alone or in conjunction with scanning infrared thermography by Hunt and Phillips, 1972; Kinn, 1977; Allen and Hurt, 1979; Hagmann et al., 1979b; Olsen et al., 1980).

Whole-body SARs were also determined in waveguide types of exposure systems by measuring the input, output, and reflected values of RFR power without and with the object present and performing the requisite arithmetic (Ho et al., 1973). The experimental results are in qualitative agreement with those derived from the theoretical models.

Burr and Krupp (1980) measured real-time temperature increases induced by 1.2-GHz RFR at 70 mW/cm^2 in homogeneous spheres (3.3-cm radius); Macaca mulatta cadaver heads (attached to the body and detached); and living, anesthetized (attached) heads of the same species. They used a sensitive, accurate temperature probe (Bowman, 1976) that essentially does not perturb, or is not perturbed by, the RFR. The bodies of the animals were exposed with their longest axes parallel to the electric or magnetic component of the incident RFR (the E and H orientation, respectively). The results indicated that temperature distributions in attached cadaver heads vary strongly with body orientation. They also found that blood flow in a live animal

affects the temperature distribution in its head in a complex manner that is not adequately predicted by current theoretical models.

Much of the dosimetry work discussed thus far was done for actual or assumed exposures to far field (planar) RFR. Because of concern with possible hazards from the use of RFR in broadcast, industrial, and biomedical applications in which personnel are occupationally in the near field of the RFR, research is also being done to determine SAR distributions induced in such exposure situations (Chatterjee et al., 1980, 1981; Iskander et al., 1980; Karimullah et al., 1980; Spiegel, 1982). As would be expected, the results are sensitive to the type, location, and orientation of the RFR source, as well as to the characteristics of the RFR and the properties of the biological entity exposed.

5.1.3 Quantum Interactions and Nonthermal Effects

The activation energies for short-range quantum interactions of CW RFR at the molecular level extend from about 0.08 eV (1.3×10^{-20} J) for hydrogen-bond disruption to about 10 eV (1.6×10^{-18} J) for ionization. The corresponding quantum frequencies range from about 19 to 2,400 THz (Cleary, 1973). However, an electromagnetic quantum at, say, 100 MHz, has an energy of only 4.2×10^{-7} eV (6.8×10^{-26} J), or approximately five-millionths of the energy required for hydrogen-bond disruption, which is at the lower end of the energy-activation range cited above. Therefore, the existence of nonthermal biological effects of CW RFR ascribable to such short-range molecular interaction mechanisms is extremely doubtful.

It has been logically postulated that cooperative or long-range quantum processes in biological entities (or the functions resulting therefrom) could be altered by exposure of the entity to external fields of magnitudes that do not produce heat as the primary or initial product. Much research has been done with models of cellular membranes by Schmitt and Samson, 1969; Frölich, 1975a, 1975b, 1980; Grodsky, 1976; Illinger, 1982; and others (see Taylor and Cheung, 1978, 1979, and the recent survey of this subject by Taylor, 1981). In general, the results indicate that cooperative processes have activation energies or exhibit resonant frequencies that can be much lower than those for short-range interactions, extending down into the RFR range as defined herein. Heretofore, it was widely believed that because the interactions of an incident field on a complex macromolecular structure such as a membrane are nonlinear, thermal equilibrium would be quickly distributed normally among the many macromolecular resonant modes of the structure. However, current theories indicate that the incoming energy can be periodically exchanged among a few resonant modes for a relatively long time before being thermalized in the sense above, and thereby give rise to effects not ascribable to heat per se.

The mean thermal energy corresponding to the physiological temperature 37 deg C is about 0.027 eV, with a classical spectral dis-

tribution around a maximum at 6.5 THz and encompassing the frequency range for cooperative processes. Therefore, as a counterargument to the manifestation of such nonthermal effects, a question has been raised whether these effects would be distinguishable from those that are spontaneously induced thermally in vivo. Alternatively, separation of such RFR interactions from those thermally induced may require that the rates of occurrence of the former exceed the rates for the latter. This requirement implies that for manifestation of such effects of RFR, the intensity of the incident field must exceed minimum values or thresholds related to the specific processes.

Because predictions from various theoretical models and related considerations conflict to a significant extent (see Adey and Bawin, 1977; Taylor and Cheung, 1978, 1979), the issue of whether weak external fields at frequencies well below the infrared range (i.e., RFR) can alter biological processes is not yet resolved. Experimental data purporting to support the conclusions derived from such theoretical models have been obtained with cell preparations and microorganisms at frequencies in the millimeter-wave region (well above 10 GHz) by Webb and coworkers (Webb and Stoneham, 1977; Webb *et al.*, 1977). However, Gandhi (1981), using more sophisticated microwave methodology, has been unable to verify these results. The data thus far are sparse, and their relationship to possible nonthermal effects of frequencies below 10 GHz is conjectural, especially in intact macroorganisms. However, increases and decreases of calcium-ion binding to cell membranes due to weak external RFR, a phenomenon called "calcium efflux," has been ascribed to alterations of cooperative processes by such fields. This phenomenon is discussed in Section 6.5.2.

Adey (1981a) reviews the phenomenology of basic interaction mechanisms and models of tissue interactions with RFR.

5.1.4 Interactions of Modulated RFR

Insofar as average power density is concerned, the effects of amplitude-modulated RFR at any given carrier frequency and power density are essentially the same as those of CW or frequency-modulated-CW (FMCW) RFR at the same carrier frequency and power density. In addition, biological effects have been ascribed to amplitude modulation per se, notably the previously mentioned calcium-efflux phenomenon, which was seen for 50-MHz, 147-MHz, and 450-MHz RFR modulated at sub-ELF frequencies, but not for unmodulated RFR at these carrier frequencies.

5.1.5 Interactions of RFR Pulses

The temperature increase of any given region within a biological entity due to the arrival of a single RFR pulse would be small because of the relatively large thermal time constants of biological materials and the operation of heat-exchange mechanisms. However, if the region contains a boundary between layers of widely different dielectric properties, then the temperature gradient (rate of change

of temperature with distance) can be large at such a boundary even though the mean temperature increase in the region is small.

One single-pulse effect known to occur *in vivo* is the phenomenon of "microwave hearing" (Frey, 1961) discussed in Section 6.5.1, or the perception of single or repetitive short pulses of RFR as apparently audible clicks. The interaction mechanisms involved are not yet completely understood. However, most of the experimental results tend to support the theory that pulse perception occurs because of transduction of the electromagnetic energy into sound pressure waves in the head at a boundary between layers having widely different dielectric properties (e.g., at the boundary between the skull and the skin or the cerebrospinal fluid). The energy in a pulse arriving at such a boundary is converted into an abrupt increase in momentum that is locally thermalized, producing a negligible volumetric temperature increase but a large temperature gradient across the boundary. Under such conditions, rapid local differential expansion would occur and create a pressure (sound) wave that is detected by the auditory apparatus. This effect is often characterized as nonthermal because the power density averaged over two or more pulses can be minuscule. Specifically, the time-averaged power density for two successive pulses is inversely proportional to the time interval between the arrival of the pulses at the perceiver, and this interval can be indefinitely long without affecting the perception of each pulse. Therefore, the time-averaged power density has no relevance to perception. Irrespective of how the RFR-hearing phenomenon is characterized, the significant point is that the preponderance of experimental evidence indicates that the pulses are converted into actual sound in the head, rather than perceived by direct RFR stimulation of the auditory nerves or the brain.

As discussed in Sections 6.5.3 and 6.6.1, pulsed RFR has been reported to produce other effects, such as alterations of the blood-brain barrier and behavioral changes.

5.2 Exposure Systems and Instrumentation for RFR Bioeffects Research

Much of the early laboratory research on RFR bioeffects suffered from the lack of adequate systems for exposing the biological entities under study and of accurate techniques and instrumentation for measuring incident fields and/or determining energy absorption rates within such entities. The environmental characteristics of the exposure systems were often inadequately characterized or controlled. In addition, the instrumentation was frequently incorrectly used, or was the source of significant errors in numerical values, or of spurious biological findings (artifacts) traceable to perturbations introduced by the presence of the sensors. For these reasons, many of the early results should be viewed as questionable, at least from a quantitative standpoint. During recent years, however, major advances have been made in specialized exposure systems and in instrumentation for determining incident-field intensities for biological research and for determining energy-absorption rates within biological entities.

5.2.1 Exposure Systems

Systems have been developed for exposing various specific classes of biological entities, including intact animals in the far field or near field (whole-body or part-body), in vitro tissue preparations of various kinds, and microorganisms and cell cultures. Representative examples of such systems are described below.

Many investigators have endeavored to simulate human exposure to RFR from a distant source by exposing laboratory animals within a chamber with inner walls and other internal structures lined with RFR-absorbing materials of appropriate properties and shapes to render the chamber anechoic (i.e., to minimize reflections) over the frequency range of interest. Another important consideration is to minimize perturbations of the RFR at the subject due to the presence of the structures used to support or confine the subject. For this purpose, such structures are assembled from materials that are relatively transparent to the RFR (e.g., various polyfoams, Lucite). The internal dimensions of such anechoic chambers are usually large enough to permit placement of the subject in the far field of the antenna used, and so that the small curvature of the spherical wavefront at the subject can be neglected (yielding essentially plane-wave RFR). Most such chambers have means for regulating the internal temperature, humidity, and air flow rate. Some exposure systems used for behavioral studies also have a source of "white" noise to mask other spurious noises that may introduce unwanted acoustical cues.

Because of cost and size considerations, it is impractical to use a set of conventional anechoic chambers for chronically exposing a group of animals individually at the same time. Therefore, Guy (1979) developed a miniature anechoic chamber (and RFR source) suitable for chronically exposing a rodent or rabbit to plane-wave RFR at 2.45 GHz or higher, with a view toward replicating such exposure systems at relatively low cost.

Another method for exposing an animal to plane-wave RFR is to insert it in a transmission line of appropriate design. Typically (Mitchell, 1970), the exposure section of the transmission line consists of a flat inner conductor and a symmetrically located rectangular outer conductor, both of dimensions suitable for accommodating the animal to be exposed, which is placed between one side of the inner conductor and the neighboring walls of the outer conductor. The exposure section is impedance-matched to the source by a tapered section of outer conductor, and another tapered section is used to match the output end of the exposure section to an absorptive load, to minimize RFR reflection toward the source in the absence of the subject. In the exposure section, the electric and magnetic components of the RFR are transverse to the propagation direction and to each other (transverse electromagnetic or TEM waves), so such exposure chambers are often called "TEM cells." (They are also sometimes referred to as "Crawford cells" even though the design and use of the Mitchell system preceded the Crawford system.) The rate of energy absorption by the

subject is the difference between the net power flow to the subject (the power propagating toward the subject from the source minus the power reflected toward the source by the subject) and the net power flow to the load, from which the whole body SAR can be calculated. Systems large enough to accommodate up to 12 nonhuman primates concurrently have been designed, constructed, and used for bioeffects research in the 10- to 50-MHz range (Bollinger, 1971), and smaller ones for frequencies up to 500 MHz (Crawford, 1974).

A laboratory animal can also be exposed to RFR in an appropriately designed waveguide section that is analogously matched to a suitable source and load. The RFR in such systems is essentially unidirectional but not plane-wave, i.e., the electric and magnetic components are not both transverse to the propagation direction. Whole-body SARs can be determined by techniques similar to those used for the TEM-cell systems. Ho et al. (1973) developed a rectangular-waveguide system for exposing small animals to 2.45-GHz RFR. In this system, the electric component is in a fixed direction transverse to the propagation direction (TE_{01} mode). The system includes provision for varying the temperature and humidity within the waveguide.

One of the considerations in using such unidirectional, fixed-polarization exposure systems is that the whole-body SAR and the internal distribution of SAR vary with the orientation of the subject relative to both the polarization and propagation directions. Therefore, such systems may not be suitable for performing chronic exposures because it is impractical to maintain the animal's orientation constant (by restraint or training) for the requisite time intervals, and not to do so may yield large variations in SAR during such intervals.

To reduce this problem, Guy and Chou (1976) developed a circular-waveguide system operated so that the electric component is transverse to the propagation direction but rotates around the waveguide axis as the wavefront progresses along that axis (circularly polarized TE_{11} mode). The whole-body SARs engendered by this propagation mode are much less sensitive to animal orientation. This type of system was developed for chronically exposing substantial numbers of rodents to 918-MHz RFR (one per waveguide). Guy et al. (1979) also developed a modification of this type of system for use at 2.45 GHz.

Another approach toward diminishing the orientation problem is to use an exposure chamber designed on the principles of the multimode, mode-stirred microwave cavity or oven. Justesen et al. (1971) modified a commercially available microwave oven to render it suitable for chronically exposing small animals, such as rodents, to 2.45-GHz RFR. Heynick et al. (1977) developed a set of chambers for chronically exposing nonhuman primates weighing up to 15 kg to RFR of the same frequency. A subject within a multimode, mode-stirred cavity is exposed to essentially unpolarized RFR, at a given frequency, from all directions simultaneously, thereby largely minimizing the problem of whole-body-SAR variation with body orientation. Measurements of RFR levels

within such a chamber without a subject present have little relevance, because the subject is usually the primary absorptive load and profoundly affects the functioning of the cavity. Rather, it is necessary to determine SARs (by use of phantoms or carcasses). It is sometimes desirable to relate whole-body SARs to some suitably defined "equivalent" plane-wave average power densities. However, because the SAR distribution obtained within a body by omnidirectionally incident RFR markedly differs from that produced by a unidirectional source, definitions of equivalence are rather arbitrary and not unique. When the whole-body SAR of a subject in a cavity has been determined, a useful approach to defining equivalence is to measure the average power density of plane-wave exposure of the subject (in a relevant orientation) needed to obtain the same whole-body SAR (at the same frequency).

It should be noted that the mode stirrers used in microwave cavities introduce some amplitude modulation, so the RFR is not truly CW even if the source (usually a magnetron) is operated in the CW mode. In addition, another form of amplitude modulation is produced if the output power of the magnetron is controlled by phase-angle variation (essentially varying the ratio of on-to-off time intervals). The latter point also applies to other types of exposure systems that use this form of magnetron control.

In the near field of an RFR source, the magnitudes of the electric and magnetic components may not have a constant ratio (as they do in the far field, i.e., 377 ohms), and their relative phases may vary widely with location. To investigate for possible RFR bioeffects in the near field, particularly at relatively low frequencies (10-40 MHz), Greene (1974, 1976) developed a type of exposure system called a "near-field synthesizer," in which a subject can be exposed simultaneously to separately generated electric and magnetic fields, each of which can be varied independently.

Waveguides, TEM cells, and other devices have also been devised for exposing excised neural, muscular, and other tissue preparations immersed in appropriate nutrient or maintenance baths, or for exposing cell cultures or microorganisms (Lords et al., 1973; Wachtel et al., 1975; McArthur et al., 1977; Guy, 1977, Chen and Lin, 1978; Lin et al., 1979b; Galvin et al., 1982). Among the difficulties encountered in developing and using such systems are measuring the incident fields or SARs accurately, measuring and controlling the specimen temperature properly, and avoiding the introduction of artifacts by the devices and techniques used in measuring the desired endpoints. (See Section 6.9.3 for pertinent comments attributed to Guy and to Michaelson.)

5.2.2 RFR Instrumentation

Instrumentation for determining incident fields is considered first. A representative device for measuring average power densities is the broadband isotropic monitor developed by Aslan (1972). Its sensors consist of linear arrays of thermocouple elements, each array

comprising a lossy antenna of relatively small length and capable of adequate response over the frequency range from 300 MHz to 18 GHz, for which a calibration curve is provided by the manufacturer. Isotropic response is obtained by incorporation of three mutually perpendicular sensor arrays. To minimize errors in the direct-current output values of the sensor assembly caused by possible induction of spurious RF currents in the lead wires, the wires used are of very high resistivity (about 200 kilohms/m or 60 kilohms/ft). Also, the sensors are only lightly coupled to the incident field, so that perturbations of the field caused by scattering are minimal. The sensors respond to the mean-square of only the electric component of the field. Nevertheless, use of the instrument to measure average power densities in the far-field region is fully justified because the ratio of the amplitudes of the electric and magnetic components has essentially the same value (377 ohms, the "impedance" of free space) at all points in that region, and the instrument is calibrated to read total average power density. (In the induction-and near-field regions of an antenna, it may be necessary to measure the intensities of both the electric and magnetic components.) The most sensitive model of this instrument has a full-scale range of 0.2 mW/cm^2.

Another type of instrument for measuring incident fields is the National Bureau of Standards (NBS) Model EDM-2 Electric Energy Density Meter, designed for the 10- to 500-MHz range (Bowman, 1974, 1976; Belsher, 1975). Its sensor consists of three mutually perpendicular integral dipole-diodes ("rectennas") that also respond only to the electric component of the field. An 18-in. handle from the sensor contains high-resistivity lead wires to minimize field perturbation and spurious pickup. The most sensitive range of the instrument is 0.003 microjoules/m^3 full-scale (equivalent to approximately 0.176 mW/cm^2), and its response time (rise time plus fall time) is about 1 ms in this range.

An improved version of this instrument is the NBS Model EFM-5 Isotropic Electric-Field Monitor (Larsen and Ries, 1981), which can be used to measure electric-field strengths from 1 to 1,000 V/m (60-dB dynamic range) over the frequency range from 200 kHz to 1 GHz. The sensitivities of the three mutually perpendicular sensors are virtually the same over the entire dynamic range, so the response of the instrument is isotropic, and the instrument can be used for near-field as well as far-field measurements.

Field survey instruments of this kind have been analyzed for possible sources of error (Wacker and Bowman, 1971). Because of the relatively long response times of such instruments, they cannot be used for measuring the pulse power densities of short pulses. Therefore, in research programs on possible bioeffects of pulsed fields, incident pulse power densities are usually calculated from measurements of average power density and duty cycle (or pulse duration and pulse repetition frequency) made with commonly available and readily calibrated components and instrumentation.

Instruments of this kind that cover various frequency ranges are available from a number of commercial organizations, some of which market meters for checking RFR leakage from microwave ovens.

Magnetic-field probes have been developed for relatively low frequency ranges, as exemplified by the two devices developed at NBS for near-field measurements in the industrial, scientific, and medical (ISM) bands within the range from 10 to 40 MHz (Greene, 1975). The probes consist of single-turn, balanced-loop antennas of 10-cm and 3.16-cm diameter for the amplitude ranges 0.5 to 5 A/m and 5 to 50 A/m, respectively. (The free-space equivalent power density is proportional to the square of the amplitude. For example, the power density equivalents to 0.5 and 5 A/m are approximately 10 and 1,000 mW/cm^2, respectively.)

A probe for simultaneously measuring the electric (E) and magnetic (H) components at the same locale in the near field has been developed for the frequency range from 10 to 100 MHz (Babij and Bassen, 1980). A single-axis probe consisting of an electric dipole suitably mounted within a magnetic loop has been tested. The linear range of the H probe is from 0.016 to 0.37 A/m, and that of the E probe from 10 to 200 V/m. An isotropic probe consisting of three mutually perpendicular single-axis probes has been designed.

For determining whole-body dose rates for biological entities and dose-rate distributions within such entities, calorimetry for the former and scanning infrared thermography for the latter (previously discussed in Section 5.1.2) continue to be important techniques that are applicable primarily to animal carcasses and physical models of various species constructed from synthetic biological materials. It is important to note that because of differences in heat-transfer characteristics and the absence of thermoregulatory mechanisms, temperature distributions measured within a carcass by infrared thermography do not represent the in vivo temperature distributions for that animal; rather, they correspond to the internal-field distributions induced by the incident RFR.

Probes have been implanted or inserted to measure local RFR-induced temperature changes or fields within animals during irradiation in vivo, often with the introduction of artifacts. However, recent developments of probes have largely diminished the problem of perturbation of the temperature or local field caused by the presence of the sensor and its lead wires. Such developments have also reduced the size of readout errors caused by pickup of the incident field in the lead wires and by the presence of spurious potentials at junctions between sensors and lead wires. The miniaturized isotropic dipole-diode probe developed by Bassen and coworkers (Bassen et al., 1975, 1977), the liquid-crystal/fiberoptic probe developed by Johnson and coworkers (Johnson et al., 1975), the fluoroptic thermometer discussed by Wickersheim et al. (1981a, 1981b), and the nonmetallic thermocouple developed by Olsen and Molina (1979) are representative examples of such progress.

Efforts are also being made to reduce errors and artifacts in measurements of biologically generated fields and potentials--such as the electroencephalogram (EEG) and the electrocardiogram (EKG)--in the presence of the incident RFR. Chou and Guy (1979a) have developed electrodes that can be implanted in the cortex or subcortex for measuring the EEG during chronic exposure to RFR. These electrodes are made of carbon-loaded Teflon that has an electrical conductivity close to that of tissue. They have been shown to be nonpolar, thereby minimizing field perturbations and spurious local potentials, and to have good tissue compatibility by histological examination after 4 to 6 months of implantation. Several high-resistivity electrodes have also been developed by Tyazhelov et al. (1977).

The use of RFR for imaging internal organs is being developed. For example, Larsen and Jacobi (1979) used a pair of waveguide antennas (one for transmitting and the other for receiving) submerged in water to obtain images of the interior of an excised canine kidney, with a resolution of about 5 mm. The kidney was suspended between the antennas, and the antennas were slowly moved as a unit perpendicular to the propagation direction in a successive line pattern (raster) relative to the kidney by a stable electromechanical scanning system. The frequency used was 3.9 GHz, which corresponds to a wavelength of about 8.5 mm in water. The use of submerged phased-array antennas to decrease the scanning time is currently under development.

6 PRESENT STATE OF KNOWLEDGE REGARDING BIOLOGICAL EFFECTS

6.1 Epidemiology

Epidemiology, as used in the context of this document, refers to studies of whether one or more health-related conditions can be associated statistically with purported or actual exposure of humans to RFR (in contrast with assessments based on extrapolation from data on animals to humans). Epidemiologic results tend to be based on imprecise estimates of exposure characteristics (frequency, power density, and duration). The extent to which the control group matches the exposed group is sometimes open to question. Because matching of all relevant factors except exposure is the basis for concluding that any observed differences between groups are related to the RFR exposure, selection of an appropriate control group is critical. Despite these limitations, such studies do provide almost the only information available on possible effects of actual RFR exposure in humans.

A group of reports was selected for review from the literature in the United States, Poland, Czechoslovakia, and the USSR. These reports are representative of the kinds of information currently available.

The U.S. Embassy in Moscow was subjected to RFR from 1953, the year after the United States moved its chancery to Chekovsky Street, until February 1977 (Pollack, 1979). Before 1962, the presence of RFR was detected intermittently during routine surveillance of the building, and continuous monitoring of the signals was instituted in that year. Details regarding signal frequencies (which were in the range from about 0.6 to 10 GHz), modulation characteristics, irradiation durations, and average power densities (or equivalent field intensities) at various locations within and on the roof of the chancery are given in a report (NTIA, 1981) recently issued by the National Telecommunications and Information Administration. Within rooms having the highest RFR levels (rooms with windows or doors in outside walls toward the irradiation sources), the average power densities were typically about 0.004 mW/cm^2 within 2 ft of a door or window, and 0.0025 mW/cm^2 elsewhere in the room. The highest power density cited was 0.024 mW/cm^2, which occurred in one room during a 2-hr period of unusual signal strength on 24 January 1976.

A study of the health of U.S. personnel assigned to the Moscow embassy during the period from 1953 to 1976, compared with the health of those assigned to other U.S. Eastern European embassies, was conducted by Lilienfeld et al. (1978). After considerable effort spent in tracing employees and dependents, 1,827 employees and 1,228 dependents were identified as having been at the Moscow embassy during the 1953-1976 period. The control population consisted of 2,561 employees and 2,072 dependents assigned to embassies and consulates in Budapest, Leningrad, Prague, Warsaw, Belgrade, Bucharest, Sofia, and Zagreb during the same time period. Periodic tests for RFR at the control sites showed only background levels.

Medical records were reviewed for 1,209 Moscow employees and 834 dependents. The corresponding numbers for the control group were 1,882 and 1,507. Health questionnaires were returned by 969 Moscow employees and 1,129 control employees. The number of completed dependent questionnaires is not clearly specified in the report.

The authors of this study recognized and commented on the limitations due to their inability to acquire complete sets of medical records, death certificates, and returned health questionnaires, and to the imprecision in classifying individual employees with regard to probable extent of RFR exposure. Furthermore, they noted that the highest exposure levels were recorded late in the study and therefore, for the subgroup with the highest exposure, the period of time during which health effects might become apparent was the shortest. They also noted that the size of the study population was insufficient to detect excess risks that were less than two-fold for many of the medical conditions studied. However, despite these acknowledged limitations, the authors were able to draw the following conclusions.

No discernible differences were found between the Moscow and control groups in total mortality or mortality from specific causes, nor were there differences in mortality between the Moscow and control groups of dependent children or adults. With the exception of cancer-related deaths among female employee groups (both Moscow and control), mortality rates for both Moscow and control groups were less than for the U.S. population at large. Although the study groups were subject to a large variety of health problems, the medical records indicate that these problems were shared nearly equally by both Moscow and control groups with two exceptions: the Moscow male employees had a threefold higher risk of acquiring protozoal infections, and both men and women of the Moscow group were found to have slightly higher frequencies of most of the common kinds of health conditions reported. However, the authors could not relate these two exceptions to RFR exposure. The health questionnaire information indicated higher incidences of some health problems in the Moscow employee groups than in controls: more correctable refractive eye problems; more psoriasis in men and anemia in women; and more frequent cases of depression, irritability, difficulty in concentrating, and memory loss. However, the authors note:

> In view of the possibilities which had been publicized of the increased danger to their health and that of their children, it is not at all surprising that the Moscow group might have had an increase in symptoms such as those reported. However, no relationship was found between the occurrence of these symptoms and exposure to microwaves; in fact, the four symptoms mentioned earlier, which showed the strongest differences between the Moscow and Comparison groups, were all found to have occurred most frequently in the group with the least exposure to microwaves (Lilienfeld et al., 1978).

For dependents, the authors found no differences between the adult Moscow and control groups. The incidence of mumps in the Moscow dependent children was twice as great as that in the control children. The incidence of congenital anomalies in children born after arrival of the parents at the duty station was comparable for the Moscow and control groups.

Finally, the authors summarized as follows:

> With very few exceptions, an exhaustive comparison of the health status of the State and non-State Department employees who had served in Moscow with those who had served in other Eastern European posts during the same period of time revealed no differences in health status as indicated by their mortality experience and a variety of morbidity measures. No convincing evidence was discovered that would directly implicate the exposure to microwave radiation experienced by the employees at the Moscow embassy in the causation of any adverse health effects as of the time of this analysis (Lilienfeld et al., 1978).

Two studies have been made of the possible relationship between the occurrence of Down's syndrome (Mongolism) in Baltimore and presumed exposure of the fathers to RFR from radars during military service (Sigler et al., 1965; Cohen et al., 1977). The first study involved 216 Down's syndrome children and 216 control children matched for hospital of birth (or home birth), sex, date of birth, and maternal age at birth; the children were all born between January 1946 and October 1962. The data for this study were derived from Baltimore hospital records and interviews with the parents. These data showed that 63.1% of the case fathers and 56.6% of the control fathers had been in the military, but that 8.7% of the case fathers and only 3.3% of the control fathers had reported close association with radars (both within and outside of military service), a statistically significant difference. The authors concluded that "the only truly puzzling association is the suggested relationship between Mongolism and paternal radar exposure," and that "one can only speculate concerning possible mechanisms, but the association between Mongolism and radar exposure deserves further investigation" (Sigler et al., 1965).

In the second study (Cohen et al., 1977), the data from the first study, denoted as the "Original Series," were examined together with data regarding 128 additional matched pairs, denoted as the "Current Series." More detailed questions about RFR exposure and military service were incorporated in the current series questionnaires, and service-record information on the fathers was acquired. An attempt was made to acquire similarly detailed data on the fathers of the original series. In addition, a chromosome study of the fathers was undertaken to determine whether there was any detectable residual damage in the chromosomes of the peripheral blood. After considering the more detailed exposure information, the following findings were reported for the current series: 15.7% of case fathers and 21.3% of control fathers had received radar exposure; combining the probably

exposed with the definitely exposed groups, the corresponding values were 16.0% and 28.3%. The reevaluated original series values for definitely exposed fathers were 18.6% for case fathers and 15.2% for controls, and when probably exposed fathers were added, the values were 20.6% and 15.7%.

When the data from the original and current series were combined, the values for case and control fathers were 17.4% and 17.5%, respectively, for definitely exposed, and 22.7% and 20.6% when "some" exposure was included. None of the foregoing comparisons showed statistically significant differences. The results of the chromosome studies have not been reported yet.

The authors concluded that the current series did not confirm the suggestions of the original series that the fathers of the Down's syndrome children had either an excess of radar exposure or a larger proportion of military experience. The authors note:

> In view of the suggestive findings of the original series with regard to a possible radar association, it was certainly necessary to investigate this question further. The initial steps were taken. A replication study was the simplest and least expensive immediate approach. Supplementing it with the independent search of service records added an objective approach eliminating any possible differential in parental responses. These methods have been attempted with inconclusive findings; it is now necessary to look to the prospective, longitudinal, surveillance studies to resolve the issue (Cohen et al., 1977).

In a study of personnel who had served in the Navy during the Korean War (Robinette and Silverman, 1977; Silverman, 1979), a group of approximately 20,000 persons was selected and classified as having had occupational exposure to RFR on the basis of their titles of electronics technician, fire control technician, or aircraft electronics technician; another group of about 21,000 persons was classified as not having had occupational exposure because of their titles of radioman, radarman, or aircraft technicians mate. For brevity, the latter group was referred to as the control group, even though these personnel may have had some RFR exposure--presumably much less than the first group. Although comparison with an unexposed group would have strengthened the study, the two groups selected were presumably similar in terms of non-RFR factors. The study utilized only extant records, covering 1955 to 1976, of mortality and morbidity (both in service and later in Veterans Administration hospitals), and of both granted and disallowed requests for disability compensation.

The report by Robinette and Silverman (1977) provides only mortality results, which show 619 deaths from all causes for the occupationally exposed group versus 579 deaths for the control group; the difference is not statistically significant. The death rates for both groups were lower than those for the comparable age group in the U.S. population at large. Examination of these decedent data in more detail

showed a significantly higher death rate from trauma in the exposed group; however, many of the trauma-associated deaths resulted from military aircraft accidents, and a higher proportion of the exposed group had subsequently become fliers. The incidence of deaths associated with arteriosclerotic heart disease was significantly lower in the exposed group. No significant differences were noted between the two groups in terms of total mortality or in terms of mortality from any of about 20 assigned categories of causes of death.

Although the later report by Silverman (1979) does not furnish details regarding morbidity and other health-related aspects, she did state:

> Differential health risks associated with potential occupational exposure to radar in the Navy more than 20 years ago are not apparent with respect to long-term mortality patterns or hospitalized illness around the period of exposure, two endpoints for which there is virtually complete information for the total study group. Later hospitalization (in Veterans Administration facilities only) and awards for service-connected disability, the two other end-points examined, provide incomplete information. While some significant differences among the occupational groups classified by level of potential exposure have been found with respect to all the endpoints studied, the differences could not be interpreted as a direct result of microwave exposure (Silverman, 1979).

Peacock et al. (1971) reported that an initial examination of birth certificates filed from July 1969 to November 1970 from Dale and Coffee Counties, Alabama, in which Fort Rucker is located, indicated that the number of clubfoot cases among white babies was much larger than the expected statewide incidence. A more detailed study of this and other congenital anomalies in the six counties surrounding Fort Rucker (Calhoun, Henry, Butler, Jefferson, Dale, and Coffee) showed a higher rate of anomalies among babies born to military personnel than for the state as a whole. However, for nonwhite populations, only Calhoun County had a significant departure from the expected incidence. No interpretation in terms of causal factors for the excess incidences was given in the report.

Burdeshaw and Schaffer (1977) reanalyzed the Alabama birth-record anomaly data for 1968-1972, but instead of using statewide averages as control data, they compared the Coffee and Dale County data with those of each of the other 64 Alabama counties on a score and rank basis. In addition, to acquire more detailed information on hospital characteristics and reporting procedures, they sent questionnaires to 46 Alabama hospitals. They used that information to predict expected values for Lyster General Hospital within Fort Rucker. They found that the two highest hospital anomaly rates were from Fort Rucker and Maxwell AFB (both military aviation centers), and that 13 of 17 Alabama counties with anomaly rates in the upper quartile were in a contiguous band from southeast to west-northwest Alabama, which indicated the exis-

tence of a geographically distributed anomaly problem. However, they also found evidence against the conclusion that the anomaly incidence rate in the Fort Rucker area was unusually high: overall rates for Coffee and Dale Counties ranked only sixth and eighth among the 67 Alabama counties; at least five other Alabama hospitals reported anomaly incidences that were not significantly lower than those for Lyster Hospital; Lyster's overall rate was within predicted limits for hospitals with its characteristics; there was no clustering of residences of mothers with anomalous children in the vicinity of radar sites; carefully controlled surveys from other (non-Alabama) hospitals revealed anomaly incidences consistent with Lyster's; and significant time-clustering of anomalies at Lyster indicated a high reporting rate for one or two particular physicians. The authors concluded that the birth record data did not demonstrate that an unusually large number of infants with congenital anomalies were born to military personnel at Fort Rucker or to other residents in the immediate area.

Pazderova (1971) reported on the results of a battery of medical evaluations carried out on 58 employees of Czech television transmitter stations. Exposure frequencies were estimated to range from 48.5 to 230 MHz at field intensities equivalent to 0 to 0.022 mW/cm^2, with a mean exposure duration of 7.2 years (10.6 hr/workday). EKGs, heart and lung X-rays, erythrocyte sedimentation rates, urinalyses, and liver function tests were conducted, as well as hematologic, serologic, ophthalmologic, neurologic, gynecologic, psychiatric, and psychological examinations. The only statistically significant finding was that the mean plasma protein levels were higher than "normal" values taken from the literature, a finding that the author describes as unexplainable. The appropriateness of the use of literature control values is highly questionable.

In a later study by Pazderova et al. (1974), the effects of RFR on blood protein levels were reexamined. In the 60- to 300-MHz range, 51 people were exposed to fields up to about 0.02 mW/cm^2; in the 3- to 30-MHz range, 19 people were exposed to about 1 mW/cm^2; and in the 640- to 1,500-kHz range, 39 people were exposed to about 0.8 mW/cm^2. A group of 59 workers served as controls, but the authors indicate that the only difference between exposed and control groups was that the members of the exposed groups had worked irregular shifts, whereas more than half of the control group had worked only morning shifts. The results showed that the levels of blood proteins and their fractions were within normal physiologic limits, both the mean and individual values, but statistically significant differences were found between mean values for the exposed and control groups. In neither study was there a control group that had received virtually no RFR exposure.

Klimkova-Deutschova (1974) surveyed various industrial worker populations in Czechoslovakia, including metal welders, steel factory workers, plastic welders, technicians operating radio or television transmitters, and people working in research institutes and other industries that involve exposure to RFR. Miscellaneous administrative staff members were studied for comparison. Frequencies varied ac-

cording to the place of exposure, ranging from 0.5 to 150 MHz, 300 to 800 MHz, or 3 to 30 GHz. The power densities, where specified, ranged from 0.1 to 3.3 mW/cm^2. A sample of 352 workers was selected from 530 people considered. The findings included EEG anomalies (consisting of synchronized waves of high amplitude and slow rhythm) and biochemical changes (such as elevation of fasting blood glucose, serum beta-lipoprotein, and cholesterol). Changes in brain-wave patterns and in blood sugar, protein, and cholesterol levels were described as more pronounced in the people exposed in the 3- to 30-GHz range. Although the author states whether differences among groups for specific manifestations were statistically significant (at the 0.05 or 0.01 level), numerical results were not reported and statistical methods were not described.

Siekierzynski (1974) compared the health status and fitness for work of 507 persons in Poland occupationally exposed to pulsed RFR exceeding 0.2 mW/cm^2 average power density (other RFR characteristics not specified) with a group of 334 workers at the same installations exposed to less than 0.2 mW/cm^2. Clinical tests included ophthalmoscopic and neurologic examinations, supplemented by psychological tests and EEG recordings. No statistically significant differences between the two groups were found. In our opinion, the lack of more definitive RFR exposure data vitiates, but does not invalidate, the negative findings of this study; i.e., the results provide no evidence for RFR-induced effects on the health status of either group.

Kalyada et al. (1974) clinically examined a group of specialists in the USSR working with RFR generators in the 40- to 200-MHz range for 1 to 9 years and reported the occurrences of functional changes in the central nervous system described as vegetative dysfunction accompanied by neurasthenic symptoms. No organic lesions were found, but among the many specific changes reported were deviations in the physiochemical and functional properties of erythrocytes and leukocytes. The authors also conducted experiments with human volunteers and reported functional changes in the thermoregulatory and hemodynamic systems and in the thermal, optical, and auditory analyzers. However, no RFR intensity values were given for either the specialists or the volunteers; most of the findings were presented in narrative form, with no actual data; and the nature of the control group studied was not described. Consequently, this paper provides little basis for affirming or denying the occurrence of possible adverse effects of occupational exposure to RFR.

Sadchikova (1974) presented clinical observations on the health status of two groups of USSR RFR workers. Those in the first group (1,000) were exposed to up to a few mW/cm^2, whereas those in the second (180) were exposed to values rarely exceeding several hundredths of a mW/cm^2, both at unspecified "microwave" frequencies. A group of 200 people of comparable backgrounds but presumably not exposed to RFR served as controls. Sixteen kinds of symptoms were reported, including fatigue, irritability, sleepiness, partial loss of memory, bradycardia, hypertension, hypotension, cardiac pain, and

systolic murmur. In the higher power density group, the indices for 5 of the 16 symptoms were higher than those in the lower power density group; they were lower for 9 symptoms and about the same for the remaining 2. Incidences in the control group were lower than those in either exposed group for 15 of the 16 symptoms. A few subjects of the first group who worked under unspecified "unfavorable" conditions developed cataracts. Although bar graphs were included that show percentages of changes in the 16 symptoms among the three groups, statistical treatments of the data were not provided, so whether any of the reported differences were statistically significant cannot be ascertained. The occurrence of cataracts in the few who were working under "unfavorable conditions" must be interpreted as an indication of exposure to power densities in excess of the cataractogenesis threshold (see Section 6.4).

Several epidemiologic studies have been performed, notably by Zaret et al. (1961), Cleary et al. (1965), Cleary and Pasternack (1966), and Appleton (1973), to ascertain whether chronic exposure to RFR could cause cataracts.

Zaret et al. (1961) looked for eye defects in a group of 475 persons who were believed to have been exposed to RFR at 11 military and nonmilitary establishments; a group of 359 persons served as controls. The investigators found a slight but statistically significant difference in defect scores between the two groups, but they expressed some doubt regarding the full validity of the scoring method used.

Cleary et al. (1965) examined Veterans Administration Hospital records of 2,946 Army and Air Force veterans of World War II and the Korean War who had been treated for cataracts. A control sample of 2,164 veterans was selected. On the basis of military occupational specialties, they classified each individual as a radar worker, a nonradar worker, or one whose specialty could not be discerned. In the radar group, they found 19 individuals with cataracts and 2,625 individuals without cataracts; in the nonradar group, 21 individuals had cataracts and 1,935 did not. (The remaining 510 subjects were in the unspecified occupational category.) These differences between the radar and nonradar groups are not statistically significant.

Cleary and Pasternack (1966) statistically analyzed the records of 736 microwave workers and 559 controls for minor lens changes, using a scoring range from 0 to 3. They reported that the defect scores increased with age for persons in both groups, but that the average score for the microwave group was significantly higher than that for the control group. They suggested that this finding is an indication that exposure to RFR may have an aging effect on the lens. However, no cataracts or decreases in visual acuity were found.

In the Appleton (1973) study, which covered 5 years, military personnel identified as having been occupationally exposed to RFR from radar and communications systems were matched as closely as possible in age and sex with other military personnel on the same bases who had

not been occupationally exposed. Several ophthalmologists independently examined exposed and control personnel (without knowledge of the group to which each individual belonged) for opacities, vacuoles, and posterior subcapsular iridescence, taken as diagnostic precursors of cataracts. Because of the complexity of the eye and the unavoidable judgmental aspects in the diagnosis of each examining ophthalmologist, each precursor was scored as either present or absent in each individual, and the binary data thus obtained were used for statistical analyses by age group and numbers of persons per age group. The results indicated that more people in older age groups exhibited these precursors, but the pooled data from several Army installations showed no statistically significant differences between exposed and control groups. The presence or absence of the three diagnostic precursors is only a crude measure of actual or possible incipient eye damage, useful primarily for statistical purposes.

As for the other epidemiologic studies reviewed above, the accuracy and detail of the exposure histories (frequencies, intensities, durations, and so on) taken for either the exposed or the control groups are difficult to determine. However, it is quite likely that the exposed groups did receive more RFR exposure than the control groups.

In summary, none of the U.S., Czechoslovakian, and Polish epidemiologic studies analyzed here offers clear evidence of detrimental effects associated with exposure of the general population to RFR. However, the Soviet findings, which are consistent with the voluminous, early Soviet literature, suggest that occupational exposure to RFR at average power densities less than 1 mW/cm^2 does result in various symptoms, particularly those associated with CNS disorders. Because the USSR symptomatology has not been reported in Western studies and because of the marked differences between Soviet and Western publications in the procedures used for reporting data, any prediction of possible RFR hazards based on the USSR epidemiologic studies would require acceptance of these Soviet findings at face value.

6.2 Mutagenesis and Cancer Induction

Over the past 30 years, several studies have been conducted on possible mutagenic and cytogenetic effects of RFR, and at least one published report has suggested the possibility of cancer induction by chronic exposure to RFR. Because cancer induction is considered to be related to mutagenesis (Ames, 1979), the two subjects are discussed together in this document.

Three studies of mutagenic effects of RFR in bacteria and yeasts gave negative results. The first study (Blackman et al., 1976) involved exposure of *E. coli* WWU to 1.70- or 2.45-GHz RFR at 2 to 50 mW/cm^2 for 3 to 4 hr. The second study (Dutta et al., 1979) involved exposure of *S. cerevisiae* D4 to 2.45-GHz RFR at 40 mW/cm^2 or to 8.5-9.6-GHz RFR at 1-45 mW/cm^2 for 120 min. Another part of the

study involved exposure of S. typhimurium at the same frequencies and power densities for 90 min. The third study (Dardalhon et al., 1981) found no significant effects on survival of repair competent and deficient strains of E. coli and S. cerevisiae when exposed to power densities below 60 mW/cm^2 (SAR 28 W/kg) at 9.4-, 17-, and 70-75-GHz RFR. There was also no effect of 17-GHz RFR on induction of mutations in E. coli above the spontaneous level; at this frequency, no effect was seen in S. cerevisiae on induction of nuclear reversions, cytoplasmic "petite" mutations, mitotic recombination, or the efficiency of sporulation.

Four separate studies of mutagenenic effects of RFR in fruit flies (D. melanogaster, a common mutagenic test animal) also gave negative results. The first study (Pay et al., 1972) involved exposure of 0 to 24-hr-old males to 2.45-GHz RFR at 6,500, 5,900, and 4,600 mW/cm^2 for 45 min. The test consisted of mating the exposed males to females to determine effects of the RFR on fertility, and then remating the offspring to determine the presence of recessive lethal mutations. The results were negative in both cases. The second study (Mickey et al., 1975) involved exposure of the flies to pulsed RFR at 20-35 MHz at an unstated power density level for 4 hr. The test consisted of observing for nondisjunction of X and Y chromosomes at mating, and the results again were negative. The third study (Dardalhon et al., 1977) involved exposure of the flies to 17- and 73-GHz RFR at 60 to 100 mW/cm^2 for 2 hr. No mutations were found. The fourth study (Hamnerius et al., 1979) involved exposure of fly embryos to 2.45-GHz RFR at 100 W/kg (200 mW/cm^2, approximately) for 6 hr. The test system was designed to measure the frequency of somatic mutations for eye pigmentation. A positive control was included in the study (X-rays), and the authors concluded that the test system would have detected the mutagenic effect of 50 rad. No mutations were found in the specimens exposed to RFR.

Varma and coworkers conducted two studies on the induction of dominant lethal mutations in mice by RFR. The first study (Varma and Traboulay, 1976) involved exposure of the testes of Swiss mice to 1.7 GHz at 50 mW/cm^2 for 30 min or at 10 mW/cm^2 for 80 min. The second study (Varma et al., 1976) involved a single exposure of the testes of Swiss mice to 2.45-GHz RFR at 100 mW/cm^2 for 10 min, 50 mW/cm^2 for three 10-min exposures given in 1 day, or 50 mW/cm^2 for four 10-min exposures given over 2 weeks. Because the studies were performed by the same principal investigator in the same laboratory and were reported at the same time, they are reviewed as a single study. The test consisted of breeding the exposed males to separate groups of unexposed females once each week for 7 to 8 weeks after irradiation. Females were killed on the 13th day of gestation and the uteri were scored for number of implants and number of resorption sites (dominant lethals). The authors concluded from the first study that the 1.7-GHz RFR was mutagenic under both conditions of exposure. They concluded from the second study that the 2.45-GHz RFR was mutagenic at the brief 100 mW/cm^2, but not at the 50 mW/cm^2 doses that were distributed over time.

These studies have a number of flaws. In the first study, errors were made in tabulating the data, leading to the question of how reliable the numbers presented may be. In the second study, the fetal late-mortality rates were significantly higher for the exposed animals than for the controls, raising the question of what other factors besides RFR might be causing dominant lethal effects. In both studies, systematic errors were made in the computation of the chi-square statistic used to evaluate the significance of the supposed mutagenic effect. If the chi-square is correctly computed, the first study shows a marginal but significant increase in the number of lethal mutations for the study as a whole, but not for individual weeks of the study, and the second study shows no increase at all. In addition, the incidence of dominant lethal mutations in control animals differed significantly for the two studies (1% in the first, 5% in the second), leading to questions about the quality of the animal source and the reliability of scoring. If the controls from both studies are consolidated, no mutagenic effect can be demonstrated at any frequency, power density, or duration. Finally, the studies involved exposure of anesthetized animals, a condition under which the animals have no temperature control; the temperature increase in the testes may have been much greater than what would be predicted from the exposure parameters.

Another study of dominant lethal mutations in rats (Berman et al., 1980) involved exposure to 2.45-GHz RFR at power densities ranging from 5 to 28 mW/cm^2 for 3 hr daily (5 days/week) for periods of up to 3 months. The study found no evidence of increase in dominant lethal mutations. Temporary sterility, as indexed by fewer pregnancies, was seen at the highest power density, where there was a significant increase in rectal and intratesticular temperatures.

Several studies have been conducted on the induction of cytogenetic effects by exposure to RFR. These studies usually involve two types of observations: (1) abnormalities in chromosomes (fragmentation, fusion, and interchromosomal bridges) at the metaphase stage of mitosis; and (2) sister chromatid exchanges.

In the earliest study (Heller and Teixeira-Pinto, 1959), garlic root tips were exposed to 27 MHz for an unstated period of time. The text is brief and the description of exposure conditions is sketchy; from the description, the power density was somewhere between 2.5 and 600 mW/cm^2. Chromosome aberrations were reportedly found.

In a second study (Chen et al., 1974), Chinese hamster cells and human amnion cells were exposed in vitro to 2.45-GHz RFR at power density levels ranging from 200 to 500 mW/cm^2 for durations ranging from 1.5 to 20 min. A variety of chromosome aberrations was observed, but the incidence of aberrations did not increase with increasing power density level or duration of exposure, and the incidence in irradiated cells was not significantly different from that in control cells; hence one can conclude that RFR did not induce chromosome aberrations.

In a third study (Stodolnik-Baranska, 1974), human lymphocyte cultures were exposed to 2.95-GHz pulsed RFR (pulse characteristics not given) at 20 or 7 mW/cm^2 average power density for periods ranging from 10 min to 4 hr. Exposure to 20 mW/cm^2 for 10 min or longer reportedly produced chromosome aberrations, but no chromosome aberrations were reported from exposure to 7 mW/cm^2 for 4 hr. The author reported a "slight" temperature increase in cultures exposed to 20 mW/cm^2 but none in cultures exposed to 7 mW/cm^2. The results suggest that, if RFR does cause an increase in chromosome abnormalities, the effect may have a power density threshold.

Mickey et al. (1975) exposed Chinese hamsters to pulsed K- and X-band RFR (approximately 18 and 10 GHz, respectively) at power densities of 200 and 500 mW/cm^2 for up to 35 hr. Chromosome aberrations were reported in lung cells, bone marrow cells, and spermatogonia. The report does not describe the experimental protocol clearly, and reporting of control incidence of chromosome abnormalities is inadequate. Finally, the calculated power density levels appear to be incorrect. It is unlikely that a Chinese hamster could survive the reported values for longer than a few minutes.

Two studies report effects of RFR on sister chromatid exchange (Livingston et al., 1977; McRee et al., 1981). In the first study, Chinese hamster ovary cells were exposed in vitro to 2.45-GHz RFR at unstated power density levels and durations. Sister chromatid exchanges were observed in RFR-exposed cells; however, the same level of exchanges was produced in control cells by heating them to the same temperature as that produced by RFR exposure. The authors concluded that the production of sister chromatid exchanges is not related to RFR exposures. In the second study, mice were exposed to 2.45-GHz RFR at 20 mW/cm^2 (SAR 21 W/kg) for 8 hr/day for 28 days. Incidences of sister chromatid exchange in bone marrow cells of irradiated mice, sham-irradiated control mice, and standard control mice were compared. No statistically significant differences were detected.

Two recent papers have looked at the effects of RFR on mechanisms involved in repair of cellular DNA. Meltz and Walker (1981) examined whether there were any RFR-induced alterations (350 MHz and 1.2 GHz) in DNA repair in normal human fibroblasts maintained in vitro after the DNA was damaged by a selected dose of ultraviolet light. Power densities of 1 or 10 mW/cm^2 caused no perturbation of the DNA repair process. Brown et al. (1981) treated mice with streptozocin, a mutagenic/carcinogenic agent known to damage DNA in the rodent liver, and exposed the mice to 400-MHz RFR to determine if excision repair of the DNA would be inhibited. Power densities of 1.6 and 16 mW/cm^2 (SAR 0.29 and 2.9 W/kg) did not alter the level of excision repair.

A study by Prausnitz and Susskind (1962) implied an association between RFR exposure and cancer incidence. They exposed male mice to pulsed 9.27-GHz RFR at 100 mW/cm^2 average power density for 4.5 min/day, 5 days/week, for 59 weeks. Each day's exposure was equal to one-half of the acute LD_{50} of the animals. The study was well-

designed and well-executed, and for its time can be considered an excellent model of a chronic toxicological study. The results were as follows: (1) beginning at about 4 weeks into the study, the mice showed increasing atrophy of the testes; (2) a number of them died during the exposure; (3) the death rate during exposure was greater in control than in irradiated animals--at the end of the exposure series, 50% of the control animals and 65% of the irradiated animals were still alive; (4) liver abcesses were found in some of the animals at necropsy, but because some of the tissues were lost by autolysis, the relative incidence in irradiated and control animals was indeterminate; (5) during irradiation a number of the animals developed leucosis, which was described in the paper as a "cancer of the white blood cells." The incidence of leucosis was greater in the irradiated than in the control animals.

The authors explained the testicular atrophy as resulting from chronic heating of the testes, a highly reasonable explanation. They attributed the deaths during exposure to a pneumonia infection accidentally introduced into the colony during the experiment, and suggested that the better survival of the irradiated animals was due to the protective effect of the daily rise in temperature ("fever") induced by the daily irradiation. The explanation is plausible, but not proven; RFR is known to have effects on the immune system. The greater incidence of leucosis in the animals during irradiation appears real, but the interpretation appears faulty. Leucosis (also spelled "leukosis") is defined in dictionaries of medicine and pathology as an abnormal rise in the number of circulating white blood cells. It is not defined as a form of cancer, though the dictionaries give detailed definitions of various types of leukemia, which <u>are</u> cancers of the circulatory system. Leucosis can arise from a number of causes, including stress, endocrine disturbances, and infection, such as that causing liver abscesses. In addition, two other factors must be considered. First, the incidence of leucosis was greater in the irradiated animals, but their survival was also greater. This would be considered unusual for most forms of mouse leukemia. Second, in the treated animals, the incidence of leucosis was greater during, but not following irradiation. This would imply that a spontaneous remission of the "cancer" occurred after irradiation ceased. For true cancer, this would be considered quite improbable. Overall, the data do not provide any evidence that chronic RFR exposure induces any form of cancer in the exposed animals.

In the first of two other studies of chronic irradiation of animals (Spalding et al., 1971), mice were exposed to 800-MHz RFR at 43 mW/cm^2 for 2 hr/day, 5 days/week, for 35 weeks. Some deaths occurred during the exposure and were attributed to thermal effects caused by faulty positioning of the animal holders. The mean life span of the remaining irradiated mice was not different from that of the controls, general indications of health were the same in the two groups, and the occurrence of cancer was the same in irradiated and control animals.

The second study (Baum et al., 1976) involved exposure of rats to electromagnetic pulses (EMP) at a rate of 5/s continuously for 94 weeks. The spectrum of the EMP corresponded to an RFR center frequency of 450 MHz, and each pulse had an intensity of 447 kV/m. The exposures had no effect on blood chemistry, blood count, bone marrow cellularity, fertility, embryological development, cytology, histology, or occurrence of cancer.

In summary, there is no evidence that exposure to RFR induces mutations in bacteria, yeasts, or fruit flies. The results of two studies indicated that RFR induces mutations in mammals. Critical review has cast doubt on these findings. Other studies have shown no mutagenic effects of RFR on mammals. Evidence for cytogenetic effects of RFR is mixed. The lowest power density at which cytogenetic effects were reported was 20 mW/cm^2 (Stodolnik-Baranska, 1974), but these results are contradicted by Chen et al. (1974), who failed to find cytogenetic effects at 200-500 mW/cm^2. There is no evidence that chronic exposure to RFR causes induction of any form of cancer, even at a power density of 100 mW/cm^2.

6.3 Studies on Teratogenesis and Developmental Abnormalities

In the narrowest sense of the word, teratogenesis refers to the production of anatomical aberrations in a developing fetus, but more generally includes fetal death and/or resorption, and physiological and cellular abnormalities in offspring observed postpartum. The term is most often applied to the development of mammalian fetuses. However, the effects of RFR on the development of eggs of birds and pupae of the darkling beetle, Tenebrio molitor, have also been studied.

Two general remarks are pertinent to the various studies of teratogenesis produced by RFR. First, the mechanism by which terata are usually produced involves alteration (often temporary) in the rate of growth of a particular tissue under development. Development of the entire fetus is a complex process requiring that individual tissues develop within a preset time frame, and interruption of this timing will result in abnormalities because a particular tissue or organ fails to complete development on schedule. Because of this, production of abnormalities is highly dependent on the time in the gestation sequence when the agent is applied and on the species of animal under study.

Second, the experimental circumstances in studying development of birds' eggs or insect pupae differ from those in studying mammalian teratogenesis. In the former instance, the experimental material is exposed to the whole environment without any protection; hence the studies must include rigorous control of all environmental parameters, including temperature. In the latter instance, the developing fetus is isolated from the environment to some extent by the dam; however, influences of the noxious agent on the dam must be considered as a potential indirect source of teratogenic effect.

Several studies have been conducted on RFR induction of teratogenesis in pupae of Tenebrio. Carpenter and Livstone (1971) exposed individual pupae to 10-GHz RFR in a waveguide at the equivalent of about 17 mW/cm^2 (SAR of 40 W/kg) for 2 hr or 68 mW/cm^2 for 20 or 30 min. As representative results, only 24% of the pupae exposed for 20 min developed into normal beetles; 25% died and 51% displayed gross abnormalities. About 90% of the sham-exposed pupae developed normally. Pupae were also radiantly heated to the temperature obtained with RFR, and about 75% emerged as normal beetles. The investigators therefore concluded that the abnormal development of RFR-exposed pupae cannot be explained as a thermal effect.

Lindauer et al. (1974), using pulsed and CW 9-GHz RFR at equivalent average power densities, also obtained statistically significant numbers of anomalies in Tenebrio exposed at 17.1 and 8.6 mW/cm^2. There were no significant differences in results for pulsed and CW RFR, and no clear dependence of the effect on dose rate or total dose was found.

Liu et al. (1975) extended this work at 9 GHz and found significant teratogenesis for 2-hr exposures at a power density as low as about 0.17 mW/cm^2. In addition, exposures at various levels and durations corresponding to a constant dosage of 4 mW-hr yielded evidence of an inverse relationship between power density and duration (reciprocity).

Green et al. (1979) found that pupae cultured and exposed at ambient relative humidities of less than 35% appeared to be more susceptible to RFR teratogenesis than pupae similarly treated at higher humidities. At the lower humidities, they observed a slight rise in the incidence of terata with increasing applied RFR power (2-hr constant exposure) up to 40 mW (34 mW/cm^2). At 320 mW, they observed a further increase in teratogenic frequency, accompanied by an increase in pupa death before completion of development. The investigators attributed the apparent "power window" at 80 mW to an antagonism between nonthermal teratogenic effects and protective effects caused by the rise in temperature.

Pickard and Olsen (1979) used pupae from two sources. "Colony-pupae" were those derived initially as larvae from one supplier and raised on Purina dairy meal; "K-pupae" were purchased as larvae in three batches from another supplier and raised on Kellogg's Special K. Groups of K-pupae from the first batch and colony-pupae were sham-exposed or exposed at 6 GHz for 2 hr to either a standing-wave electric (E) field of 91 V/m (equivalent free-space power density of 2.2 mW/cm^2) or a magnetic (H) field of 1.53 A/m (88.3 mW/cm^2), or for 13 hr to a traveling-wave electromagnetic (far) field of 11 mW/cm^2. There were no significant differences in the frequencies of abnormalities between the groups exposed to the E field and the corresponding control groups of pupae of either type. However, the proportion of nonnormal beetles from the control K-pupae was significantly larger than that from the colony-pupae. In addition, exposure

to the H field (of higher intensity) produced a significant effect on the K-pupae but not on the colony-pupae. The H-field experiment was repeated with K-pupae from the other two batches, yielding RFR effects ranging from "doubtfully deleterious" to "significantly beneficial." Ambiguous results were also obtained from exposures for 13 hr at 6 GHz and 4 hr at 10 GHz. These variations appear to be due to uncontrolled differences in such non-RFR factors as the source of larvae, pupae maintenance regimes and handling protocols, the pupae containers used for pupation, and ambient temperature, an explanation that could account for the variabilities among the results of the other investigators cited.

Pickard and Olsen (1979) nevertheless concluded that their results indicate that RFR can be teratogenic in Tenebrio. However, the hypothesis of Carpenter and Livstone (1971) that the effect is nonthermal remains unproved. Specifically, Olsen and Hammer (1982) measured spatial distributions of absorbed RFR in pupae by thermographic imaging during irradiation at 1.3, 6, and 10 GHz; they found large local variations of SAR, which would not be obtained with the radiant heating used by Carpenter and Livstone.

Fisher et al. (1979) studied the development of chicken embryos in eggs exposed to 2.45-GHz RFR continuously for 4 or 5 days. The eggs were irradiated in 6 x 6 arrays. The power density ranged over the array from 1.4 to 6.2 mW/cm^2, with a mean of 3.46 mW/cm^2; the exposures were done for incubator temperatures of 32 to 36 deg C. Control eggs were sham-exposed under similar conditions. Cranial lengths and wet masses of embryos were measured after exposure. At 36 deg C incubator temperature, cranial lengths and wet masses of RFR-exposed embryos were lower than those of the controls, but the rate of growth was higher for the RFR-exposed embryos than for the controls. By contrast, at 32 deg C the cranial lengths and wet masses were higher, and the rate of growth was lower, for the RFR-exposed embryos. The investigators observed no difference in incidences of sterility or premature death between the RFR and control groups. From the description of the method it is difficult to determine whether the temperatures of the RFR-exposed eggs were actually measured or whether possible differences in their temperatures might have occurred because of the spatial variation of power density. Finally, the significance of the findings in relation to possible human hazard is unclear, especially since the embryos were not carried to hatching.

McRee and Hamrick (1977) exposed Japanese-quail eggs in 6 x 5 arrays to 2.45-GHz CW RFR at 5 mW/cm^2 (SAR about 4 W/kg) for 24 hr/day during the first 12 days of development. They found no gross deformities in the quail when euthanized and examined at 24-36 hr after hatching, and no significant differences in total body weight or the weights of the heart, liver, gizzard, adrenals, and pancreas between RFR- and sham-exposed groups. Hematological assays showed statistically significant higher hemoglobin and lower monocyte counts in the RFR-exposed birds, but no differences in the other blood parameters. The differences in mean temperature from egg to egg in

the RFR-exposed arrays were as much as 0.5 deg C, rendering it difficult to associate these positive findings with RFR per se.

In another study (Hamrick et al., 1977), groups of eggs were similarly exposed and the birds were reared for 5 weeks after hatching. No significant differences in mortality or mean body weights at 4 and 5 weeks were found between RFR- and sham-exposed groups.

Teratogenic effects of RFR have been reported in a number of studies in mice and rats. The subject was reviewed recently by O'Connor (1980), who observed that, because of the high power density levels employed, the probability of killing the mother rat was somewhat larger than the probability of producing a teratogenic effect.

A major study in which a significant number of mouse terata were produced without significant mortality of the dams was that of Rugh et al. (1974, 1975). These researchers determined the average dose per unit mass (D/M) for lethality in female mice by exposing groups of CF-1 mice to 2.45-GHz RFR at 138 mW/cm^2 for various durations (at 23.5 deg C and 50% relative humidity). The mean D/M value was approximately 11 cal/g (10.65 for mice in estrus and 11.50 for mice in diestrus). They then exposed pregnant mice on day 8 of gestation at 123 mW/cm^2 for 2 to 5 min, corresponding to sublethal values of D/M ranging from 3 to 8 cal/g. On gestational day 18, the litters were examined for resorptions, and for dead, stunted, malformed, and apparently normal fetuses. A plot of the percentage of normal fetuses in each litter versus the value of D/M showed a considerable number of litters (too dense to count) with 100% normal fetuses (over the exposure range from 3.4 to 7.8 cal/g), six litters with no normal fetuses (over the range from 5.8 to 7.7 cal/g), and the remainder with various intermediate percentages. A similar plot of the percentage of resorptions per litter showed many with none (up to 7.7 cal/g), three with 100% (all above 6 cal/g), and the remainder with intermediate values. The incidence of exencephaly (brain hernia) was also similarly plotted. Many litters showed none (spanning the entire dose range). The maximum was 60% (two litters at about 7 cal/g), and the average expectancy at 8 cal/g was only 12%. Apparently no control mice were used, presumably under the assumption that the natural incidence of exencephaly is relatively rare.

Despite a statement by Rugh et al. to the contrary, reanalysis of their data indicates the existence of a threshold of about 3.6 cal/g for exencephaly.

Berman et al. (1978) exposed pregnant CD-1 mice in 5 x 5, 7 x 4, or 3 x 5 arrays to far-field 2.45-GHz RFR for 100 min daily on gestational days 1 through 17 at 3.4, 13.6, or 14.0 mW/cm^2, or on gestational days 6 through 15 at 28 mW/cm^2 (at 20.2 deg C and 50% relative humidity). Control mice were sham-exposed similarly. All mice were euthanized on day 18 and their uteri were examined for the number of resorbed and dead conceptuses and live fetuses. The live fetuses were examined for gross morphological alterations and weighed. Ten

types of anomalies were tabulated by the numbers of litters affected. (The numbers of fetuses affected in each litter were not presented.) A total of 27 of the 318 RFR-exposed litters, irrespective of power density, had one or more live abnormal fetuses, versus 12 of the 336 sham-exposed litters. For most of the individual anomalies, the numbers of litters affected were either too small for statistical treatment or no RFR-related pattern was apparent. As an example of the latter, four litters exposed at 3.4 mW/cm^2 exhibited hematoma, with none in the corresponding sham-exposed group; however, two litters exposed at 13.6 mW/cm^2 and three sham-exposed litters were affected, and no litters were affected at 14.0 or 28.0 mW/cm^2, compared with one litter in each of their corresponding controls. By contrast, cranioschisis (akin to exencephaly or brain hernia) was exhibited by seven litters exposed to RFR (one litter each at 3.4 and 13.6 mW/cm^2, three at 14.0 mW/cm^2, and two at 28.0 mW/cm^2), but by none of the control groups. However, there is no apparent pattern relating these numbers to power density. The investigators indicate that the number at each power density was not significantly different from zero, but that their sum over all power densities (7 of 318 RFR-exposed litters versus none of 336 sham-exposed litters) was significant. The mean live fetal weights of the litters exposed at the three lower power densities were not significantly different from those of the corresponding sham-exposed litters; however, the mean weight of the litters treated at 28.0 mW/cm^2 was significantly lower than that of the sham-exposed litters.

These investigators used twin-well calorimetry to measure positional values of SAR in their arrays. For 5 x 5 arrays exposed at 10 mW/cm^2, the values of SAR ranged from 4.05 to 7.37 W/kg, possibly an indication of mutual RFR interactions among the mice. The authors correctly state that despite such variations, there was no overlap of SAR between arrays exposed at 13.6 and 3.4 mW/cm^2, corresponding to a power density ratio of 4:1. However, no SAR distribution data were given for the 3 x 5 arrays exposed at 28.0 mW/cm^2, or the 7 x 4 arrays exposed at 14.0 mW/cm^2, for which the power density ratio was only 2:1, thereby raising the question of possible SAR overlap in these experiments. Regarding abnormal fetuses, statistical treatment of the number of litters rather than the numbers of fetuses affected is of questionable validity. Also questionable is the summation of all litters exhibiting cranioschisis (irrespective of power density) and ascribing the statistically significant result to RFR exposure. Nevertheless, taken together, the results indicate that the levels of RFR used (which were not lethal to the dams) were marginally teratogenic to mice, a conclusion that is consistent with the findings of Rugh et al. (1974, 1975).

In a subsequent investigation, Berman et al. (1982) exposed a group of time-bred CD-1 mice to 2.45-GHz RFR at 28 mW/cm^2 for 100 min daily on gestational days 6 through 17. Another group was similarly sham-exposed. The mice in half of each group were examined on day 18. The incidence of pregnancy; the number of live, dead, and resorbed fetuses; and the total number of fetuses were found to be

similar for the exposed and sham-exposed mice. However, the mean body weight of the live fetuses in the RFR-exposed group was significantly smaller (by 10%) than those in the sham-exposed group, a finding consonant with their previous results. In addition, ossification of sternal centers was significantly delayed in the RFR-exposed mice. The mice in the other half of each group were permitted to come to term. At 7 days of age, the mean body weight of the suckling mice of the RFR-exposed group was also significantly smaller (by 10%) than that for the sham-exposed group. The survival rate was not affected, but the investigators indicate that the growth retardation is permanent.

Chernovetz (now O'Connor) et al. (1975), in the first of two regimens, exposed one group of five pregnant C3H-HeJ mice to 2.45-GHz RFR for 10 min on day 11 of gestation, and one each of three other groups on days 12, 13, and 14 (totaling 20 dams). Each group was exposed concurrently in a multimode, mode-stirred microwave cavity (at about 22 deg C and 50% relative humidity) with the mice free to move about. At an estimated mean SAR of 38 W/kg, the energy absorbed was 22.8 J/g or 5.44 cal/g. The investigators stated that in a pilot study, 10-min exposures at 40 mW/g (24 J/g or about 5.7 cal/g) were fatal to about 10% of a large number of pregnant mice, so 38 W/kg was just sublethal. Four other groups were similarly sham-exposed. In addition, eight groups were injected with cortisone (a teratogen); four of these were similarly exposed to RFR and the other four were sham-exposed. All mice were euthanized on day 19, the numbers of implantations and resorptions were counted, and the fetuses were examined for structural abnormalities. There were no statistically significant differences in the percentage of fetal mortality or structural abnormalities between RFR and sham-exposed groups not administered cortisone, and no dependence on gestational day of treatment; however, the percentage of normal fetuses was 61% for those injected with cortisone and sham-exposed, and 50% for the cortisone-with-RFR groups. These percentages were significantly lower than those for the noncortisone group (both 81%), but they did not differ significantly from each other.

In the second regimen used by Chernovetz et al. (1975), which was designed primarily as a behavioral study, similar treatments were administered, but the exposures were done only on gestational day 14 and involved a total of 60 dams equally divided among the four treatments (RFR, sham-RFR, cortisone-with-RFR, cortisone-with-sham-RFR). All dams carried to term, and the numbers of pups that survived to weaning at postpartum age 21 days were noted. The results for the noninjected groups were 81 pups from those sham-exposed and 93 from those RFR-exposed, not a significant difference. From the cortisone-injected groups, the results were 25 pups from those RFR-exposed and only 2 from those sham-exposed. These values were significantly lower than those for the noninjected groups, and the difference between them was also significant. (The surviving pups were used in a behavioral study.)

These results indicate that absorption of about 5 cal/g of 2.45-GHz RFR is not teratogenic to mice, a finding that is at variance with those of Rugh et al. (1974, 1975) and Berman et al. (1978). Note also that the dosage for lethality reported by Chernovetz et al. was about 5.7 cal/g, or about half the mean value found by Rugh et al., hence their conflicting characterizations of doses with respect to lethality. Among the possible reasons for these apparently contradictory findings are the respective differences in exposure systems (cavity versus waveguide), the use of multiple versus individual animal exposures, gross uncertainties in actual doses, the mouse-strain difference (C3H/HeJ versus CF-1), variations in dam handling, and differences in gestational day of treatment (day 11 through 14 versus day 8). Also, Chernovetz et al. found fetal anomalies in about 20% of their control mice, whereas Rugh et al. apparently used no controls. Both groups of investigators indicate that extrapolation of their findings to higher mammalian species is an open question subject to experimental validation, a statement with which we concur.

In an abstract describing a recent study, O'Connor and Monahan (1981) exposed time-bred ICR mice to 2.45-GHz RFR at 1 mW/cm^2 during one of three stages of gestational development. One group was exposed for 3 hr each day during gestational days 1 through 6, another group during days 7 through 12, and a third group during days 13 through 18. For each exposure session, a group of 24 mice, housed individually in Plexiglas cages, was simultaneously exposed in an anechoic chamber. Another group of 24 was concurrently sham-exposed in an adjacent chamber, with an air supply common to both chambers maintained at 24 deg C. Caesarian sections performed on day 19 indicated that 31 RFR-exposed, 30 sham-exposed, and 10 passive control mice were gravid. For these mice, no significant differences were found in total incidence of resorption or abnormality between the RFR- and sham-exposed mice or among the mice exposed to RFR during the three stages of gestational development. However, the investigators found, by chi square analysis, that the number of litters having an abnormality was larger for the RFR-exposed mice than for the other gravid mice (cf. Berman et al., 1978). The other results reported were significant differences in fetal body mass and brain mass associated with the gestational stage, but not with RFR-versus-sham exposure.

Nawrot et al. (1981) exposed groups of CD-1 mice to 2.45-GHz CW RFR for 8 hr each day during gestational days 1-6 or 6-15 at power densities of 5 mW/cm^2 (SAR of 6.7 W/kg), 21 mW/cm^2 (SAR of 28.1 W/kg), or 30 mW/cm^2 (SAR of 40.2 W/kg). Colonic temperature increases for the latter two power densities were 1 and 2.3 deg C, respectively. Other groups were sham-exposed at elevated ambient temperatures of 30 and 31 deg C to obtain the same colonic temperature increases, but were otherwise handled similarly. Some control groups were handled similarly but sham-exposed at normal ambient temperature, and other groups were neither handled nor sham-exposed. Body weights of all mice were recorded on days 1, 6, 15, and 18. Significant reductions in maternal weight gain were noted for all handled groups exposed or sham-exposed during either gestational period. This effect

was greatest for the groups handled and sham-exposed at elevated temperatures during gestational days 6-15. On day 18, the uteri of all mice were examined. For the group exposed at 30 mW/cm^2 during gestational days 1-6, there was a significant decrease in implantation sites per litter and a reduction in fetal weight. For the groups exposed at the same power density during gestational days 6-15, there was a significant increase in the percentage of fetal malformations, predominantly cleft palate.

In the first of two studies, Stavinoha et al. (1975, 1976) exposed 4-day-old mice in plastic containers for 20 min at 10.5, 19.27, or 26.6 MHz in a coaxial rectangular waveguide system, in which the electric field was 5.8 kV/m. Control groups were kept in similar containers outside the exposure chamber. The mice were weighed daily for the next 21 days. Graphs of weight versus age for the three frequencies showed virtually no differences between exposed and control animals. In the second study, litters of 4-day-old pups from 20 female mice were divided into three groups: (1) control pups; (2) thermal-control pups, held at 37 deg C for 40 min/day on 5 consecutive days; and (3) irradiated pups, exposed at 19 MHz for 40 min/day on 5 consecutive days in a near field synthesizer, in which the electric field was 8 kV/m, the magnetic field was 55 A/m, and the two fields were in coincident planes. The pups were weighed daily before each treatment and until they were 21 days old, at which time the males and females were separated. The mice were then weighed weekly for 13 additional weeks. Statistical analyses of growth curves showed no significant differences among the three groups either for the males or the females. As the investigators pointed out, although the fields used were very intense, relatively little RFR energy was absorbed by the mice because their sizes were very much smaller than the wavelengths used. Thus, it would be inappropriate to apply these negative findings to humans exposed at frequencies in the same range.

Dietzel (1975) exposed pregnant rats abdominally at 27.12 MHz with a diathermy machine and applicator to 55, 70, or 100 W for up to 10 min on 1 day between gestational days 1 and 15. The rectal temperatur of each rat was monitored during exposure, and the rat was removed from the field when its temperature reached 39, 40.5, or 42 deg C (in lieu of any other dosimetry). On day 20, the fetuses were removed, counted, weighed, and examined for malformations. Typical predominant abnormalities included neurocranial malformations from RFR exposure on days 9 and 10, kinked or short tails and "hand" defects for days 13 and 14, and cleft palate for day 15. The maximal numbers of abnormalities occurred for exposure on days 13 and 14 and correlated well with rectal temperature, indicating that the abnormalities resulted from heating by the RFR. The lack of adequate dosimetry renders it difficult to compare these results with those of other investigators.

Larry et al. (1981) (abstract) exposed four groups of 20 pregnant Sprague-Dawley rats to 27.12-MHz RFR (near field) at 55 A/m and 300 V/m on gestational day 9. The SAR was about 13 W/kg. Exposure of the first group of rats was terminated when the colonic temperature

reached 41.0 deg C (about 20 min). In the second group, this colonic temperature was maintained for two additional hours by manually adjusting the field strength. Exposure of the third group was terminated when the colonic temperature reached 42 deg C (about 25 min). This temperature was maintained in the fourth group for an additional 15 min. A fifth group was sham-exposed for 2.5 hr. This group yielded only one malformed fetus (0.3% of the fetuses), whereas about 1% of the fetuses in the first group, 2% in the second group, 4% in the third group, and 53% in the fourth group were malformed. The investigators concluded that developmental processes appear to be relatively stable up to 41.0 deg C but are severely affected at slightly higher temperatures.

Because of the high intensities of RFR used by Dietzel (1975) and Larry et al. (1981), the relevance of their findings to possible teratogenesis in humans exposed to much lower levels of RFR in the HF range is questionable.

Chernovetz et al. (1977) exposed pregnant rats for 20 min on only 1 day during gestational days 10 through 17 to 2.45-GHz RFR in a multimode, mode-stirred microwave cavity at a mean SAR of 31 W/kg in an ambient temperature of 22 deg C and 50% relative humidity. They also exposed rats to infrared radiation (IR) in an incubator at 47 deg C and 10-15% relative humidity. The incubator ambient was selected to produce the same colonic temperature rise of 3.5 deg C as the RFR exposure. Control groups were sham-irradiated in the microwave cavity.

Sixty-four pregnant rats were studied. Three dams died after IR exposure, seven died after RFR exposure, and none died in the control group. On day 19 of gestation, the 54 surviving dams were euthanized and the numbers of implantations and resorptions were counted. In addition, each fetus was examined for morphological abnormalities and its viability and mass were determined. The percentages of living fetuses per dam were about 98% each for the control and IR groups and 87% for the RFR group; this is a statistically significant decrease. The mean fetal mass for the control groups was 1.63 g, and the values for the IR and RFR groups were 1.53 and 1.54 g, respectively, both significantly lower than the mean for the control groups. No structural abnormalities were evident in any of the 468 formed fetuses, all of which were alive when taken, but severe edema and hemorrhagic signs were endemic in the IR and RFR groups. The brains of 60 fetuses were assayed for norepinephrine (NE) and dopamine (DA) in four groups each of five pooled brains from control, IR-exposed, and RFR-exposed animals. The average level of NE for the RFR group was significantly lower than that for the controls, but only marginally lower than that for the IR group. The averaged levels of DA ranked similarly, but the differences were not statistically significant. In their discussion, the authors concluded that "considered in sum, our findings could be taken as evidence that a brief but highly thermalizing application of 2,450-MHz microwaves or of infrared energy have biological effects both comparable and different when averaged colonic temperature changes are equal" (Chernovetz et al., 1977).

One problem with this investigation was the small number of rats involved (a point recognized by the investigators), which necessitated averaging the data in each group over the 10- to 16-day gestational period, a questionable procedure both biologically and statistically. Perhaps a minor point was the use of the sham-RFR rats as controls for the IR group instead of a separate set of sham-IR controls, in view of the relative humidity difference. Because of such problems, the validity of either the positive or negative results of this investigation is difficult to assess.

Berman et al. (1981) exposed 70 time-bred CD rats to 2.45-GHz CW RFR for 100 min daily on gestational days 6 through 15 at 28 mW/cm^2 (estimated SAR of 4.2 W/kg). The mean colonic temperature at the end of each exposure period was 40.3 deg C. A group of 67 rats was similarly sham-exposed. No significant differences between groups were found in pregnancy rates; numbers of live, dead, or total fetuses; incidences of external, visceral, or skeletal anomalies or variations; or body weight of live fetuses. The investigators surmised "that this lack of an effect may hold true at any exposure level less than that which will kill a significant number of the dams by hyperthermia (colonic temperature greater than 40 deg C)," a conclusion similar to that of O'Connor (1980).

In an investigation under way, Hardy (1981) exposed ten time-bred rats essentially continuously for 16 days to 2.45-GHz pulsed RFR in individual circular waveguides (Guy et al., 1979), with a pulse duration of 10 microseconds and 830 pulses per second. The average-power SAR was held constant at 0.4 W/kg. Ten other rats were sham-exposed in similar waveguides. In the two series of exposures performed thus far, none of the rats was allowed to come to term. Instead, their uteri were removed and examined. In a preliminary analysis of the data, no gross visual or histological abnormalities or differences in number of offspring between the RFR- and sham-exposed groups were evident.

In a study designed primarily for seeking possible effects of chronic RFR exposure on mother-offspring behavioral patterns and the EEG, Kaplan et al. (1982) exposed 33 female squirrel monkeys near the beginning of the second trimester of pregnancy to 2.45-GHz RFR in multimode, mode-stirred microwave cavities at whole-body SARs of 0.034, 0.34, or 3.4 W/kg (the last value equivalent to about 10 mW/cm^2 of plane-wave RFR) for 3 hr/day, 5 days/week, until parturition. Eight pregnant monkeys were sham-exposed for the same periods. After parturition, 18 of the RFR-exposed dams and their offspring were exposed to RFR for an additional 6 months; then the offspring were exposed without the dams for another 6 months. No differences were found between RFR- and sham-exposed dams in the numbers of live births or in the growth rates of the offspring. The major difference between RFR- and sham-exposed offspring was that four of the five exposed at 3.4 W/kg both prenatally and after birth unexpectedly died before 6 months of age. Although the numbers of animals used in the behavioral and EEG studies were adequate, the mortality values were too

small to place much confidence in statistical inferences. Moreover, a follow-up study of mortality per se (Kaplan, 1981), which involved sufficient numbers of squirrel monkeys for adequate statistical treatment, did not confirm the RFR-induced offspring mortality results.

In summary, the investigations of RFR-induced teratogenesis and developmental abnormalities support the conclusion that such effects result from the heat produced by the RFR rather than from any special teratogenic properties of RFR.

6.4 Ocular Effects

The fear that RFR can cause cataracts is a recurring theme in newspapers and other popular media. Indeed, based on many investigations with animals by various researchers during the past 30 years, it is undoubtedly true that if a person's eyes were exposed to intensities high enough to elevate the temperature of the lens of the eye by about 5 deg C (9 deg F) or more, the lens would quickly suffer damage. The lens is the region of the eye most vulnerable to RFR because other regions have more effective means of heat removal, such as greater blood circulation, evidenced by much smaller temperature elevations in these regions than in the lens at the same incident power density. Therefore, the basic controversy regarding ocular effects is centered on whether exposure to much lower intensities (i.e., to power-density levels that would produce much smaller lens temperature elevations) for long periods of time, either continuously or intermittently, can cause eye damage. Implicit in this controversy is the issue of whether effects (if any) of long-term, low-level exposure in the eye are cumulative, as are the effects of continual or repeated ingestion of certain toxic substances in individual doses that are well below rapid-toxicity levels.

6.4.1 Humans

Some cases of ocular damage in humans ascribed to occupational exposure to RFR were reported during the 25 years after World War II (Hirsh and Parker, 1952; Shimkovich and Shilyaev, 1959; Zaret, 1969). Although the exposure histories of these individuals could not be ascertained with any degree of certitude, it is likely that their actual or incipient vision impairment resulted from exposure to average power densities substantially greater than the threshold found in animal studies (about 150 mW/cm^2).

More recently, the occurrence of cataracts in two editors with the New York Times was ascribed, in newspaper accounts during 1977 and 1978, to their exposure to supposed RFR from the cathode-ray tubes in video-display terminals used by them (Justesen, 1979). Cases of RFR-induced birth defects and abortions were also linked, in other newspaper stories, to exposure to video terminals. The New York Times arranged for measurement surveys of the terminals in question. These surveys yielded negative results; the only measurable radiations emitted by the terminals were well above the RFR spectrum. Independent

surveys of the same terminals by personnel from NIOSH (1977, cited in Justesen, 1979) confirmed these findings.

Epidemiologic studies have been conducted, notably by Zaret et al. (1961), Cleary et al. (1965), Cleary and Pasternack (1966), and Appleton (1973), to determine whether prolonged exposure to RFR is cataractogenic. These studies are discussed in Section 6.1.

6.4.2 Animals

During the past 30 years, various investigations have been conducted on the effects of RFR exposure on the eyes of live experimental animals. Many of the results indicate that intraocular temperature increases of about 5 deg C or more are necessary for eye damage (Richardson et al., 1948; Daily et al., 1952; Williams et al., 1955; Guy et al., 1974). Also, lens opacifications caused by RFR exposure alone were not produced at the same average power density when the eye was cooled during exposure (Baillie, 1970; Baillie et al., 1970; Kramar et al., 1975).

Many results of RFR exposure indicate the reciprocity (inverse relationship) between average power density and exposure duration for cataract formation and the existence of a threshold average power density of about 150 mW/cm^2 for single or multiple exposures for tens of minutes or more (Williams et al., 1955; Guy et al., 1974; Carpenter, 1977; Ferri and Foti, 1977). As a representative example (Guy et al., 1974), for average power densities decreasing from about 500 to 200 mW/cm^2, the exposure duration needed to cause eye damage in the rabbit increased from 1-2 min to about 20 min. Also, cataracts were not produced at 100 mW/cm^2 for exposure durations of up to at least 100 min (exposures for longer periods were not done in this investigation). Thus, curves of average power density versus exposure duration show that the average power density for cataractogenesis asymptotically approaches a value of about 150 mW/cm^2. Cataractogenesis thresholds of comparable magnitude are evident from the experimental results of others (Williams et al., 1955; Birenbaum et al., 1969; Carpenter, 1977). In reviewing RFR cataractogenesis from a clinical viewpoint, Carpenter (1979) presents a detailed description of the postexposure progression of eye changes, based on experimental results with animals.

Kramar et al. (1975) measured intraocular temperatures in vivo at 200 mW/cm^2 over a 40-min period by quickly inserting a thermocouple probe during brief shut-off of the RFR at the end of successive 5-min exposure periods. They found that the temperature of the vitreous humor rose from about 37 deg C to about 42 deg C during the first 10 min of exposure and remained there for the rest of the exposure period. Equilibrium between the rates of energy absorption and heat removal in that region of the eye is believed to be the determining factor in attaining the 42 deg C plateau temperature. In the orbit, which is cooled by blood flow to a greater extent than the vitreous humor, the corresponding plateau temperature was less than 40 deg C.

The effects of temperature increases produced by non-RFR means on isolated (in vitro) rat lenses were studied by Stewart-DeHaan et al. (1981). Lenses incubated in tissue culture medium M 199 (containing 10% fetal calf serum) at the normal physiological temperature of 37 deg C maintained their clarity for up to 2 weeks. When ten times the normal concentration of serum glucose was included in the medium, opacities and associated globular degeneration of the lens cells developed in 1 day. Similar effects were observed when lenses were warmed to 39 or 41 deg C for 1 hr and then incubated at 37 deg C for 24 hr. Lenses heated to 60 or 75 deg C for 1 hr did not become opaque. The authors surmise that the lenses became histologically "fixed." Radioactive tracer studies by these investigators suggest that membrane changes may be involved in temperature-induced cataract formation.

A number of investigators (Richardson et al., 1951; Reider et al., 1971; Ferri and Foti, 1977) compared the ocular effects of pulsed and CW RFR at equivalent average power densities. In representative investigations, the average power densities were greater than 100 mW/cm^2 and the exposures were for about 1 hr/day for several weeks. No significant differences were found between the effects of pulsed and CW RFR.

McAfee et al. (1979b) trained monkeys to face an RFR source and then exposed them to 9.3-GHz pulsed RFR at average and peak power densities of 150 mW/cm^2 and 286 W/cm^2, respectively. Each of 12 monkeys was exposed for up to 20 min/day for 30 to 40 sessions over several months. Seventy-five monkeys neither exposed nor sham-exposed served as controls. No cataracts or corneal lesions were seen in any of the 12 exposed animals up to 12 months after exposure.

The existence of a cataractogenesis threshold of about 150 mW/cm^2 is regarded as evidence that single or multiple exposure for indefinitely long durations at average power densities well below the threshold would not cause eye damage to humans or any other species. This conclusion is supported by preliminary results of an investigation by Chou et al. (1982). They exposed one group of six rabbits to 2.45-GHz CW at 1.5 mW/cm^2 for 2 hr/day over several months, and another group to pulsed RFR at the same frequency and average power density (10-microsecond pulses at a repetition rate of 100 pulses/second, comprising a duty cycle of 0.001 and a pulse power density of 1.5 W/cm^2); a third group was sham-irradiated. Periodic eye examinations for cataract formation yielded no statistically significant differences among the three groups.

Guy et al. (1980b) exposed four rabbits to 2.45-GHz CW RFR at 10 mW/cm^2 (maximum whole-body SAR of 17 W/kg) 7 days/week, 23 hr/day, for 6 months. For controls, four other rabbits were sham-exposed for the same durations. Periodic eye examinations with a slit-lamp microscope showed normal aging changes in the lenses but no significant differences between the exposed and control groups. (Other physiological parameters studied in this investigation are discussed in Section 6.8.1.)

In an abstract, Kues et al. (1981) reported exposing one eye each of several anesthetized rabbits to 2.45-, 9.0-, or 26.0-GHz CW RFR at 10 to 40 mW/cm^2 for 1 to 4 hr, with the other eye of each animal as control. Corneal endothelial specular microscopy was used to examine and photograph endothelial cells. Some changes in such cells were reported at 12 to 16 hr after exposure, but no information was included regarding specific frequencies, power densities, and exposure durations for which these changes were seen. The number of rabbits used for each regimen was not stated and no details were given about how the control eye in each animal was shielded from the RFR or what the SARs were in each eye. Thus, these results are open to question.

In general, the results from animal studies indicate that RFR cataractogenesis is essentially a gross thermal effect that has a threshold power density at which the difference between the rates of heat generation by RFR and heat removal is large enough to result in damage to the lens of the eye. The mean threshold values probably vary to some extent from species to species, but are of the order of 100 mW/cm^2.

6.5 Studies of the Nervous System

Several types of studies have been conducted on effects of RFR on the nervous system of animals. These studies are considered particularly important in the USSR, where RFR is believed to stimulate the nervous system directly and thereby cause a variety of physiological effects. Scientists in the United States tend to doubt that RFR interacts directly with the nervous system except, possibly, under special circumstances (to be discussed later in this section), and they consider most effects of RFR on the nervous system to be indirect results of other physiological interactions.

6.5.1 RFR Hearing Effect

Humans in the vicinity of some types of pulsed radar systems have perceived individual pulses of RFR as audible clicks (without the use of any electronic receptors). This phenomenon, first investigated by Frey (1961), has attracted much interest--especially in the United States--because it has often been cited as evidence that nonthermal effects can occur and because an initial hypothesis was that one of the possible mechanisms for perception is direct stimulation of the central nervous system by RFR. Various theoretical and experimental studies, the latter with both human volunteers and laboratory animals, have been conducted to determine the conditions under which pulsed RFR is audible and to investigate the interaction mechanisms involved. Many of the results support the hypothesis that a pulse of RFR having the requisite pulse power density and duration can produce a transient thermal gradient large enough to generate an elastic shock wave at some boundary between regions of dissimilar dielectric properties in the head, and that this shock wave is transmitted to the middle ear, where it is perceived as a click. Persons with impaired hearing are unable to hear such clicks, and experimental animals in which the

cochlea (the inner ear) has been destroyed do not exhibit brainstem-evoked responses. Representative investigations of this phenomenon are summarized below.

White (1963) reported that acoustic transients can be generated in various metals and plastics, in a piezoelectric crystal, and in liquids such as water by transient surface-heating with pulses of RFR (or from an electron beam). Such transients were detectable in a barium titanate crystal at calculated surface temperature rises of the order of only 0.001 deg C.

Foster and Finch (1974), using 2.45-GHz RFR, confirmed White's findings that such transients can be produced in water, and they measured the audiofrequency pressures generated by several combinations of pulse power density and pulse duration. The results indicated that the peak pressures would be sufficient to induce human perception of such RF pulses as auditory clicks. They also showed that the effect vanished when the water was cooled to 4 deg C, at which its thermal expansion coefficient is very small. These results support the thermoelastic hypothesis.

Cain and Rissman (1976, 1978) used 3.0-GHz RFR to study the auditory effect in two cats, two chinchillas, one beagle, and eight human volunteers. For the animals, surface or brainstem-implanted electrodes were used to measure the responses to RFR pulses and the responses evoked by audio clicks from a speaker. They found that, depending on the pulse width, the threshold energy density for RFR responses ranged from 8.7 to 14 microjoules/cm^2 per pulse for the cats, from 7.5 to 20 microjoules/cm^2 for the chinchillas, and that it averaged 5.0 microjoules/cm^2 for the beagle. For a pulse width of 10 microseconds, the pulse power densities were 1.3 W/cm^2 for both cats, 1 and 2 W/cm^2 for the two chinchillas, and 300 mW/cm^2 for the beagle. The eight humans were given standard audiograms. Because such audiograms do not test hearing above 8 kHz, binaural hearing thresholds were also determined for seven of the subjects for frequencies in the range from 1 to 20 kHz. Five of the subjects could detect 15-microsecond pulses as clicks; the other three required a pulse duration of 200 microseconds for perception. No correlation between the results and the audiograms was apparent; however, there was a strong correlation between RFR perception and hearing ability above 8 kHz as determined from the binaural thresholds. The average threshold energy density for the humans was 10.6 microjoules/cm^2 per pulse. For 15-microsecond pulses, this value corresponds to a pulse power density of about 700 mW/cm^2; however, three of the subjects were able to perceive 15-microsecond pulses at a pulse power density of 300 mW/cm^2. This value of pulse power density can be regarded as the nominal threshold for the RFR hearing effect. Note that these investigators exposed the human volunteers to pulse power densities as high as 2,000 mW/cm^2 without apparent ill effects.

Lebovitz and Seaman (1977) reported on single auditory unit responses to pulsed 915-MHz RFR and acoustic clicks. They found that the response of a typical single auditory unit was very similar to the response of the unit to acoustic click stimuli, differing primarily only in amplitude.

Lin (1977a, 1977b) reported on detailed theoretical studies of the RFR auditory effect. He assumed that the auditory sensation from individual pulses results from acoustic waves generated in the tissues of the head by rapid thermal expansion of the tissues upon microwave absorption, in consonance with the investigations cited above. His results indicate that the audiofrequencies produced are independent of the frequency of the RFR, but are dependent on head size. The predicted fundamental frequency is 13 kHz for an adult human and 18 kHz for an infant. (These frequencies should not be confused with those due to repetitive pulses at audio rates.)

Lin (1978a) has published a monograph covering various theoretical and experimental aspects of the RFR hearing phenomenon. Lin (1980) is a briefer review of the subject.

Chou et al. (1977) studied cochlear microphonics (CM) produced by pulses of 918- and 2,450-MHz RFR in guinea pigs and cats. They found that the CM frequencies correlated well with the longest dimension of the brain cavities of the two species, but poorly with other brain cavity dimensions. Extrapolation of the results indicates that CM frequencies in humans should be between 7 and 10 kHz, in reasonable agreement with Lin's theoretical calculations.

Chou and Galambos (1979) investigated the effects of external-ear blocking, middle-ear damping, and middle-ear destruction on brainstem-evoked responses to both acoustic and RFR stimuli. They found that only animals with intact cochleas could respond to pulsed RFR.

Chou and Guy (1979b) used 918-MHz RFR to investigate the thresholds for brainstem-evoked responses in guinea pigs. They found that for pulse durations of 10, 20, and 30 microseconds, the threshold incident energy density was approximately constant (1.56-1.87 microjoules/cm^2 per pulse), corresponding to incident power densities of 156, 78, and 62.4 mW/cm^2, respectively. However, for pulse durations longer than 70 microseconds, the incident pulse power density necessary for obtaining responses was approximately constant (about 90 mW/cm^2), representing corresponding increases of incident energy density per pulse with pulse duration. Chou and Guy indicated that their experimental results agree well with the predictions of the thermal expansion theory.

More recently, Chou et al. (1981) (abstract) exposed anesthetized rats to 2.45-GHz pulsed RFR and determined the dose-response relationships for RFR-induced auditory evoked responses to pulses of 1, 2, 5, and 10 microseconds. The rats were exposed in three head orientations within a circularly polarized waveguide. The largest responses were

obtained with the major body axis parallel to the propagation direction and the head toward the source. The responses were dependent on the energy density per pulse irrespective of the pulse duration, with a threshold specific absorption per pulse of about 2.3 mJ/kg. The corresponding pulse power densities for the pulse durations above were 2,000, 1,000, 400, and 200 mW/cm^2, respectively. Again, the results are consistent with the thermal expansion theory.

Tyazhelov et al. (1979) reported some peculiarities regarding auditory perception of repetitively pulsed 800-MHz RFR in humans. The pulse widths used ranged from 5 to 150 microseconds at pulse repetition frequencies (PRFs) of 50 to 2,000 (the latter for short pulse durations). Each subject could be presented with sinusoidal audiofrequency (AF) sound waves alternately or concurrently with the pulsed RFR and could adjust the amplitude, frequency, and phase of the AF signal to match the timbre and loudness of the perceived RFR. Using AF signals, the high-frequency auditory limit (HFAL) of each subject was tested first. Three of the subjects who had HFALs below 10 kHz could not perceive such pulses. These results are consonant with those of Cain and Rissman. Among the peculiarities noted by Tyazhelov et al. was the biphasic dependence of RFR-perception thresholds on pulse width. They also reported that subjects could detect beat frequencies when concurrently presented with 8-kHz AF sound and RFR having PRFs above or below 8 kHz, and that when the PRF was the same as the AF, the subject could cancel perception by adjusting the phase of the AF. Their conclusion is that the thermoelastic model is inadequate to explain these observations.

Frey and Coren (1979) used dynamic time-averaged interferometric holography to try to detect tissue movement in successive layers of heads of animals exposed to pulsed RFR; for comparison, they used holograms obtained for the same animals during sham exposure. No movements were detected. The authors concluded that perception of pulsed RFR is most likely due to thermoelastic expansion within the cochlea rather than anywhere else in the head. However, the adequacy of the sensitivity of this holographic technique for detecting such movements is in dispute (Chou et al., 1980a; Frey and Coren, 1980).

Olsen and Hammer (1980, 1981) and Olsen and Lin (1981) exposed muscle-equivalent and brain-equivalent models to 5.7- and 1.1-GHz RFR, respectively, at high pulse power densities and detected RFR-induced acoustical responses with hydrophone transducers implanted in the models. Lin and Olsen (1981) also reported that they were able to detect RFR-induced acoustic pressure waves in the brains of anesthetized cats and guinea pigs by means of a piezoelectric transducer implanted in the cortex.

In conclusion, the preponderance of experimental results indicates that auditory perception of RFR pulses is due to induction of thermoelastic waves in the head, rather than to direct brain stimulation by the RFR. Also, because individual pulses can be perceived, it is not meaningful to calculate average power densities for two or more

widely spaced pulses and cite such values as evidence that the phenomenon is nonthermal in nature.

6.5.2 Calcium Efflux

Over the last 8 years, Adey and Bawin and their colleagues have reported extensively on their studies of changes in radioactive-calcium-ion ($^{45}Ca^{++}$) efflux from neonate chick brain preparations and isolated samples of cat cortex under very specific frequency and power density regimes of unmodulated sub-ELF fields and of amplitude-modulated VHF and UHF fields. Reviews of this work are given in Adey (1979, 1980, 1981b), and details of the experimental protocol are given in Bawin and Adey (1976, 1977). Briefly, following decapitation, forebrain hemispheres of neonate chicks were obtained by rapid dissection. The hemispheres were separated and one was used for exposure and the other as control. Each was incubated in a specified physiological solution containing $^{45}Ca^{++}$ for 30 min. At the end of incubation, the samples were rinsed three times with nonradioactive solution, transferred to new glass test tubes, bathed in 1.0 ml of solution, and exposed or sham-exposed for 20 min. Sets of ten brain samples (ten exposed hemispheres, ten control hemispheres) were used simultaneously. At the conclusion of exposure, aliquots of 0.2 ml of the bathing solution were taken, and their radioactivity was assayed by scintillation counting. Radioactivities (counts per minute, CPM, per gram) were normalized to the mean value of counts obtained in control effluxes. All normalized data were compared (by t-test) with matched samples of control values.

Adey (1977, 1978) presents data from experiments with approximately 190 chick brains for 450-MHz exposures. Power densities of 0.05, 0.1, 0.5, 1.0, 2.0, and 5.0 mW/cm^2 were used for 16-Hz amplitude modulation of the field. Statistically significant increases in $^{45}Ca^{++}$ efflux were seen at 0.1, 0.5, and 1.0 mW/cm^2, but not at 0.05, 2.0, or 5.0 mW/cm^2.

In a subsequent paper, Bawin et al. (1978) described experiments aimed at a better definition of the calcium sites responding to weak electrical stimulation. Changes in calcium efflux were studied with and without imposed RFR (450 MHz, 16-Hz amplitude modulation, 0.375 or 2.0 mW/cm^2) to ascertain the effect of calcium concentration in the exchanging medium. Also tested were the effects of changes of pH and the use of bicarbonate-free solutions. They also examined modification of calcium release, by the addition of lanthanum to the bathing solution, for both no-field and with-field stimulation conditions. Efflux of $^{45}Ca^{++}$ in the standard physiological solution was the "control" for these experiments.

The results confirmed the previous findings by Bawin and Adey that amplitude-modulated 450-MHz fields can stimulate the release of preincubated $^{45}Ca^{++}$ from isolated brain tissue. The authors state

that the results support the hypothesis that a limited number of extracellular cationic binding sites are involved in the transaction of weak extracellular electrical events.

Adey et al. (1982) also reported on results from a study involving the monitoring of calcium efflux from the intact exposed cortex of 23 awake, paralyzed cats. The methods were similar to those used in the chick brain experiments. The cats were exposed for 60 min to 450-MHz RFR amplitude-modulated at 16 Hz. The power density was 3.0 mW/cm^2. Calcium efflux was monitored at 10-min intervals over an experimental period of approximately 180-210 min. Exposure to RFR commenced usually 80-120 min after completion of incubation of the cortex with $^{45}Ca^{++}$. Control runs omitted the RFR exposure. By comparison with controls, mean efflux increased in the range 10 to 15% with RFR exposure. Additionally, efflux curves from RFR-exposed brains were disrupted by irregular waves of increased $^{45}Ca^{++}$ efflux.

Adey et al. (1981) measured the electric fields existing in the cerebral interhemispheric fissure in cats during exposure to CW 450-MHz fields (1.0-5.0 mW/cm^2), using a calibrated BRH-Narda miniature E-field probe. The cat's body was horizontal. Fields of 1 mW/cm^2 (61.4 V/m) produced interhemispheric gradients 1 cm below the cortical surface of about 20 V/m anteriorly and 25 V/m posteriorly in the fissure in cats aligned facing the radiation source. In cats oriented transversely to the source, these readings were 17 and 22 V/m. The calvaria were removed bilaterally, under pentobarbital anesthesia, for access to the fissure. It is not clear how much this procedure modified the preparation used for the calcium efflux studies in awake cats or whether the removal of the calvarium would result in significantly larger interhemispheric gradients. Measured interhemispheric E-field gradients were a significant fraction of the incident E-field gradients.

Blackman et al. (1979) conducted experiments that verified and extended Bawin and Adey's findings for chick brain at 147 MHz. Treated tissue was exposed in a Crawford cell to power densities between 0.5 and 2.0 mW/cm^2 and amplitude modulation of the carrier at selected frequencies between 3 and 30 Hz. They found a statistically significant increase in calcium efflux when the frequency modulation was 16 Hz and the power density was 0.750 mW/cm^2. (Preliminary findings indicating the existence of the power window, in addition to the frequency window discovered by Adey and Bawin, were reported by Blackman et al., 1977.) The 0.750 mW/cm^2 value was corrected to 0.830 mW/cm^2 in Blackman et al. (1980b) following more accurate calibration.

Blackman et al. (1980a) extended this work for 147-MHz RFR, amplitude-modulated (greater than 95%) at 9 Hz or 16 Hz, to examine a potential artifact apparently arising from differences in the number of samples simultaneously exposed. Brain tissues were from 1- to 7-day-old chicks. Tissues were exposed for 20 min with 0-, 9-, or 16-Hz sinusoidal modulation at power densities of 0.11, 0.55, 0.83,

1.1, 1.38, and 1.66 mW/cm^2. One-half of each chick brain was exposed to the RFR, and the other half, which was neither exposed nor sham-exposed, served as the control. Halves of other brain pairs were sham-exposed, and the corresponding halves served as controls. In one series, four brain pairs were treated at the same time. In another series, four brain pairs and six dummy loads were treated simultaneously. Statistically significant differences of normalized calcium efflux were found between exposed and sham-exposed tissues for eight of the combinations of power density, modulation frequency, and number of tubes (brains plus dummy loads). These combinations were: 0.83 mW/cm^2 for 16 Hz and four tubes/chamber; 0.55, 0.83, 1.11, and 1.38 mW/cm^2 for 16 Hz and ten tubes/chamber, and 0.55, 0.83, and 1.11 mW/cm^2 for 9 Hz and ten tubes/chamber. For unmodulated exposure at 0.83 mW/cm^2, no differences were found between the efflux values for exposed and sham-exposed groups. Two aspects of the results are puzzling: sham-exposed brain halves inside the transmission line generally gave higher values for calcium efflux than their corresponding control halves outside the transmission line, and the four-tissue-plus-six-dummy-load configuration gave a broader power density window than the four-tissue-without-dummy-load configuration. The reasons for these discrepancies are unresolved.

To determine whether changes in carrier frequency altered the range of power densities effective in producing statistically significant alterations in calcium efflux, Blackman et al. (1980b) conducted experiments at 50 MHz, amplitude-modulated at 16 Hz. Exposure conditions and protocol were similar to those previously used by these investigators. The results of a power density series demonstrated three effective power densities: 1.44, 1.67, and 3.64 mW/cm^2. No statistically significant effects were found at 0.72, 2.17, and 4.32 mW/cm^2. Of interest was the calculation that peaks of positive findings were associated with nearly identical rates of energy absorption, 1.4 mW/kg at 147 MHz and 1.3 mW/kg at 50 MHz.

Joines and Blackman (1980) modeled the 16-Hz amplitude-modulated exposure conditions of Adey at 450 MHz and of Blackman at 147 MHz and 50 MHz. Calculations showed that the average electric-field intensity within a spherically modeled sample remained the same at different carrier frequencies if the incident power density was adjusted by an amount that compensated for the change in complex permittivity of the brain tissue and for the change of internal wavelength as a function of carrier frequency. When this was done, all positive and negative results obtained at these three frequencies, when compared by average electric-field intensity within the sample, were in agreement. No result, positive or negative, was contradicted by a corresponding experimental result at a different carrier frequency. However, the model did not take into account the amplitude-modulation frequencies per se. Because not all modulation frequencies are effective, comparisons among average electric-field intensities within the samples cannot be extended to other modulation frequencies. The mechanisms whereby modulation effects are mediated are speculative.

Athey (1981) challenged the above analysis. He pointed out that the uncertainties in values of electrical properties of the brain material, the fact that the sample was predominantly saline and therefore different from the brain material assumed in the model, and the fact that the simple geometry assumed may have been too unrealistic, all led to uncertainties that were too large to permit meaningful conclusions. He recommended that further work be based on experimental dosimetry to avoid these uncertainties.

In rebuttal, Joines and Blackman (1981) reported on an improved model, that of a layered sphere. Their revised calculations were conducted for various worst-case situations and were used to show that the relationship of incident power density to internal power density is relatively insensitive to small changes in permittivity. However, the point made by Athey (1981) about experimental dosimetry should still be pursued as the final arbiter of this disagreement.

To demonstrate the predictive nature of their model, Blackman et al. (1981a) calculated and tabulated various values of incident power density that had been shown to either cause or not cause an effect, or had not been tested, for carrier frequencies of 50, 147, and 450 MHz. From this table they chose two values, 0.37 and 0.49 mW/cm^2 at 147 MHz (modulated at 16 Hz). The first value, 0.37 mW/cm^2, was predicted to show a statistically significant difference, based on previous studies at 50 MHz. The second was predicted not to show a statistically significant difference. These predictions were confirmed experimentally, impressive support for their theory. In a parallel study, Blackman et al. (1981b) exposed brain tissue samples in vitro to the sub-ELF signal alone (16 Hz) rather than to a carrier modulated at sub-ELF frequencies. Preliminary analysis of the results confirmed the early results of Bawin and Adey (1976), namely that there are frequency-dependent, field-induced calcium ion efflux changes within the range 1 to 70 V/m peak-to-peak incident field in air.

Shelton and Merritt (1981) examined whether pulsed RFR (instead of sinusoidally amplitude-modulated RFR) might also elicit alterations in calcium efflux from cerebral tissue. Rat cerebral tissue preloaded with $^{45}Ca^{++}$ was exposed to pulsed RFR (1-GHz carrier, 0.32 duty factor) at one of several pulse-width, power-density exposure schemes: 16-Hz PRF at 0.5, 1.0, 2.0, or 15 mW/cm^2 average power density; or 32 Hz PRF at 1.0 or 2.0 mW/cm^2 average power density. Measurements of radioactivity (CPM) in the efflux medium and in the tissue sample were used to calculate an efflux value for each sample. (This measure of efflux differs from that used by other investigators.) The results of exposing or sham-exposing cerebral tissue from 167 rats showed no statistically significant differences between any of the $^{45}Ca^{++}$ efflux values when irradiated samples were compared with the accompanying sham-irradiated control samples. As Shelton and Merritt point out, though, no direct comparisons can be made between their results and those of the other investigators presented above because of the differences in radiation exposure parameters, carrier frequency, and modulation.

Calcium is known to play a major role in the regulation of not only secretion of neurotransmitters by nerve cells, but also secretory proteins by endocrine and exocrine glandular cells (Schramm, 1967). The foregoing RFR studies were all concerned with nervous system tissue. To investigate whether increased calcium efflux from exposure to amplitude-modulated RFR is a response of glandular cells, Albert et al. (1980) used rat pancreatic tissue slices in an experimental protocol essentially identical to that used in the brain tissue studies of Blackman and coworkers, and similar to the protocols used by Bawin and Adey, described above. Albert et al. (1980) also measured changes in pulse-labeled secretory proteins. For the calcium efflux study, data from 14 paired sets of pancreatic slices (irradiated or sham-irradiated slices paired with control slices) showed an 11% increase in calcium-ion efflux after 1-hr exposure, significant at the 0.03 level.

Sham-irradiated tissue slices did not show statistically significant alteration in calcium efflux when compared with nonirradiated controls. Thus, 16-Hz amplitude-modulated 147-MHz RFR at 2.0 mW/cm^2 increased calcium efflux from pancreatic tissue slices to approximately the same extent as that from neonate chick brain tissue incubated and exposed under similar conditions.

The pulse-labeled secretory protein study (Albert et al., 1980) found that RFR had no effect on the release of these proteins from either normal or carbamylcholine-stimulated pancreatic tissue slices. However, because of physical constraints of the apparatus, the tissue slices could be incubated in only 1 ml of incubation medium, instead of the 15 ml used in other established in vitro secretion studies on pancreatic tissue slices. Therefore, the investigators believe that the conditions did not permit them to test most effectively for an RFR effect. When the incubation medium was increased to 15 ml, carbamylcholine resulted in the release of 30% of the pulse-labeled secretory protein. Albert et al. (1980) therefore suggested that the experimental conditions that promoted increased calcium efflux in their experiments, in the experiments of Blackman and colleagues, and in the experiments of Bawin and Adey and colleagues may not be optimal for testing the full potential effects of RFR. They also suggested that such RFR-induced calcium-ion efflux changes have little physiological significance.

In the studies already cited in this section, Bawin and Adey attributed the increase in release of calcium ion to an interaction between the amplitude-modulated RFR and specialized binding sites on the outside surface of plasma membranes of brain cells. Allis and Fromme (1979) pointed out that calcium is also transported across biological membranes by energy-dependent processes, and that sinusoidally modulated RFR may exert an effect on the function of membrane-bound enzyme systems mediating such transmembrane transportation. They therefore conducted experiments wherein specially prepared membrane-bound enzyme systems were irradiated with sinusoidally modulated RFR in a spectrophotometric apparatus in which enzyme activity was measured

during irradiation. Cytochrome oxidase (a key enzyme located in the inner membrane of mitochondria) and adenosine triphosphatase from red-blood-cell membrane (involved in maintaining the sodium-potassium balance of the cell) were studied. The SAR was 26 W/kg for irradiation with 2.45-GHz RFR amplitude-modulated at 16, 30, 90, and 120 Hz. No statistically significant differences in enzyme activities were found between irradiated and control samples at any of the modulation frequencies for either enzyme system. However, as Allis and Fromme point out, these results are not definitive for several reasons: the membranes were tested for two functions under highly artificial conditions, e.g., the resting electrical potential across the membrane was not maintained in the in vitro preparation they used; the exposure levels used were much higher than the "power window" demonstrated by the previously cited research; and only the 16-Hz modulated frequency is within the "frequency window" claimed for nervous-tissue effects.

In summary, there is now a large volume of work by Adey and coworkers and by Blackman and coworkers that reports alterations of calcium efflux from chick brain in vitro and from pancreatic tissue in vitro as a result of exposure to various regimens of electromagnetic fields at frequencies in the sub-ELF range and at 50-, 147- and 450-MHz RFR carriers sinusoidally amplitude-modulated at sub-ELF frequencies. Efflux changes are a complex function of incident power density and modulation frequency. A model relating efflux "windows" with respect to internal power density in the tissue has been developed and successfully used to predict an effective and a noneffective incident power density at a carrier frequency of 50 MHz, sinusoidally modulated at 16 Hz. No experimentally verified model exists to explain the modulation-frequency window effect. Experiments using rat brain tissue in vitro at a carrier frequency of 1 GHz and pulse-modulated instead of sinusoidally amplitude-modulated have failed to demonstrate an altered efflux effect. The studies reporting RFR-induced calcium efflux changes have been the subject of a comprehensive and detailed critical analysis (Myers and Ross, 1981), and some doubts have been raised about certain aspects of the methods used, statistical treatment of data, and interpretation of results. Because of the potential significance of this area, stemming from the pivotal importance of calcium ions in the normal functioning of the brain, it is likely that much additional work will be carried out to clarify the situation.

6.5.3 Blood-Brain Barrier Effects

The existence of a blood-brain barrier (BBB) in most regions of the brain has been established experimentally, although its specific morphology is still conjectural. This barrier normally provides high resistance to movements of large-molecular-weight, fat-insoluble substances (e.g., proteins or polypeptides) from the blood vessels into the surrounding cerebral extracellular fluid, presumably to protect the brain from invasion by various blood-borne pathogens and toxic substances. Several investigators have reported that low levels of RFR can increase the permeability of the BBB to certain substances of large molecular weight. However, others were unable to confirm such effects, and the subject remains controversial.

Horseradish peroxidase (HRP), a high-molecular-weight protein, is frequently used as a tracer that is detectable both morphologically and quantitatively. Certain substances, notably dimethyl sulfoxide (DMSO), can be demonstrated to open the BBB. Broadwell et al. (1982) showed that, in mice, a single injection of HRP in 10 to 15% DMSO into the tail vein along with 10 to 15% DMSO delivered intraperitoneally allowed HRP to fill the extracellular clefts throughout the brain within 2 hr. Normally, peroxidase is excluded from brain parenchyma except in the region of the choroid plexus and the median eminence. Opening of the BBB by DMSO is reversible.

Rodzilsky and Olszewski (1957) found that permeability changes in cerebral blood vessels could be induced by various non-RFR means, including those that produce heat necrosis. Sutton and coworkers (Sutton et al., 1973; Sutton and Carroll, 1979), who were interested in the use of RFR for selective hyperthermic treatment of brain tumors, determined the maximum temperatures and exposure durations that would not alter the integrity of the BBB in the rat. They used 2.45-GHz RFR to induce hyperthermia and HRP as a tracer. Heads of rats were heated with RFR to a brain temperature of 40, 42, or 45 deg C. They found that BBB integrity was diminished, in orthonormic animals (37 deg C), by heating the brain to 45 deg C for 10 min, to 42 deg C for 15 min, and to 40 deg C for 60 min. The corresponding durations in rats precooled to 30 deg C were 15, 30, and 180 min, respectively.

Frey et al. (1975) exposed groups of anesthetized rats to pulsed or CW RFR at 1.2 GHz for 30 min. For the pulsed RFR, the pulse and average power densities were 2.1 and 0.2 mW/cm^2, respectively, and for the CW RFR, the power density was 2.4 mW/cm^2. Sham-exposed rats were used as controls. After exposure or sham exposure, sodium fluorescein was injected into the femoral vein. Five minutes after injection, the blood of the rat was removed by perfusion, and the brain was removed, embedded in gelatin, refrigerated, and sectioned. The sections were viewed under ultraviolet light for fluorescence, the intensity of which was scored by the viewer. Greater fluorescence was reported for pulsed than for CW RFR, and some control specimens also exhibited slight fluorescence. The investigators regarded these results as evidence that exposure to RFR altered the BBB.

Spackman et al. (1978) performed a similar investigation in mice, using fluorescein and several nonphysiological amino acids as test substances. Groups of mice were exposed to sham, CW, or pulsed RFR at 918 MHz for 30 min. Average power densities of 2.5 and 33 mW/cm^2 were used in both the CW and pulsed modes. Also, some mice were exposed to CW RFR at 132 mW/cm^2. After exposure, the concentration of each test substance in the brain relative to the concentration of that substance in the blood plasma (the "specific concentration") was determined. A spectrofluorometer and an automatic amino acid analyzer were used to measure the concentrations of fluorescein and the test amino acids, respectively. The specific concentrations of all substances tested in the RFR-exposed animals were found to be in the same ranges as for the controls.

Subsequently, Spackman et al. (1979) used whole-body heating or intraperitoneal (i.p.) injection of glycerol, urea, metaraminol, or DMSO as alternative agents to RFR exposure. All of these agents purportedly alter the BBB. They found that heating mice to 50 deg C in an incubator for 22 to 25 min caused no apparent increase in BBB permeability to the test substances. Negative results were also obtained for all of the injected agents except DMSO, which produced a significant increase in BBB permeability relative to controls. As pointed out previously (Broadwell et al., 1982), DMSO exerts a powerful effect in altering BBB permeability. Heat and the other substances--glycerol, urea, and metaraminol--are all reported as being capable of altering the BBB (Rapoport, 1976). The failure of the analytical techniques of Spackman et al. (1979) to detect any BBB permeability changes, except for DMSO, is perhaps an indication that the techniques lack sufficient sensitivity. If so, this would cast some doubt on their negative findings with RFR.

Albert et al. (1977) also used HRP as a tracer and reported regions of leakage in the microvasculature of the brains of Chinese hamsters exposed to 2.45-GHz CW RFR at 10 mW/cm^2 for 2 to 8 hr. In control animals, extravascular reaction product was found only in brain regions normally lacking a BBB.

In a later study, Albert (1979) exposed 52 animals (34 Chinese hamsters and 18 rats) to 2.8-GHz RFR for 2 hr at 10 mW/cm^2. Of these, 30 were euthanized immediately, 11 at 1 hr after exposure, and 11 at 2 hr after exposure. Twenty animals (12 hamsters and 8 rats) were sham-exposed. Leakage of HRP in some brain regions was reported for 17 of the 30 animals euthanized immediately after RFR exposure and for 4 of the 20 sham-exposed animals. Fewer areas of increased BBB permeability were evident for animals euthanized 1 hr after RFR exposure, and except for one rat, virtually no leakage of HRP was seen for the animals euthanized 2 hr after RFR exposure. These results indicate that increased BBB permeability due to RFR exposure at levels insufficient to denature brain tissue is a reversible effect. (Albert suggests that such BBB changes may be clinically subacute and would probably cause no lasting ill effects.) However, the increased BBB permeability seen in 4 of the 20 sham-exposed animals may indicate that factors other than RFR in the experimental procedure could alter the BBB. One possible confounding point in the use of injected HRP as a tracer is the existence of endogenous peroxidase, the detection of which could yield false positive results. Also, no positive (BBB-altering) control agent was used in these studies for comparative purposes.

Almost identical data and results were reported by Albert and Kerns (1981) for 51 Chinese hamsters exposed to 2.45-GHz CW RFR for 2 hr at 10 mW/cm^2. There were 39 original sham-irradiated controls. Twelve of the RFR-exposed animals were allowed to recover for either 1 or 2 hr prior to HRP injection and subsequent fixation. This study appears to be an extension (for Chinese hamsters) of the work reported by Albert (1979) for 2.8-GHz RFR exposure, with the same conclusions as that paper.

Oscar and Hawkins (1977) reported changes in BBB permeability to D-mannitol after exposure of rats to 1.3-GHz pulsed or CW RFR for 200 min at various average power densities. Permeability changes were measured by the Oldendorf (1970, 1971) technique; that is, 0.2 ml of a mixture of 14-C-labeled mannitol and tritiated water was injected rapidly into each rat's carotid artery after exposure, the animal was euthanized 15 s later, and brain sections were dissected out and prepared for assays of radioactivity using a liquid scintillation counter. The ratio of counts of 14-C-labeled D-mannitol to counts of freely diffusible tritiated water in samples of brain tissue was normalized to a similar ratio for the injected solution. This normalized ratio, expressed as a percentage, is defined as the brain uptake index (BUI). Oscar and Hawkins found statistically significant changes in the BUI at average power densities less than 3 mW/cm^2. They also found that, depending on the specific pulse characteristics used, pulsed RFR could be either more or less effective in altering BBB permeability than CW RFR of the same average power density. For pulses of long duration and high pulse power density but only a few pulses per second, mannitol permeation could be induced at average power densities as low as 0.03 mW/cm^2. Their results also indicated the possible existence of a power density "window"; i.e., permeability is not altered for power densities above or below the window.

Because the Oldendorf technique does not permit discriminating between local cerebral blood flow (LCBF) and small BBB permeability changes, Oscar et al. (1981) used a different technique involving ^{14}C-iodoantipyrine to measure LCBF in rats. Male rats weighing 250-300 g were individually sham-exposed for 5, 30, or 60 min, or individually exposed for 5, 15, 30, 45, or 60 min to pulsed RFR at 15 mW/cm^2 average power density. Carrier frequency was 2.8 GHz, pulse rate was 500 pps, and pulse width was 2 microseconds. Within 5 min after sham or RFR exposure, the previously venous-catheterized but conscious animals were infused with isotonic saline containing 5 microCurie per ml of ^{14}C-iodoantipyrine. Fifty seconds after start of infusion, the rats were decapitated. Brain regions were dissected out and assayed for radioactivity by routine liquid scintillation counting. Local cerebral blood flow was then calculated by established procedures. The results showed that microwave exposure caused a significant increase in LCBF (minimum 39%, some well over 100%) in all 17 brain regions sampled. Because of these findings, the authors indicated that their earlier reported ratio measurements (Oscar and Hawkins, 1977) may be overly high. However, the ^{14}C-iodoantipyrine results clearly demonstrated an alteration of brain activity at 15 mW/cm^2. The mechanism of this alteration is presently unresolved.

Preston et al. (1979), using methods similar to those of Oscar and Hawkins (1977), attempted to determine whether exposure to 2.45-GHz CW RFR increased BBB permeability to 14-C-labeled D-mannitol. They exposed rats to 0.1, 0.5, 1, 5, or 10 mW/cm^2, with sham-exposed rats for controls, and found no evidence that RFR exposure increased the permeability of the BBB for mannitol. In a second series, rats were

exposed to 0.3, 1, 3, 10, and 30 mW/cm^2. Again there were no differences between results from exposed and sham-exposed animals. Like Oscar et al. (1981), Preston et al. (1979) believed changes in LCBF confounded the results of earlier studies.

Chang et al. (1982) used a technique involving 131-I-labeled albumin to investigate alterations of the BBB in dogs. The heads of dogs were exposed to various average power densities between 2 and 200 mW/cm^2. In general, no statistically significant differences were found between exposed and sham-exposed animals, but the number of animals used in this study was too small to ascribe a high level of statistical confidence.

Merritt et al. (1978) endeavored to replicate the studies of Frey et al. (1975) and Oscar and Hawkins (1977). They exposed rats for 30 min to 1.2-GHz pulsed RFR at peak power densities in the range from 2 to 75 mW/cm^2 and 0.5 duty cycle, corresponding to average power densities of 1 to 38 mW/cm^2, or for 35 min to 1.3-GHz pulsed or CW RFR at average power densities in the range from 0.1 to 20 mW/cm^2. They examined brain slices under ultraviolet light for transfer of fluorescein and under white light for transfer of Evans blue dye (a visual tracer) across the BBB, and chemically analyzed various brain regions for fluorescein content. They also measured the brain uptake of 14-C-labeled D-mannitol and determined the BUI values. To validate these detection methods, they used hypertonic urea, known to alter the BBB, as an alternative agent to RFR. Last, sham-exposed rats were heated for 30 min in a 43 deg C oven to appproximate the hyperthermia obtained at 38 mW/cm^2. In their examination of brain slices, Merritt et al. (1978) found no evidence of fluorescein or Evans blue dye transfer across the BBB of RFR-exposed rats, whereas penetration of the BBB was apparent for rats treated with urea instead of RFR. The analyses of fluorescein content corroborated these findings. However, fluorescein uptake was higher for the sham-exposed rats that were heated in the oven, an indication that hyperthermia of the brain is necessary to alter BBB permeability. In the 14-C-mannitol study of the various brain regions, there were no significant differences in BUI between RFR- and sham-exposed rats, whereas BUI changes were evident for rats treated with urea. Also, the results showed no evidence of the power density window reported by Oscar and Hawkins (1977).

By using a small dielectrically loaded coaxial applicator, Lin and Lin (1980, 1982) were able to irradiate only the heads of anesthetized adult male Wistar rats with pulsed 2,450-MHz RFR (10 microseconds, 500 pps) for 20 min at average power densities of 0.5 to 3000 mW/cm^2. The distribution of absorbed microwave energy inside the head was determined by thermographic procedures, and average SARs were found to range from 0.04 to 240 W/kg. Evans blue dye was injected into a catheterized femoral vein following sham or RFR exposure, and 5 min later the animal was perfused via the left ventricle with normal saline. The brain was removed, examined, and scored for degree of tissue staining by the tracer. For average power densities up to and including 2,600 mW/cm^2 (200 W/kg), staining was not significantly

different between exposed and control animals. For exposures of 3,000 mW/cm^2 (240 W/kg), extravasation of Evans blue dye could be seen in the cortex, hippocampus, and midbrain. The degree of staining decreased with increasing time to euthanasia postexposure, indicating that the effect was reversible.

In summary, the uncertainty in most earlier research on this topic involves whether significant artifacts are introduced by the kinds of biological techniques used. Several investigators have indicated that exposure to RFR may alter the size of vascular and extravascular volumes and cerebral blood flow rate, thereby yielding changes in the BUI that are not necessarily related to BBB permeability alterations. Blasberg (1979) reviewed many of the methods previously used for investigating BBB changes and the problems associated with these methods. Rapoport et al. (1979) developed a method for measuring cerebrovascular permeability to 14-C-labeled sucrose that yields results independent of cerebral blood flow rate. As described earlier, Oscar et al. (1981) confirmed experimentally that LCBF is increased in the rat brain by exposure to pulsed RFR at 15 mW/cm^2 average power density.

Recent findings such as those mentioned above indicate that little quantitative confidence can be placed in the results of early experiments on RFR-induced BBB alterations. Qualitatively, hyperthermic levels of RFR clearly can alter the permeability of the BBB. It is also possible that exposure at average power densities of the order of 10 mW/cm^2 may result in randomly distributed, clinically subacute, reversible alterations. However, additional research using current or improved methodology is necessary to ascertain whether chronic exposure to nonhyperthermic levels of RFR affects the BBB. Recent reviews of this topic were published by Justesen (1980) and Albert (1979).

6.5.4 Histopathology and Histochemistry of the Central Nervous System (CNS)

Tolgskaya and Gordon (1973) reported a number of effects of RFR (frequencies 500 kHz to 100 GHz) on approximately 650 animals, predominantly rats. Pathological effects they reported for high-intensity (20 to 240 mW/cm^2) RFR in their so-called decimeter band (500 MHz to 1 GHz) included multiple perivascular hemorrhages in the brain and other organs, degeneration of apical dendrites in the cortex, cloudy swelling of cytoplasm, cytoplasmic shrinkage, formation of vacuoles, unevenness of staining, disappearance of cytoplasmic structures, fatty degeneration, decrease in ribonucleoprotein, and occasional karyocytolysis. The intensities of exposure were capable of causing death of the animals (clinical signs of hyperthermia, temperature increases up to 42-45 deg C) in several minutes to several hours. Photographs of the exposure arrangement show multiple animal exposures at the same time in a room appearing not to have RFR-absorbing material on the walls. It is likely that the SARs for individual animals under these conditions varied widely and that all effects were clearly thermal in nature.

Exposures referred to as "low-intensity" were also performed. The authors define threshold field intensities for nonthermal effects ("intensity not raising body temperature") for decimeter microwaves as 40 mW/cm^2 (Tolgskaya and Gordon, 1973, Table 3, p. 56). Exposures were generally at or slightly below 10 mW/cm^2 for 60 min daily for 10 months. Investigation of the animals by ordinary morphological methods revealed practically no vascular disorders in the nervous system. "Delicate elective neurohistological methods" (unspecified) showed disappearance of spines from cortical dendrites, the appearance of beading and irregular thickening of dendrites, swelling of cytoplasm of individual cells (with appearance of vacuoles) in the basal ganglia and hypothalamus, focal and diffuse proliferation of microglial cells, with microglial processes showing initial signs of degeneration.

Many of these "low-intensity" effects are similar to those described for the high-intensity exposures. In view of the exposure levels (approximately 10 mW/cm^2), the previously described exposure arrangement, and the knowledge of the possibility of localized regions of high SAR, it *seems* likely that the described effects (more subtle than those of frank hyperthermia) were also thermal in origin.

Albert and DeSantis (1975) reported changes in the hypothalamus and subthalamus of Chinese hamsters exposed to 2.45-GHz RFR at either 50 mW/cm^2 for durations from 30 min to 24 hr, or 25 mW/cm^2 for 14 hr/day for 22 days. Changes were not evident in the hippocampus, cerebellum, thalamus, or spinal cord ventral horn. In the discussion printed after the paper by Albert and DeSantis (1975), Guy pointed out that his laboratory had measured mean SARs as high as 4 W/kg per incident mW/cm^2 in animals of similar size. Peak SARs could have reached 40 to 200 W/kg in selected brain regions of the animals studied by Albert and DeSantis; this range far exceeds that normally used for diathermy treatment in 20-min exposures of patients. Rectal temperature would not necessarily reflect such high SARs in other localized areas.

Albert and DeSantis (1976) also studied CNS histological effects in 60 Chinese hamsters exposed to 1.7-GHz RFR at power densities of 10 and 25 mW/cm^2. After 30 to 120 min of exposure, cytopathology was observed in hypothalamic and subthalamic areas, but not in other areas. These observed effects were also likely to have been thermal in origin, for the reasons previously mentioned.

Albert et al. (1981a) looked at the effects of RFR exposure pre- and postnatally on the Purkinje cells of the rat cerebellum. In one experiment, Sprague-Dawley rats were exposed <u>in utero</u> to 100-MHz CW RFR at 46 mW/cm^2 (SAR of 2.81 W/kg) for 6 hr/day on days 16 to 21 of gestation, and then for 4 hr/day for 97 days after birth. Four exposed and four sham-exposed animals were sacrificed 14 months after cessation of irradiation. Quantitative assessment of the cerebella showed that the relative number of Purkinje cells was significantly smaller (12.7%) in experimental animals than in control animals. In another experiment, Sprague-Dawley rats were exposed <u>in utero</u> to 2.45-GHz CW RFR at

10 mW/cm^2 (SAR of 2 W/kg) for 21 hr/day on days 17 to 21 of gestation. Power density measured was variable from 4 to 30 mW/cm^2 because of group exposure conditions. Half of the litters were used shortly after delivery and the other half 40 days after cessation of irradiation to assess effects of the exposure on cerebellar Purkinje cells. Because of the immaturity of the neonates, the Purkinje cell layer was not clearly displayed, and quantitative results could not be obtained. Those animals sacrificed 40 days postexposure showed significantly fewer (25.8%) cells in the experimental animals than in the controls. In a final experiment, rat pups were exposed to 2.45-GHz RFR at 10 mW/cm^2 for 7 hr/day on postnatal days 6 to 10. Half the pups were sacrificed at the end of exposure and half at 40 days postexposure. Only those sacrificed immediately showed a significant decrease in the relative number of Purkinje cells as compared with sham-exposed controls. Thus, exposure to two frequencies of RFR at similar SAR values (2.8 and 2 W/kg) yielded a reduction in the relative number of Purkinje cells for fetuses and newborn rats. Although the change appeared permanent for rats exposed in utero, it appeared to be reversible for those exposed postnatally.

In a related study, Albert et al. (1981b) examined the effect of RFR exposure on the Purkinje cells of squirrel monkey cerebella. Pregnant squirrel monkeys were exposed to 2.45-GHz pulsed RFR at an equivalent power density of 10 mW/cm^2 (SAR of 3.4 W/kg) for 3 hr/day starting in the first trimester of pregnancy. The offspring were exposed similarly for the first 9.5 months after birth. At the end of the irradiation period, seven exposed and seven sham-exposed animals were sacrificed and their cerebella examined. There were no statistically significant differences between control and exposed animals in any of the Purkinje cell parameters examined. Several factors were suggested by Albert et al. (1981b) to explain the discrepancy between these results and those with the rat. Factors that might have contributed were differences in geometrical configurations of the head, exposure methods, and daily exposure durations, as well as variations in gestational periods and species differences. However, referring to the discussion of Albert and DeSantis (1975) above, the possibility that high local SAR values in the rat brain but not in the squirrel monkey brain at comparable whole-body SARs is the major factor should be emphasized.

Merritt and Frazer (1975) conducted a study to determine whether HF (19 MHz) RFR altered the whole brain level of certain neurotransmitters in mouse brain. The neurochemicals they studied were serotonin and its metabolite, 5-hydroxyindole acetic acid; dopamine and its metabolite, homovanillic acid; and norepinephrine. Male adult Swiss Webster mice were housed individually in plastic cages and exposed in groups of 5 to 14 to either predominantly E- or predominantly H fields in a near-field synthesizer. E-field exposure was at 6 kV/m with an impedance of approximately 940 ohms. H-field exposure was at 41 A/m with an impedance of approximately 49 ohms. Exposures were for 10 min, which did not produce measurable rises in rectal temperature. Two sets of control animals were sham-exposed in the

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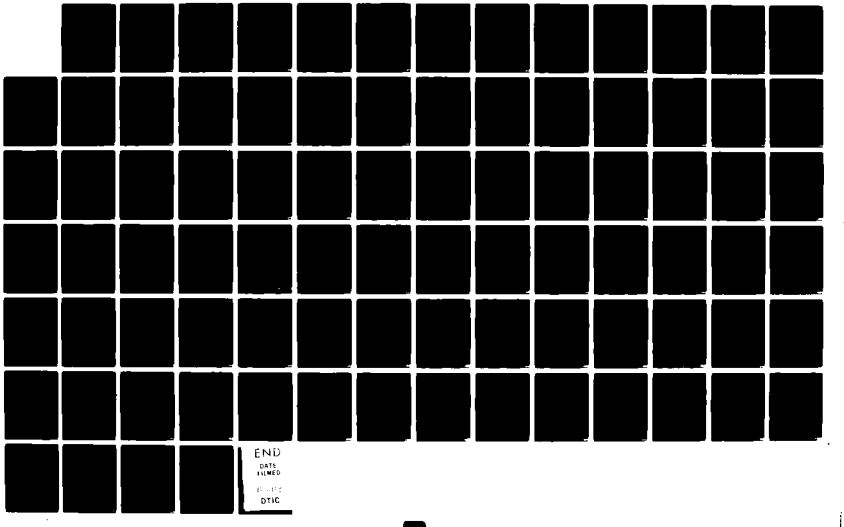

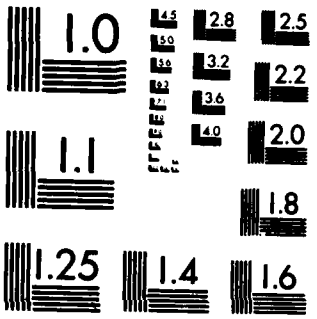

near-field synthesizer. Fifteen minutes after completion of exposure (or sham exposure), one set of controls and all sets of exposed animals were euthanized very rapidly by high-power-density microwave inactivation of brain enzymes in a specially modified microwave oven plus waveguide system. The second set of controls was euthanized 15 min after exposure by cervical dislocation, and their brains were rapidly dissected out and immediately frozen in liquid nitrogen for enzyme inactivation. The enzyme-inactivated brains were then assayed for the five stated neurochemicals by a modification of a standard spectrofluorometric technique.

Results of the assay indicated that there were no statistically significant differences in whole-brain-averaged values between the microwave-inactivated controls and either E- or H-field-exposed animals for any of the neurotransmitters or their metabolites. The microwave-inactivated controls did show a statistically significant difference (microwave-control values higher) for all neurochemicals except homovanillic acid when compared with the conventional controls. Because of the rapidity of the microwave enzyme-inactivation technique, this probably indicates rapid turnover of the neurotransmitters under study. Frequency-scaling comparisons between human and mouse at 19 MHz indicates that for mouse exposure, approximately 30-40 times more incident power density is required to give the same whole-body average SAR as in a human. Therefore, for humans, short-duration E-field exposure up to approximately 150 V/m, or H-field exposure up to approximately 1 A/m, at 19 MHz, may be expected to have no effects on serotonin, 5-hydroxyindole acetic acid, dopamine, homovanillic acid, or norepinephrine in the brain.

Sanders et al. (1980) examined whether the effects of RFR exposure would alter mitochondrial electron transport chain function. Rat brain was exposed in vivo to 591-MHz CW RFR at 5.0 or 13.8 mW/cm^2 for 0.5, 1, 2, 3, and 5 min. Nicotinamide adenine dinucleotide (NAD), reduced nicotinamide adenine dinucleotide (NADH), adenosine triphosphate (ATP), and creatine phosphate (CP) levels were examined during exposure. On initiation of exposure, NADH measured fluorimetrically by fiberoptic techniques rapidly increased to a maximum of 4.0% to 12.5% above preexposure controls at 0.5 min, then decreased slowly to 2% above controls at 3 min, and then increased slowly to 5% above controls at 5 min. ATP and CP assays were performed on exposed and sham-exposed brain at each exposure time. Similar significant decreases in brain CP level and brain ATP concentration were observed for both the 5- and 13.8-mW/cm^2 exposures. Changes in NADH, ATP, and CP levels during RFR exposure were supposedly not attributable to general tissue hyperthermia because measurements of brain temperatures showed temperature falls, attributed to the heat sink formed by the aperture made in the skull to permit the fiberoptic observations. The results of this study appear to support the hypothesis that the RFR exposure inhibited brain mitochondrial electron transport chain function, i.e., inhibition of respiratory chain function followed by decreased ATP and CP concentrations.

In summary, RFR can cause observable histopathological changes in the CNS of animals, but it appears that these changes are thermal in nature. The study by Sanders et al. (1980) is of considerable interest because of the positive results obtained in the absence of measurable tissue hyperthermia. The significance of the findings (inhibition of respiratory chain function) is presently unclear.

6.5.5 EEG Studies

Many studies have been conducted on the effects on the electroencephalogram (EEG) and/or evoked responses (ERs) of animals exposed to RFR. Some of these have been performed with metal electrodes either implanted in the brain or attached to the scalp during exposure. Johnson and Guy (1972) pointed out that such metallic electrodes grossly perturb the fields and produce greatly enhanced absorption of energy (i.e., field enhancement) in the vicinity of the electrodes. Examples of the magnitude of this enhancement were provided in a National Academy of Sciences publication (NAS, 1979). For an implanted insulated wire, with the end of the conductor in direct contact with the tissue and a length-to-radius ratio of the wire of 100:1, the enhancement factor for SAR is of the order of 100,000. Such increases probably result in highly localized transient heating in the immediate vicinity of conductive implants in tissue exposed to microwave fields with time-averaged intensities greater than 0.001 mW/cm^2. The greatly enhanced fields themselves are also likely to cause artifacts in nervous system tissue function in the volume immediately around the electrode because of the sensitivity of such tissue to electrical stimulation by induced currents. Such artifacts are not to be confused with the recording artifact that is produced by pickup of fields by the electrodes and leads during the recording of EEGs or ERs while the animal is being exposed. Recording artifact is usually removed by appropriate filtering, but field-enhancement artifact is not. Note also that many EEG studies are performed on heavily sedated animals, with barbiturates as the usual drugs. Hence the responses reported do not necessarily reflect those that would be expected in normal alert animals.

Tyazhelov et al. (1977) discussed these problems and pointed out that even for the coaxial electrode developed by Frey et al. (1968), diffraction of electromagnetic waves is still a major source of error because of the electrode's metallic nature and large dimensions. Tyazhelov solved the problems by developing electrodes of high linear resistance (greater than 100 kilohms/m) and properly filtering the recorded signal. This report indicates an awareness in the USSR that questions may be raised about the validity of data and conclusions from many experiments involving animals with indwelling electrodes, both in the USSR and the United States.

Bruce-Wolfe and Justesen (1979) investigated the effects of RFR-induced hyperthermia on the visually evoked electrocortical response (VER) in five female guinea pigs. The VERs were recorded for animals after exposure to modulated 2.45-GHz RFR in a multimode, mode-stirred

cavity for durations ranging from 4 to 15 min. Such exposures raised rectal temperature to as high as 43 deg C and brain temperature to as high as 41 deg C. The mean latency from onset of photic stimulation to the N_1 peak diminished from 42.8 to 37.7 ms for a cortical temperature increase from 37.0 to 40.5 deg C. For a cortical temperature above 41.5 deg C, the VER became highly variable, and above 43.0 deg C the animals died. The authors recognized the possibility of local brain damage resulting from the use of implanted metal electrodes and stainless-steel screws, and stated that this aspect was being explored in further studies in the rat and guinea pig.

Takashima et al. (1979) studied the effects of modulated RFR fields on the EEGs of rabbits. Male rabbits were exposed for 2 hr/day for 6 weeks to 1- to 10-MHz RFR modulated at 15 Hz. Although the authors claimed an enhancement of low-frequency components and an increase in high-frequency activity after 3 weeks, the data presented do not support this conclusion, and the authors themselves state that the results presented are still incomplete. They did note that for acute irradiation, "enhanced slow waves and unusually low high-frequency activities were due to the local field created by the presence of the (recording) metal electrodes in the cranial cavity."

Dumanskij and Shandala (1974) reported changes of the biocurrents in the brain cortex of rabbits after 60 days of exposure to RFR (50 MHz, 2.45 GHz, or 10 GHz). Changes (vaguely specified as "an increase in the rhythm of slow waves and a decrease in the rhythm of intermediate and fast waves") were described at 0.01 and 0.0019 mW/cm^2, but not at 0.00001 mW/cm^2. Although the rather sketchy nature of their description precludes any definitive evaluation of these results, the use of indwelling electrodes may have contributed artifacts, as described above.

In a more recent presentation, Shandala et al. (1979) reported on observations of rabbits with implanted EEG electrodes, and again claimed quite variable, but statistically significant, EEG changes from 0.01-mW/cm^2 exposures (2.375 GHz) for 7 hr/day for 1 month. The same questions about the possibility that implanted electrodes caused artifacts may be raised.

Goldstein and Cisko (1974) studied the EEGs of sedated rabbits to determine whether RFR exposure would evoke arousal. They used 9.3-GHz RFR at 0.7 to 2.8 mW/cm^2. The EEG of each rabbit was recorded for about 1 hr. After the first 10 min, the rabbit was sedated with sodium pentobarbital. Five minutes later, the rabbit was exposed or sham-exposed to the RFR for 5 min. The EEGs showed no arousal during RFR exposure but indicated alternations of arousal and sedation characteristics starting 3 to 12 min after exposure. However, control animals also exhibited alternations having shorter arousal durations, rendering interpretation of these results difficult. These investigators were aware of the potential problem of metals in the pathway of the RFR and claimed to have mitigated it by using thin (0.01-in.), insulated, implanted stainless steel electrodes. It is unlikely that

this reduced the artifacts significantly, if at all, because the thickness of the metal was still much greater than the metallic "skin depth," and also because using thinner electrodes actually increases the length-to-thickness ratio and increases the field enhancement (NAS, 1979). They also stated that "under everyday conditions, the EEG patterns of rabbits are quite variable. The animals oscillate between sedation and arousal unpredictably." This variability is another potential source of error in any experiments on the EEG of rabbits.

Chou et al. (1982) used implanted carbon electrodes to avoid the artifactual problems associated with metal ones. Two groups of rabbits (six animals/group, three males, three females) were exposed to 2.45-GHz, 1.5 mW/cm^2 RFR for 2 hr daily for 3 months. One group received CW-, the other pulsed RFR (10 microseconds, 100 pps, 1.5 W/cm^2 pulse power density). A similar group of six animals was sham-exposed. No significant differences in EEG and evoked potentials were observed at the end of 3 months.

Chou and Guy (1979a) implanted a carbon-loaded Teflon electrode in the subcortex of the rabbit and examined the EEGs before and during exposure to 2.45-GHz RFR at 100 mW/cm^2 (SAR in the hypothalamus of about 25 W/kg). There was no obvious RFR interference picked up by the electrode, and no obvious differences were found between the preexposure and RFR-exposure EEGs.

Kaplan et al. (1982) reported that, from the beginning of the second trimester of pregnancy, 33 squirrel monkeys were exposed for 3 hr/day in special cavity/cage modules to 2.45-GHz pulsed RFR at whole-body mean SARs equivalent to those resulting from plane-wave exposure to 0.1, 1, and 10 mW/cm^2. Eight pregnant monkeys were sham-exposed. Eighteen of the RFR-exposed mothers were exposed with their offspring for an additional 6 months after parturition, and then their offspring were exposed alone for another 6 months after weaning. No statistically significant differences were found between exposed and sham-exposed adults nor between exposed and sham-exposed offspring in resting EEG and photically driven EEG parameters. (No chronically attached or indwelling electrodes were used.)

Rosenstein (1976) exposed one group of eight female rats to 10 mW/cm^2 at 425 MHz for 4 hr/day from the 12th day after breeding until parturition, and another group of 12 dams to 5 mW/cm^2 at 2.45 GHz for 4 hr/day from the 6th day after breeding until parturition. The offspring were then exposed for 92 days. Control groups with equal populations were used for each frequency. Evaluation of the EEGs and the visual ERs of the offspring at 140 days of age indicated no significant difference between the exposed and control groups. (Again, indwelling electrodes were not used.)

In summary, the use of indwelling metallic electrodes in studies of the effects of RFR on the EEG and/or evoked potentials may be questioned as a procedure likely to introduce artifactual effects in the preparation under study, as well as in the recordings themselves. These artifacts may be minimized by use of electrodes appropriately designed from high resistivity materials. Experiments in which such specially constructed electrodes were used, or in which electrodes were applied after exposure, showed no evidence of statistically significant differences in EEGs or evoked responses between control and RFR-exposed animals.

6.6 Effects on Behavior

The very large number and variety of behavioral studies in animals exposed to RFR precludes a detailed review of each study. The papers reviewed in this section were selected as representative of the types of behavioral investigations conducted, which include studies of RFR perception; RFR effects on reflex activity, learning, and performance of trained tasks; interactive effects of RFR and drugs on behavior; and RFR alteration of behavioral thermoregulation.

McRee et al. (1979), Shandala et al. (1979), and Shandala (1980) are summaries of recent studies on behavioral effects being conducted under an ongoing cooperative program between the USSR and the United States on the biological effects of RFR. The Soviet studies (Shandala et al., 1979; Shandala, 1980) evaluated the effects on rats of 2,375-MHz exposures at 0.005, 0.01, 0.05, and 0.50 mW/cm^2 for 1 to 3 months by measuring parameters giving "characteristics of the inborn forms of behavior (investigative behavior, feeding behavior, and aggressiveness), conditioned reflex activity (the rate of development of conditioned reflexes), effector and receptor behavioral reactions (locomotor activity, working capacity, and skin sensitivity to irritation by electricity)." For all of these parameters, the results presented showed differences between exposed and control animals after approximately 10 days of exposure. The Soviet investigators concluded that "even exposure of animals to 10 microwatts/cm^2 results in disturbance of various forms of ... behavior ... (which) makes it possible to assume the presence under these conditions of a general suppression effect of the radiation on the function of the central nervous system." Unfortunately, insufficient detail is provided in the report to assess the validity of these claims for effects at such low levels.

The U.S. studies (McRee et al., 1979) reported on related parameters under higher exposure power densities (0.5 to 30 mW/cm^2) for exposure durations that varied from acute (55 min) to chronic (92 days). Measurements of reflex development (startle response, righting reflex) and age of eye opening showed no differences between exposed and control animals for power densities up to 10 mW/cm^2 for the continuing exposure conditions. For the same subjects, no consistent effects on locomotor activity were found at 120 and 240 days of age. In another of the U.S. studies, effects of a single exposure (55 min

or 15 hr) on performance of a fixed ratio schedule of reinforcement were studied. The results indicated that performance decreased at power densities from 5 mW/cm^2 and up, but not at 0.5 or 1 mW/cm^2. Conflicts between Soviet claims of effects at low (equal to or less than 0.5 mW/cm^2) power densities under long-term exposure conditions and the absence of similar effects in the same power density range in the studies of U.S. researchers recur frequently in the RFR bioeffects literature.

The RFR hearing effect discussed in Section 6.5.1 is, by definition, perception of RFR. Other studies of modulated RFR have been conducted to determine whether perception can serve as a behavioral cue.

Frey and Feld (1975) showed that rats exposed to 1.2-GHz RFR pulsed at 100 to 1,000 pps would tend to avoid the radiation by moving into an RF-shielded area. The authors interpreted this behavior as indicating that the RFR produced a noxious stimulus, but the noxious stimulus was probably the RFR hearing effect. This interpretation is substantiated by the observation of avoidance behavior at average power densities of 0.6 and 0.2 mW/cm^2 for the 100 and 1000 pps exposures, respectively, although exposure to 2.4 mW/cm^2 CW RFR did not produce any avoidance behavior.

King et al. (1971) showed that 2.45-GHz RFR, modulated at 60 and 12 Hz, could serve as a cue to warn rats of impending electrical shock. The effect had a threshold of 1.2 to 2.4 W/kg. Because the study was conducted in a cavity system, plane-wave power densities were not available; however, a reasonable estimate is that the power-density threshold would be between 2.5 and 6 mW/cm^2.

Several other RFR-perception studies were designed to determine whether animals would avoid CW RFR as a noxious stimulus. A first approach involved studies of orientation and thermoregulation. Monahan and Ho (1977) observed that mice exposed for various periods to 2.45-GHz RFR at various power densities and ambient temperatures were able to orient themselves to reduce the percentage of microwave energy absorbed. The effect would occur at ambient temperatures between 20 and 35 deg C, with a fortyfold reduction in SAR necessary to cause the effect at 35 deg C compared with that necessary at 20 deg C.

In a subsequent study, Gage et al. (1979a) observed rats and mice by closed-circuit TV during exposure to 2.45-GHz RFR and failed to observe orientation effects. However, comparison of the power levels and ambient temperatures in the two experiments suggests that the power density and ambient temperatures used by Gage et al. may have been too low to produce the orientation behavior.

Studies specifically designed to examine thermoregulatory behavior in the presence of 2.45-GHz RFR were performed with rats by Stern et al. (1979), and with squirrel monkeys by Adair and Adams (1980a) and Adair (1980b). For the rats, behaviorally significant levels of

heating (as determined from alterations in the rate at which the animals turned on an infrared heating lamp while they were in a cold environment) occurred at power densities ranging from 5 to 20 mW/cm^2. For the squirrel monkeys, alterations in thermoregulatory behavior (controlling the environmental temperature by adjusting the rate of warm air flowing into a cold chamber) occurred at a threshold of approximately 6 to 8 mW/cm^2. Exposure to 4 mW/cm^2 did not modify thermoregulatory behavior no matter how long it lasted. The 10-mW/cm^2 exposure produced a response within 5 min of onset. Both of these results were in highly trained animals and occurred in the absence of measurable changes in other parameters such as colonic, rectal, or skin temperatures.

Additional studies on thermoregulation were carried out by Ashani et al. (1980), who administered anticholinesterase drugs to rats and exposed or sham-exposed them to 10-mW/cm^2 RFR. RFR-exposed, drug-treated animals showed a statistically significant enhanced hypothermic response when compared with sham-exposed control groups. The mechanisms underlying this paradoxical enhancement of decrease in body temperature with exposure to RFR are presently only speculative.

A second approach to the question of RFR avoidance (Monahan and Henton, 1979) involved exposing mice to 2.45-GHz RFR at an average SAR of 45 W/kg (90 to 100 mW/cm^2), coupled with a sonic cue. The mice learned to turn off the RFR by interrupting a beam of light; this was interpreted as escape behavior. Carroll et al. (1980) found that in the absence of other sensory clues, rats failed to learn to escape from an intense 918-MHz field (SAR of 60 W/kg, or approximately 125 mW/cm^2), whereas positive control rats motivated by electric shock to the feet and tail all learned to escape. The authors speculated that without timely sensory feedback (slow because of large thermal time constants of mammalian tissues), stimulus-response association would be impaired in the RFR-exposure situation. If exposure was signalled by light (photic cuing), escape response acquisition was reliably demonstrated, but was less rapid and efficient than for shocked animals (Levinson et al., 1982). In one study conducted with human subjects (Justesen et al., 1982), comparative sensory thresholds were determined using 2.45-GHz RFR and far-infrared radiation (IR). The pooled mean RFR threshold of 26.7 mW/cm^2 for warning was 15 times greater than the 1.7 mW/cm^2 for IR. Although the same set of superficial thermoreceptors was being stimulated, the more deeply penetrating, more diffusely absorbed RF energy was less efficient than IR as a sensory stimulant.

A third approach involved pairing exposure to RFR with consumption of sucrose solution and subsequently testing for avoidance of the sucrose. Monahan and Henton (1977) produced no evidence that the sucrose was associated with a noxious experience. In a subsequent test (Sessions, 1979), saccharin (instead of sucrose) was paired with RFR exposure of rats. The animals developed aversion to the saccharin (indicating association with a noxious experience) at a power density of 41 mW/cm^2 or greater, but not at lower levels.

All of the authors cited above who tested for avoidance behavior have interpreted their results as indicating that RFR is a noxious or unpleasant stimulus to the animal. However, the orientation behavior observed by Monahan and Ho (1977) appears to be related to thermoregulatory behavior of the animals, and the saccharin aversion appears to require relatively high power densities of the RFR. The escape by interrupting the beam of light (Monahan and Henton, 1979) also involved relatively high power densities, and in addition, appeared to require the coupled sonic cue. Levinson et al. (1982) observed that rats exposed to nearly lethal levels of RFR in the absence of other cues (e.g., photic cues) made no attempt to escape, even though the means of escape were readily available. Overall, it can be concluded that, as demonstrated by Thomas et al. (1982), pulsed or otherwise modulated RFR can be perceived readily by animals at moderate-to-low power densities, but that CW RFR is, at best, an extremely feeble perceptual cue.

Many studies have been conducted on the effects of RFR on the performance of trained tasks. Animals studied have been rats, rhesus monkeys, and squirrel monkeys. Acute exposures at power density levels ranging from 10 to greater than 100 mW/cm^2 (D'Andrea et al., 1977; Lin et al., 1977; Sanza and de Lorge, 1977; McAfee et al., 1979a; Scholl and Allen, 1979; de Lorge, 1979, 1980; de Lorge and Ezell, 1980) resulted in somewhat inconsistent results. The overall conclusion is that RFR will suppress performance of learned tasks, but that the effect depends on power density, duration of exposure, animal species, and the demand characteristics of the behavior. The studies of de Lorge and Ezell (1980) indicate that suppression of learned behavior tasks by exposure to high levels of RFR depends on the amount and distribution of energy absorbed by the animal.

Chronic exposure to RFR has also been reported to disrupt learned behavior in animals. Lobanova (1974) reported a weakening of conditioned reflexes in rabbits and rats, as shown by increased latency or absence of response and failure to recognize the conditioned stimulus. Power density levels in her studies were 1 to 10 mW/cm^2.

Mitchell et al. (1977) reported that rats showed an increase in locomotor activity and a disturbance of differential responding to operant behavior over a 22-week exposure at 2.3 W/kg (5 to 6 mW/cm^2). Lebovitz (1981), however, found no disturbance in lever-pressing performance in rats chronically exposed at up to 2.6 W/kg.

Studies of the effect of RFR on learning are more recent and fewer. Schrot et al. (1980) investigated the effects of RFR on the ability of rats to learn a novel sequence of responses to obtain food reinforcement. Decrements of learning occurred at power densities of 5 and 10 mW/cm^2, but not at 1 mW/cm^2 or less. Gage et al. (1979b) exposed rats daily for 4 hr to 50 mW/cm^2 from day 6 of gestation until the age of 126 days, and found no effect of the RFR on the learning of two tasks during the last 2 weeks of exposure.

Several behavioral studies of interaction of RFR and drugs that affect the CNS have been conducted on rats (Monahan and Henton, 1979; Thomas and Maitland, 1979; Thomas et al., 1979; Maitland, 1979). In the first study, chlordiazepoxide was found to interfere with avoidance responses to 2.45-GHz CW RFR at a mean SAR of 45 W/kg, but chlorpromazine and d-amphetamine gave variable results. In the other studies, the effect of a drug alone on animal behavior and then the effect of the drug and RFR together were tested. Pulsed 2.45-GHz RFR at an average power density of 1 mW/cm^2 (SAR of 0.2 W/kg) was found to enhance the effects of dextroamphetamine, chlordiazepoxide, and pentobarbital. An interesting aspect of these studies, taken together, is that the drugs have pharmacologically different and opposite properties. Dextroamphetamine is a CNS stimulant, whereas chlordiazepoxide and pentobarbital are CNS depressants, but the RFR enhances the effect in either case.

Thomas et al. (1980) extended their work on chlordiazepoxide to include the interactive effects between RFR (pulsed 2.8 GHz) and chlorpromazine, and between RFR and diazepam. In contrast to the findings with chlordiazepoxide, exposure to 1 mW/cm^2 of RFR in conjunction with either chlorpromazine or diazepam did not produce any alterations in the behavioral dose-effect functions. Diazepam and chlordiazepoxide are in the same class of drugs, whereas chlorpromazine is in a different class. Therefore, pharmacological activity or classification is not sufficient to predict synergistic or antagonistic effects with low-level RFR exposure.

In summary, some of the behavioral studies seem to have originated from studies in the USSR claiming that RFR had direct effects on the CNS at low power densities. The association is discussed by King et al. (1971). Evidence to support this claim from neurophysiological studies in the United States is meager, and the behavioral evidence also does not generally support the claim. The studies on RFR as a noxious stimulus do not show that the animals can perceive RFR as such. The radiation avoidance observed appears to be part of the thermoregulatory behavior of animals; when the environment is cold, animals will use RFR as a source of warmth (Stern et al., 1979). In addition, Adair and Adams (1980b) showed that RFR enhanced dermal vasodilation in the squirrel monkey (a thermoregulatory response). The effect appeared to be mediated by the CNS, but a minimum of 8 mW/cm^2 was required to elicit the response. Disruption of performance or learning appears to have rather high power density thresholds. Interaction of RFR with certain drugs affecting the CNS appears to be the most sensitive behavioral response to RFR, occurring in some cases at power densities of approximately 1 mW/cm^2, but even these studies do not prove a direct effect of RFR on the CNS. Overall, the behavioral studies do not indicate a special effect of RFR on the nervous system, and the mechanism of most of the results remains conjectural.

6.7 Endocrinological Effects

Exposure of animals to RFR has produced somewhat inconsistent effects on the endocrine system of mammals. In general, the effects produced appear to be related to either the heat load associated with the RFR or the stress induced in the animals by the RFR and, possibly, other experimental circumstances. Some effects also appear to be related to alteration of the circadian rhythm by RFR. There do not appear to be any effects clearly demonstrated to be associated with nonthermogenic stimulation of the endocrine system or the associated parts of the CNS.

Because of the known sensitivity of the testes to heat, several investigations of the effects of RFR on gonadal function have been conducted. Prausnitz and Susskind (1962) exposed mice to 9.27-GHz RFR at 100 mW/cm^2 for 4.5 min/day (which increased mean body temperatures by 3.3 deg C) for 5 days/week over 59 weeks. Testicular degeneration was found in 40% of the RFR-exposed and in 8% of the control mice that had died during the course of the experiment. In an abstract, Cairnie and Harding (1979) reported that exposure of mice to 2.45-GHz RFR at 20 to 32 mW/cm^2 for 16 hr/day for 4 days had no effect on sperm count or percentages of abnormal sperm. No endocrinological measurements were reported for either study.

Saunders and Kowalczuk (1981) exposed the rear halves of anesthetized mature male mice to 2.45-GHz RFR in a waveguide system for 30 min. Half-body SARs ranging from 18 to 75 W/kg were estimated from measurements of forward, reflected, and transmitted powers. The corresponding rectal temperatures at the end of exposure ranged from 35.3 to 42.2 deg C. Other anesthetized mice were sham-exposed. Their mean rectal temperature was 32.6 deg, about 4-5 deg C lower than for conscious mice. For comparison, the rear halves of still other anesthetized mice were inserted for 30 min in a copper well heated by a water bath to 37, 41, 43, or 45 deg C, which resulted in rectal temperatures from 36.4 to 40.7 deg C. Six days after treatment, sections of testes were scored for cell damage and sperm counts were made. Extensive degeneration of the spermatogenic epithelium was evident for RFR exposure at 75 W/kg and for direct heating to 45 deg C. At SARs of 57 and 46 W/kg or temperatures of 43 and 41 deg C, marked depletion of spermatids and spermatocytes but not spermatogonia was observed. At the lower SARS (37, 30, 18, and 0 W/kg) or a temperature of 37 deg C, no effects were seen. Temperature-sensing probes were also implanted in the testes of other groups of mice, and testicular temperatures were related to SAR values. Such measurements of testicular temperature indicated the existence of a threshold of about 39 deg C for depletion of spermatocytes and of about 41 deg C for 50% cell death after 6 days of RFR exposure or direct heating. The corresponding SARs for these two thresholds were 20 and 30 W/kg, respectively.

Lancranjan et al. (1975) reported that men occupationally exposed to RFR in the 3.6- to 10-GHz range at power densities of tenths to hundredths of a mW/cm^2 for 1 to 17 years (a mean of 8 years)

showed slightly reduced sperm counts, but normal plasma levels of 17-ketosteroid and gonadotropic hormones.

Czerski et al. (1974) presented evidence that exposure to RFR could alter circadian rhythms. They exposed mice to 2.95-GHz RFR at 0.5 mW/cm^2 for 4 hr in either the morning or the evening and detected shifts in amplitude and phase of the circadian rhythm of mitosis (cell division) of precursor or "stem" cells in the bone marrow that differentiate and mature into various types of cells involved in immunologic functions.

Mikolajczyk (1974, 1976) exposed male rats to 2.9-GHz RFR at 10 mW/cm^2 for 6 hr/day, 6 days/week over 6 weeks. Control rats were sham-exposed. Extracts of the pituitary gland (hypophysis) of these rats were then assayed for follicle-stimulating hormone (FSH) and growth hormone (GH) in female rats that had been hypophysectomized, and for luteinizing hormone (LH) in hypophysectomized male rats. No statistically significant differences in levels of FSH or GH between RFR- and sham-exposed animals were found. However, significantly higher levels of LH were reported for the RFR-exposed rats.

Magin et al. (1977a, 1977b) surgically exposed the two thyroid glands of anesthetized dogs and used a diathermy unit and special applicator to irradiate one gland in vivo with 2.45-GHz RFR for 2 hr at 72, 162, or 236 mW/cm^2. The corresponding SARs in the gland were 58, 131, and 190 W/kg, and the resulting temperatures therein were about 39, 41, and 45 deg C. The other thyroid gland served as control. The release rate of the hormone thyroxine (T-4) into the blood was measured for both glands and was found to be higher by factors of 150, 350, and 1000%, respectively, for the gland exposed to the RFR. In addition, the blood flow rate in that gland was higher by 140 and 170% for temperatures of 41 and 45 deg C, respectively.

Lotz and Michaelson (1977) surgically removed the hypophysis of rats and exposed the rats to 2.45-GHz RFR for 60 min at 50, 60, or 70 mW/cm^2 (mean SARs of 8.0, 9.6, or 11.2 W/kg). Assays of plasma samples for corticosterone (CS) indicated the absence of the increases in level found for intact and sham-hypophysectomized rats that were exposed for 60 min at 60 mW/cm^2. In addition, intact rats were treated with dexamethasone before exposure to RFR. For exposures at 50 mW/cm^2 for 60 min, the increases in CS level found in sham-injected rats exposed to the RFR were absent. These results indicate that the adrenal gland is not primarily stimulated by exposure to RFR, but is stimulated secondarily by ACTH secreted by the pituitary during exposure.

Lotz and Michaelson (1978) "gentled" rats for 2 weeks and then exposed groups of four rats each to 2.45-GHz RFR for 30 or 60 min at power densities in the range from 0 (sham) to 60 mW/cm^2 or for 120 min at 0 to 40 mW/cm^2. (The mean SARs were 0.16 W/kg per mW/cm^2.) Plots of colonic temperature versus exposure duration

at the various power densities showed a small but statistically significant temperature increase after 30-min exposure at 13 mW/cm^2; exposures for the same duration to higher power densities produced temperature increases approximately proportional to the power density. Plasma CS levels were rather variable. At each power density, increases in mean level with exposure duration were discernible, but the results were not significantly different from baseline values for durations of up to 120 min at 13 mW/cm^2, up to 60 min at 20 mW/cm^2, and for 30 min at 30 mW/cm^2; these results are indicative of a threshold pattern of response. All other increases were significant. The increases in CS level were highly correlated with the increases in colonic temperature. Estimates of the threshold SARs were 4.8 to 8.0 W/kg for 60-min exposure and 2.4 to 3.2 W/kg for 120-min exposure, with the latter range being somewhat less than half the resting metabolic rate for the rat. A major point demonstrated in this investigation is the necessity for gentling the rats and also equilibrating them for at least 3 hr prior to RFR or sham exposure, to minimize the non-RFR stresses imposed by the experimental situation.

GH levels for similarly treated rats were measured by Lotz et al. (1977). For 30- and 60-min exposures, GH levels were lower than control values only at 50 and 60 mW/cm^2. For 120-min exposures, the GH levels were lower than those of controls at 13 mW/cm^2, and decreased progressively with increasing power density.

In an abstract, Travers and Vetter (1978) reported exposing rats to 2.45-GHz RFR at 0, 4, or 8 mW/cm^2, 8 hr/day for 0, 7, 14, or 21 days. At 8 mW/cm^2, significant, highly correlated decreases in T-4 and thyroid-stimulating hormone (TSH), as well as changes in several serum-protein levels, were observed; these results suggest that the depressed thyroid activity results from decreased TSH secretion by the hypothalamus in response to RFR exposure.

Lu et al. (1977) subjected rats first to a 2-week gentling period, and then sham-exposed or exposed them to 2.45-GHz RFR at 1, 5, 10, or 20 mW/cm^2 for 1, 2, 4, or 8 hr starting at the same hour on the same day of the week. After treatment, each rat was decapitated, blood was collected, and body mass and rectal temperature were measured. In addition, the pituitary, adrenal, and thyroid glands were weighed. The levels in blood serum of CS, T-4, and GH were assayed.

For the sham-exposed rats, mean rectal temperatures increased with treatment duration, an effect ascribed to circadian rhythmicity. The rectal temperatures of the RFR-exposed rats varied in an inconsistent manner. For example, for the 1-hr exposures, increases in mean temperature were noted for the groups exposed at 5 and 20 mW/cm^2, but not for those exposed at 1 and 10 mW/cm^2. The CS level increased with treatment duration for the sham-exposed rats and was correlated with the rectal temperature increase. Increases of CS level occurred in the RFR-exposed rats but were not significantly correlated with rectal temperature. The only significant changes in T-4 level were an

increase for 4-hr exposure at 1 mW/cm^2 and decreases for 4-hr and 8-hr exposures at 20 mW/cm^2. No significant changes in GH level or in body mass or pituitary mass due to RFR exposure were noted. Several statistically significant alterations of thyroid and adrenal masses were observed, but no obvious pattern related to power density, exposure duration, or circadian rhythmicity was apparent. In view of the large variations in values for each endpoint in the rats sham-exposed for various durations (which presumably resulted from unknown differences in residual stress reactions after gentling, as well as circadian variations), it is difficult to discern any clear-cut effects ascribable to RFR exposure per se in these studies.

In another study reported in an abstract (Lu et al., 1979), acclimated rats were sham-exposed or exposed to the same frequency for 4 hr at 0.1, 1, 10, 25, or 40 mW/cm^2, and the CS levels were assayed. The results showed decreases for 0.1 and 1 mW/cm^2, no significant changes for 10 and 25 mW/cm^2, and increases at 40 mW/cm^2. The authors ascribed the decreases at the lower power densities to RFR-induced circadian rhythm changes and the increases at the higher power density to RFR-induced stress in the animals.

In a still later study, Lu et al. (1980b) exposed gentled rats to the same frequency at power densities ranging from 1 to 70 mW/cm^2 (equivalent SARs of 0.21 to 14.7 W/kg) for periods ranging from 1 to 8 hr at an environmental temperature maintained at 24 deg C. Sham-exposed rats were used as controls. After treatment, the rats were decapitated, colonic temperatures were taken, and blood was collected for assays of T-4, TSH, GH, and CS. For exposures of 1 hr, colonic temperatures increased with power density at 20 mW/cm^2 and higher, but consistent elevation of serum CS did not occur below 50 mW/cm^2. 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/cm^2, but they were not consistently related to power density values. For sham exposures and exposures at 1-20 mW/cm^2 for longer durations (2-8 hr), the results were rather equivocal, presumably because such exposures encompassed significant portions of the circadian cycle. Specifically, in the sham-exposed rats, the level of T-4 did not change significantly with exposure duration, and significant increases of CS and decreases of TSH and GH were seen, so it was difficult to discern consistent differences in these hormones ascribable to RFR exposure.

The most sensitive parameter measured proved to be the colonic temperature. For example, for rats exposed at 20 mW/cm^2, colonic temperature increases were consistent for any exposure duration, and smaller increases were noted for exposures at 10 mW/cm^2 for 2 hr and at 1 mW/cm^2 for 4 hr.

The investigators suggest that the divergent responses may be due to two different mechanisms that are dependent on RFR intensity and the timing of the exposures relative to circadian rhythms.

In a review article, Lu et al. (1980a) discuss evidence for the existence of threshold intensities for various RFR-induced neuroendocrine effects. They indicate that such thresholds are dependent on the intensity and duration of exposure and can be different for each endocrine parameter.

Abhold et al. (1981) exposed rats to 2.45-GHz CW RFR for 8 hr (continuously) at 2 or 10 mW/cm^2 (SARs of 0.44 or 2.2 W/kg with the long body axis of the rat parallel to the electric component of the RFR). Other rats were sham-exposed for the same period, and still others served as untreated controls. Within 15 min after treatment, the rats were euthanized and their blood was assayed for serum T-4, triiodothyronine (T-3), and T-3 uptake. In addition, serum CS concentrations were measured. The results indicated that concentrations of T-4, T-3, and T-3 uptake were not altered by the treatments. However, the rats that were sham-exposed or exposed to RFR at 2 mW/cm^2 had higher levels of CS than for the untreated rats, whereas the rats exposed at 10 mW/cm^2 had values similar to those of the untreated rats. As in the studies of Lu et al. (1977, 1979), the changes observed were more likely ascribable to stress and other factors in the experimental protocols than the RFR exposure.

The involuntary thermoregulatory mechanisms of warm-blooded animals have been shown to respond to RFR exposure of such animals. In an abstract, Adair (1980a) reported exposing squirrel monkeys to 2.45-GHz CW RFR for 10 min or 90 min in relatively cool ambient temperatures of 15, 20, or 25 deg C. The power densities ranged from 2.5 to 10 mW/cm^2 (SARs from 0.4 to 1.5 W/kg). Skin and rectal temperatures were monitored continuously during exposure. The metabolic heat production was calculated from the oxygen deficit in the expired air of each monkey. At all three ambient temperatures, 10-min exposures of two monkeys to a threshold power density of 4 mW/cm^2 and one monkey to 6 mW/cm^2 reliably initiated a reduction of their metabolic heat production, and the magnitudes of the reduction were linear functions of the power density above the threshold values. At exposure termination, the metabolic heat production often rebounded sharply and overshot normal levels. For the 90-min exposures at 20 deg C, the initially large reduction of metabolic heat production gradually diminished toward normal levels, so as to ensure precise regulation of internal body temperature at the normal value.

Adair (1981) also exposed four squirrel monkeys to 2.45-GHz CW RFR in warm ambient temperatures ranging from 32 to 35 deg C. After an initial 90-min or longer equilibration period, each monkey was exposed for 10-min periods to power densities in an increasing sequence from 2.5 to 20 mW/cm^2, with sufficient time between exposures for reequilibration. The rectal temperature and the skin temperature at the abdomen, tail, leg, and foot were monitored continuously. As in the previous investigation, the metabolic heat production was determined from the oxygen deficit in the expired air. In addition, thermoregulatory sweating from the foot was determined by sensing the

dewpoint of the air in a special boot over the foot. The results indicate that at ambient temperatures below about 36 deg C, at which sweating in a sedentary monkey may occur spontaneously, the threshold power density (or SAR) for initiating thermoregulatory sweating from the foot decreased with decreasing ambient temperature.

Adair and coworkers also investigated behavioral patterns toward thermoregulation in trained squirrel monkeys in response to RFR exposure, as discussed in Section 6.6.

Smialowicz et al. (1981a) rendered unrestrained, unanesthetized mice hypothermic by injecting them with 5-hydroxytryptamine (5-HT) in a controlled environment of 22 deg C and 50% relative humidity. Mice injected with saline were used as controls. Colonic temperatures were measured prior to injection. Following injection, groups of mice were exposed to 2.45-GHz CW RFR for 15 min at 10, 5, or 1 mW/cm^2 (equivalent SARs of 7.2, 3.6, and 0.7 W/kg) or were sham-exposed, after which their colonic temperatures were measured again. The experiments were performed with BALB/C and CBA/J mice. For saline-injected mice of either type, there were no significant rectal-temperature differences between mice exposed at 10 mW/cm^2 and sham-exposed mice. For BALB/C mice rendered hypothermic with 5-HT, rectal temperatures were significantly higher for those exposed at all three power densities than those sham-exposed, and the differences increased monotonically with power density. The results for the CBA/J mice were similar, but the increases were statistically significant only at 5 and 10 mW/cm^2. The investigators conclude that subtle heating by RFR can alter the thermoregulatory capacity of mice rendered hypothermic by 5-HT, whereas the colonic temperature of normal (saline-injected) mice was not significantly altered by exposure at 10 mW/cm^2.

In summary, although some effects of RFR exposure on the endocrine system appear to be relatively straightforward and predictable from physiological considerations, other, more subtle effects require further study, notably those related to the interactions among the pituitary, adrenal, thyroid, and hypothalamus glands and/or their secretions. Part of the problem in interpreting results appears to arise from uncertainties regarding stress mechanisms and accommodations thereto. Animals placed in novel situations are much more prone to exhibit stress responses than animals that have been adapted to the situation. However, there may be large variations in adaptation among animals in a given situation or among experimental situations in different laboratories. Moreover, the use of sham-treated controls may not always reduce the problem. A recent review of the effects of RFR on the endocrine system was published by Michaelson (1982).

Because the reported effects of RFR on the endocrine systems of animals are largely ascribable to increased thermal burdens, stresses engendered by the experimental situation, or both, there is no evidence that such effects would occur in humans exposed to RFR at power densities below 1 mW/cm^2.

6.8 Immunological Effects

Many reports indicate that RFR has definite effects on the immune system of mammals. Most of the reported effects were detected after exposure at power density levels of about 10 mW/cm^2 and higher; a few have been detected following exposure to power densities as low as about 0.5 mW/cm^2; and in some cases, effects obtainable with the higher power-density range were not found at lower power densities. In most studies, the mechanisms for the effects seen were not investigated, and the various reports are somewhat inconsistent. Because of the complexity of the immune system and the variety of test procedures used, the representative studies discussed in this subsection are grouped into appropriate categories.

6.8.1 In Vitro Studies

An important question is whether human or animal lymphocytes (a type of white blood cell of key importance in the immune system) can be stimulated by RFR exposure to transform into lymphoblasts (mitotically active form of lymphocytes) and undergo cell division (mitosis). In vitro studies directed toward this question are those in which lymphocytes are removed from the body, cultured, exposed to RFR (or exposed, then cultured), and examined for RFR-induced effects. Usually such cells are cultured in the presence of a mitogen (an agent, usually chemical) that stimulates blastic transformation (i.e., lymphocyte to lymphoblast) and cell division.

One of the early studies was by Stodolnik-Baranska (1967, 1974), who cultured specimens of human lymphocytes, added the mitogen phytohemagglutinin (PHA) to one set of specimens, and exposed groups from both sets to 2.95-GHz pulsed RFR at an average power density of either 7 or 20 mW/cm^2 for various durations. The results for the PHA-stimulated cultures exposed at the higher power density showed no significant changes in percentages of blastoid forms, but there were significant decreases in percentages of lymphocytes and increases in mitotic index correlated with exposure duration (up to 40 min). The investigator indicated that similar results were obtained for exposures at the lower power density (for durations up to 4 hr), but presented no data. Regarding the cultures without PHA, she stated that RFR exposure induces the appearance of blastoid forms and macrophage-like (scavenger) cells; she illustrated the point with one micrograph but gave no data.

As part of a larger study primarily involving exposure of animals, Czerski (1975) endeavored to repeat the experiments of Stodolnik-Baranska with human lymphocytes; he encountered difficulties in obtaining reproducible results. Czerski's 1975 work is discussed on p. 133 of Baranski and Czerski (1976), who implicated uncontrolled temperature increases in the specimens (which were not cooled during exposure). They stated that "exposures at power densities between 5 and 15 mW/cm^2, if continued till the moment when the temperature of

the medium attained 38 deg C, could induce lymphoblastoid transformation; no such phenomenon could be obtained by exposure below 5 mW/cm^2."

Smialowicz (1976) prepared suspensions of mouse-spleen cells and exposed them to 2.45-GHz CW RFR at 10 mW/cm^2 (SAR of about 19 W/kg) for 1, 2, or 4 hr. Similar cell suspensions held at 37 deg C (without RFR exposure) for the same periods served as controls. After either treatment, specimens were cultured with or without one of four different mitogens (including PHA). Although changes in the extent of blastic transformation with exposure duration were seen, there were no statistically significant differences between corresponding values for each duration from RFR-exposed and control specimens. This was true for the specimens not stimulated with mitogen and for those stimulated with any of the four mitogens. This investigator also measured the temperature and percentage viability of the specimens immediately after each treatment and found no significant differences in results between RFR-exposed and control specimens for each treatment period.

Lin et al. (1979b) prepared suspensions of colony-forming-units-in-culture (CFU-c) bone-marrow cells from mice, and exposed the suspensions to 2.45-GHz RFR for 15 min in a special fluid-filled waveguide system at 30 to 1000 mW/cm^2 (SARs of 60 to 2000 W/kg). The fluid of the system was maintained at 37 deg C. Similar suspensions were sham-exposed. Immediately afterward, there were no significant differences in the numbers of viable cells from sham-exposed suspensions and suspensions exposed to RFR at 500 mW/cm^2 (SAR of 1000 W/kg). Cell samples were then treated with a colony-stimulating factor, permitted to grow in an appropriate medium, and examined on days 5, 6, or 7 and 12, 13, or 14 following exposure. For samples examined on days 5-7, no significant differences were found between the number of colonies from sham-exposed samples and from the samples exposed at 30 mW/cm^2 (SAR of 60 W/kg). However, at higher power densities, the ratio of the number of colonies from RFR-exposed to sham-exposed samples was found to decrease with increasing power density. Similar results were obtained for days 12-14.

In a similar investigation, Ottenbreit et al. (1981) sham-exposed or exposed bone-marrow specimens from children with acute leukemia in remission or other disorders at 31, 62, 125, 250, 500, or 1000 mW/cm^2 for 15 min. As before, the fluid of the exposure system was held constant at 37 deg C. In this investigation, sample colonies from each treatment were stained to determine the subpopulations of cells. It was found that irrespective of sham or RFR exposure at any of the power densities, the cell colonies consisted of 86-90% pure neutrophils, with the remainders consisting of macrophages (0-3%), mixtures of neutrophils and macrophages (7-10%), and unclassifiable cells (1-2%). Cells treated with a colony-stimulating factor and grown were examined on days 6-7 and 12-14. Variations of the data among series of experiments performed under each set of conditions were quite large. Presumably for this reason, the results were expressed as the ratio of mean numbers of colonies from RFR-exposed specimens to mean

numbers of colonies from sham-exposed specimens in each series. The results showed no significant reductions in this ratio in either examination period for those exposed at 31 or 62 mW/cm^2 (SARs of 62 or 124 W/kg). Above the latter power density, the ratio tended to decrease with increasing power density.

To ascertain whether the ratio reductions were due to heating of the specimens by the RFR, one set of experiments was performed at 1000 mW/cm^2 with the fluid of the exposure system held at 7, 22, or 37 deg C, and another set at 37 or 41 deg C. Ratio reductions were obtained irrespective of the fluid temperature, a possible indication that the effect was not due to specimen heating by RFR exposure. However, the results for the two sets at 37 deg C were inconsistent, i.e., for the data taken at this temperature on days 6-7, the ratio for the second set was considerably different than that for the first set. Such large data variability may indicate the presence of uncontrolled experimental factors.

Sultan et al. (1981) in an abstract described the exposure of suspensions of B lymphocytes from normal mouse spleens to 2.45-GHz RFR for 30 min at 5, 10, 25, 50, or 100 mW/cm^2 (SARs of 0.45 W/kg per mW/cm^2) and at 37, 41, or 42.5 deg C. Cell suspensions heated to the same temperatures without RFR exposure served as controls. Immediately after treatment, the specimens were incubated for 9 min at 37 deg C with fluorescein-isothiocyanate-conjugated goat anti-mouse immunoglobulin (Ig) and tested by fluorescence microscopy for antigen-antibody capping. The results for the controls showed reduction of the percentage of capped cells from 90.1% at 37 deg C to 51.6% at 41 deg C and total inhibition of capping at 42.5 deg C, but no significant differences between RFR-exposed and control specimens held at the same temperature.

Sultan et al. (1982a) (abstract) reported similar results with cell suspensions exposed for 30 min to 147-MHz RFR amplitude modulated at 9, 16, or 60 Hz. The average power density ranged from 0.1 to 48 mW/cm^2. Again, capping inhibition increased with temperature and no significant differences were obtained between RFR-exposed and control specimens held at the same temperature. They also found that for temperatures not exceeding 42 deg C, cytotoxicity and capping returned to normal levels 2 hr after heat treatment.

Sultan et al. (1982b) (abstract) also exposed spleen cells taken from normal mice and from mice 3, 6, or 10 days after they had been immunized against herpes simplex. Exposures were for 1 hr to 147-MHz RFR amplitude modulated at 60 Hz at an average power density of 25 mW/cm^2. Both RFR-exposed and control suspensions were maintained at 37 deg C. Immediately following treatment, the cells were tested as effectors against herpes-simplex-injected and noninjected mouse sarcoma-virus-transformed fibroblast (SV3T3) cells. The T-lymphocytes taken 6 days after immunization showed maximal cytotoxic

activity. Again, exposure to RFR had no observable effect on the cytotoxic activity of T-lymphocytes or the cytolytic activity of natural killer cells.

6.8.2 In Vivo Studies: Acute Exposures

In most in vivo investigations involving acute (i.e., short-duration) exposures, animals were exposed one time for a period typically ranging from a few minutes to an hour at power densities high enough to produce substantial temperature increases in various tissues or organs or of the body as a whole. In general, the effects of such acute RFR exposure on the immune system appear to be stimulatory. The number of circulating lymphocytes in the blood increases, as does the ability of the immune system to manufacture antibodies to foreign substances. The number of cells involved in producing immune complement (a complicated series of interacting chemicals in the blood) also increases. The mechanisms of those effects are not completely understood, but in some cases they may be a secondary result of the stress induced in the animals by the RFR-produced heat or by other stresses, such as from handling.

Rotkovska and Vacek (1975) exposed mice to 2.45-GHz CW RFR at 10 mW/cm^2 for 5 min. Other mice were heated for 5 min in a ventilated chamber held at 43 deg C. Mean rectal temperatures increased by 2.3 and 2.5 deg C, respectively, for the two groups. The leukocyte (white blood cell) counts for the circulating blood of both groups increased, reaching maxima at 4 and 7 days after treatment for those exposed to RFR and at 4 days for those heated in the chamber. This effect was accompanied by increases in the numbers of nucleated cells in the spleen and the bone marrow of the femur over the same time period after treatment.

Krupp (1977a) exposed mice to 2.6-GHz RFR at 10, 15, or 20 mW/cm^2 for various durations. The mice were sensitized by inoculating them with sheep red blood cells (SRBC) at various times before and after exposure to the RFR, and the numbers of SRBC-antibody producing cells in the spleen were determined. The greatest increases in such cells (as compared with the values for sham-exposed, sensitized mice) were obtained when the mice were sensitized 4 hr after exposure to the RFR. The effect was obtained when the exposure conditions produced a 3 deg C increase in rectal temperature. In addition, the effect could be elicited by the administration of cortisone, instead of RFR exposure, implying that the increases were adrenal-mediated responses to thermal stress.

Huang et al. (1977) exposed Chinese hamsters to 2.45-GHz RFR for 15 min/day on 5 consecutive days at power densities ranging from 0 to 45 mW/cm^2 (SARs from 0 to 20.7 W/kg). One hour after RFR (or sham) exposure, blood was drawn and cultured for 1 day if not mitogen-stimulated or for 3 days if stimulated with PHA. Cultures not stimulated with PHA exhibited a variation of the Transformation Index (percentage of transformed cells relative to the total number) with

power density. The curve is in the shape of an inverted U; values peak at 30 mW/cm^2 and then gradually return to control values. Cell counts done when the blood was collected showed no net gain of lymphocytes from other sources, such as the lymph nodes or the spleen, and no significant changes in leukocyte differential counts; these counts support the contention that RFR does not cause lymphocytosis. For cultures stimulated with PHA, the mean value of the Mitotic Index (percentage of cells in mitosis relative to the total number of lymphocytes) diminished from 3% for controls to about 0.04% and 0.05% for the 30 and 45 mW/cm^2 exposure groups, respectively.

Huang and Mold (1980) also exposed mice to 2.45-GHz RFR for 30 min/day at 5 to 15 mW/cm^2 (SARs of 3.7 to 11 W/kg) for 1 to 17 days, after which the spleens were removed and cells therefrom were cultured for 72 hr with or without the T-cell mitogens PHA or Concanavalin A (Con A) or the B-cell mitogen lipopolysaccharide (LPS). Tritiated thymidine, a radioactively labeled substance whose uptake is an indication of the DNA synthesis involved in cell proliferation, was added 4 hr before the end of the culturing period. The cells were then harvested and assayed for thymidine uptake. Plots of uptake versus exposure duration (made from the data in the authors' Table 1) showed biphasic or cyclical responses for cells from both mitogen-stimulated and nonstimulated cultures from the RFR-exposed mice. The investigators suggested that such cyclical fluctuations could account for the differences in results from various laboratories. However, similar plots for the sham-exposed mice also showed cyclical fluctuations, evidently resulting from factors other than RFR, such as circadian rhythms and estrus cycle changes in female mice; therefore, the proliferative effects of RFR per se could not be ascertained. In another part of the study, RFR exposure at 15 mW/cm^2 for 5 days (30 min/day) did not diminish the cytotoxic activity of lymphocytes on leukemic cells injected after, or concurrently with, the last exposure.

Liburdy (1979) exposed mice to 26-MHz RFR at 80 mW/cm^2 (SAR of 5.6 W/kg) for 15 min. These exposures produced core (rectal) temperature increases of 2 to 3 deg C. For comparison, he heated mice in a dry-air oven at 63 deg C for the same period to obtain approximately the same increase in core temperature. (He also immersed mice in water at 41 deg C, but the rate of core temperature increase did not follow that for RFR exposure as closely as the rate for the warm-air treatment.) Lymphopenia (diminution of the numbers of lymphocytes) and neutrophilia (increase in the proportion of neutrophils) were evident in the RFR-exposed mice, effects that persisted for about 12 hr after exposure. The effects could be sustained and the recovery period prolonged by additional RFR exposures at 3-hr intervals. The effects were only slight for the mice heated in the oven. In addition, the effects were absent for mice exposed to 26-MHz RFR at 50 mW/cm^2 or to 5-MHz RFR at 800 mW/cm^2, both corresponding to 0.36 W/kg, or about one-sixteenth of the SAR used previously. Because heating may constitute a significant stress, this investigator determined the plasma corticoid levels, as a measure of such stress, after acute and chronic (longer term, lower level) RFR exposure, and found

about a threefold increase in corticoid level relative to controls, whereas acute and chronic warm-air heating produced only modest, statistically insignificant increases.

Liburdy (1980) injected mice with radioactively labeled spleen lymphocytes and sham-exposed or exposed the mice to 2.6-GHz CW RFR for 1 hr at 5 or 25 mW/cm^2 (SARs of 3.8 or 19 W/kg) immediately after injection. Other injected mice were subjected to warm, dry air at 63 deg C for the same duration. Rectal temperatures were monitored continuously. At 1, 6, or 24 hr after injection, the lungs, liver, spleen, and long bones of the rear legs were removed, and the relative populations of lymphocytes in these tissues were determined by scintillation counting. For positive controls, a group of mice, in lieu of RFR or warm-air treatment, was injected with a synthetic glucocorticoid previously reported to induce peripheral-blood lymphopenia and alterations in splenic T- and B-lymphocyte populations. Exposure at 25 mW/cm^2 produced a core temperature increase of 2 deg C, during the first 15 min, to a plateau of 39 deg C, the latter ascribed to thermoregulation; heating at 63 deg C yielded the same plateau but at a slower rate of rise. Exposure at 5 mW/cm^2 did not alter the core temperature. The lymphocyte counts indicated that normal lymphocyte migration patterns were obtained for the mice exposed at 5 mW/cm^2 or heated to 63 deg C. However, for the mice exposed at 25 mW/cm^2, a 37% decrease in the number of lymphocytes that normally migrate from the lungs to the spleen, and a threefold increase in the number of lymphocytes entering the bone marrow occurred. Qualitatively similar results were obtained for the steroid-treated group. The investigator suggests that RFR at relatively high levels (e.g., 25 mW/cm^2) can affect the immune system indirectly as a nonspecific stressor that induces steroid release.

Wiktor-Jedrzejczak et al. (1977) exposed mice to 2.45-GHz RFR in a waveguide at a mean SAR of 14 W/kg for either a single 30-min session or three such sessions, one per day, 3 days apart. Control mice were sham-exposed. After exposure, the spleens were removed and tested for various effects of the RFR. First, the relative numbers of T and B lymphocytes in the spleens of the RFR-exposed mice were compared with those in the control mice. The results indicated that the total numbers of T cells were unaffected by either the single-session or triple-session exposures. However, the single exposures produced statistically significant increases in the population of one subclass of B cells (complement-receptor-positive, or CR+) but not in another subclass of B cells (immunoglobulin-positive, or Ig+), whereas the triple exposures yielded increases in both types of B cells. Next, splenic cells from RFR- and sham-exposed mice were cultured after the addition of various T-cell-specific or B-cell-specific mitogens, and the numbers of cells undergoing blastic transformation were determined. Both the single and triple exposures yielded significant increases in blastic transformation of B cells but had insignificant corresponding effects on T cells. Last, groups of mice were inoculated with the antigen SRBC, which induces the production of antibodies

by B cells if T cells are also present, or with another antigen (DNP-lys-Ficoll) that does not require the presence of T cells for antibody production by B cells. The mice were then given triple-session RFR exposures or sham exposures, after which their spleens were removed and assayed for antibody production. RFR-induced decreases in response to both antigens were observed, but only the difference for SRBC was statistically significant.

Taken together, the results of Wiktor-Jedrzejczak et al. (1977) indicate that acute exposures to the thermogenic levels of RFR used can have weak stimulatory effects on splenic B cells but none on T cells.

Regarding possible mechanisms, the observed increases in the numbers of CR+ B cells and of B cells undergoing blastic transformation could be manifestations of either RFR-induced proliferation of the B cell populations, which would be consonant with the findings of Stodolnik-Baranska (1967, 1974) and Czerski (1975), or RFR stimulation of immature B cells already present. In a subsequent paper, Wiktor-Jedrzejczak et al. (1980) presented data that support the latter hypothesis. In a paper by Schlagel et al. (1980), coauthored by members of this group, results were presented indicating that the RFR-induced increases in CR+ B cells were dependent on genetic factors. Specifically, mouse strains having the histocompatibility $H\text{-}2^k$ haplotype showed marked increases in CR+ cells due to RFR exposure, whereas those bearing $H\text{-}2^a$, $H\text{-}2^b$, and $H\text{-}2^d$ haplotypes did not.

Sulek et al. (1980), in another paper from this group, reported on threshold values for this effect. They exposed groups of mice once to 2.45-GHz RFR at a mean SAR of 11.8 W/kg for 5 to 120 min or for 30 min at SARs from about 2 to 18 W/kg, and determined the numbers of CR+ cells on days 3 and 6 after exposure. They obtained significant increases in CR+ cells on day 6 for single exposures of 15 min minimum at 11.8 W/kg, and on day 3 (as well as 6) for single exposures of 30 min at a mean SAR of 5.0 W/kg, corresponding to a threshold energy absorption of about 10 J/g. (The values calculated from these specific SARs and exposure durations are 10.6 and 9.5 J/g, respectively.) They also found that multiple exposures at subthreshold values were cumulative if the exposures were done within 1 hr of one another. In addition, multiple exposures at subthreshold values spaced 24 hr apart did not increase the numbers of CR+ cells, even if the sum of the energy absorption values exceeded the threshold.

In a recent abstract, Schlagel and Yaffe (1982) presented more evidence that the RFR effect on CR+ cells is under genetic control. They found that the regulatory gene is on chromosome 5.

Smialowicz et al. (1981c) exposed mice 10-12 weeks old once to 2.45-GHz far-field CW RFR at 15, 20, 30, or 40 mW/cm^2 (SARs of 11, 14, 22, and 29 W/kg) for 30 min in an anechoic chamber having a controlled ambient temperature of 22 deg C and relative humidity of 50%.

(The authors state that the mice exposed at 40 mW/cm^2 were clearly under thermal stress and that a 60-min exposure at this power density is lethal.) Six days later, the percentage of CR+ spleen cells and the number of nucleated spleen cells were determined. No significant differences in these endpoints were found between sham-exposed mice and the mice exposed at any of the power densities. As the authors indicate, the negative results for CR+ cells is at variance with the findings of Wiktor-Jedrzejczak et al. (1977) and subsequent work by that laboratory (Schlagel et al., 1980; Sulek et al., 1980). On the assumption that older mice may be more responsive, Smialowicz et al. (1981c) exposed mice 14, 16, and 24 weeks old at 30 or 40 mW/cm^2 for 30 min. Only the 16-week-old group exposed at 40 mW/cm^2 yielded significantly higher percentages of CR+ cells and smaller numbers of nucleated spleen cells than sham-exposed mice of the same age. The authors hypothesize that the internal SAR distributions in the mice exposed in their anechoic chamber were considerably different than for the mice exposed at the same whole-body SARs in the waveguide system used in the other laboratory.

6.8.3 In Vivo Studies: Effects of Chronic Exposures on Immunological Parameters

In many investigations involving chronic (long-term) exposures of animals to RFR, changes in various components of the immune systems of usually healthy animals are sought, under the often tacit assumption that such changes could be detrimental (or perhaps beneficial) to the subjects exposed. Investigations of this kind are discussed in this section. Other in vivo investigations are directed toward determining whether chronic exposure to RFR actually alters the incidence or severity of diseases imparted to the subjects. Studies of the latter kind are described in the next section.

Czerski (1975) exposed 100 mice to pulsed 2.95-GHz RFR at an average power density of 0.5 mW/cm^2 for 2 hr/day, 6 days/week over 6 weeks, and another 100 mice over 12 weeks. After exposure, these mice were immunized with SRBC. For controls, 100 unexposed mice were immunized and two other groups of 100 each were exposed for 6 and 12 weeks each but not immunized. On days 4, 6, 8, 12, and 20 after such treatments, the percentages of lymphoblasts and plasmocytes in suspensions of lymph-node cells and the numbers of antibody-forming cells were determined for subgroups of five mice each. For all three immunized groups (two RFR-exposed and one unexposed), the percentage of blast cells peaked on day 6 and diminished to baseline values by day 20. The smallest maximum was for the unexposed group; the next larger maximum was for the group exposed for 12 weeks; the highest maximum was for the 6-week-exposure group. Smaller peaks on day 6 were seen for the two nonimmunized RFR-exposed groups; again the higher value was for the group exposed for 6 weeks. Qualitatively similar results were obtained for the percentage of plasmocytes and the number of antibody-producing cells. The investigator surmised that the lower maxima obtained for the group exposed for 12 weeks and immunized is an indication of adaptation to the RFR.

In another series, 12 rabbits were exposed to the same RFR at 5 mW/cm^2 for 6 months. Each month, the percentage of lymphoblast cells in peripheral blood was ascertained. The results showed an increase from about 3% initially to 9 and 10% respectively for months 1 and 2 of exposure, after which the percentage returned to baseline; these data also support the adaptation hypothesis. A smaller increase, to about 6%, was also seen for month 7 (1 month after cessation of exposure); values returned to baseline for months 8 and 9.

In an abstract, Pazderova-Vejlupkova (1979) reported using pulsed RFR at 2.74 GHz to expose rats for 4 hr/day, 5 days/week over 7 weeks. The average power density was 24.4 mW/cm^2, which caused a maximum rectal temperature rise of 0.5 deg C. Blood was taken before exposure; at weeks 1, 3, 5, and 7 during exposure; and at weeks 1, 2, 6, and 10 after exposure. There were significant decreases in leukocyte and absolute lymphocyte counts during the second half of the exposure period. In a similar experiment with 3.0-GHz pulsed RFR at 1 mW/cm^2 average power density, conducted in cooperation with the USSR Academy of Medical Sciences, the results were negative.

Smialowicz et al. (1979a) exposed rats to 2.45-GHz RFR at 5 mW/cm^2 for 4 hr/day, 7 days/week on day 6 of pregnancy until term. Following birth, pups were exposed until age 20 days; then half of these were exposed until age 40 days. Equal numbers of pregnant rats and pups were sham-exposed for controls. The mean SARs for the pups diminished with age from 4.7 to 0.7 W/kg due to growth. Blood counts were made at ages 20 and 40 days, and the blastogenic responses of blood and lymph-node lymphocytes were determined by measuring the uptake of tritiated thymidine after stimulation of cell cultures with T- and B-cell mitogens. Two such experiments, each with a different exposure arrangement, were performed. The mean leukocyte counts at 20 days were found to be significantly lower for the RFR-exposed pups than for the controls in the first experiment but not in the second, and they were not significantly different at 40 days in either experiment. The results for the mitogen-stimulated cultures were widely scattered, and no consistent pattern was evident. Increases in thymidine uptake were seen in several cases, mostly for the cultures from the 40-day-old rats; such results are difficult to interpret because the mean SAR had diminished by more than a factor of two since 20 days, and by a factor of five since the first few days of exposure.

In an abstract, Smialowicz et al. (1979b) described exposure of mice to 425-MHz pulsed and CW RFR for 1 hr on each of 5 consecutive days. The power densities for the CW RFR were 39, 10, and 2.5 mW/cm^2; the corresponding SARs were 8.6, 2.2, and 0.55 W/kg. The average power densities for the pulsed RFR were 9, 2.5, and 0.63 mW/cm^2; the SARs were 2.0, 0.55, and 0.14 W/kg, respectively. No differences in the primary immune response to SRBC were found between mice exposed to the CW RFR and the sham-exposed mice or between mice exposed to the CW and pulsed RFR.

Hamrick et al. (1977) exposed fertile Japanese quail eggs for 24 hr/day during the first 12 days of embryology to 2.45-GHz CW RFR at 5 mW/cm^2 (SAR about 4 W/kg), and reared the birds for 5 weeks after hatching. At this age, the levels of anti-SRBC antibodies were determined before, and 4 days after, challenge with SRBC. There were no significant differences between antibody levels for the quail from RFR-exposed eggs and control quail, either before or after challenge. In addition, no significant differences were found in the weights of the bursa of Fabricius (source of B lymphocytes in birds) or the spleen.

In a subsequent investigation by this group, Galvin et al. (1981) similarly exposed eggs and reared the quail for 22 weeks after hatching, along with nonexposed controls. From 6 weeks of age, exposed quail were housed as male-female pairs in mating cages; control quail were similarily housed. In one set of experiments, the quail were immunized with chukar (partridge) red blood cells (CrRBC) at 22 weeks; blood samples were drawn on days 0, 4, and 7 following immunization and assayed for anti-CrRBC hemagglutinins (antibodies) as a measure of humoral response; and total and differential leukocyte counts were made on days 0 and 7. In another set of experiments, each quail was administered the mitogen PHA intradermally in one wing web and saline in the other wing web, and the ratio of skin thickness 18 hr after PHA injection to the thickness before injection (web index) served as an indicator of cell-mediated immune potential. The results indicated that immediately prior to immunization, the exposed quail of both sexes had significantly higher levels of nonspecific antibodies; however, there were no significant differences in the levels of anti-CrRBC antibodies between exposed and control birds of either sex on days 4 and 7 after immunization. The PHA web-index data yielded no significant differences between exposed and control males, but the mean for the exposed females was significantly lower than for the control females. Also, the saline web-index data showed no significant differences. The total and differential leukocyte counts were found to be significantly increased (leukocytosis) only in the exposed females. The investigators were unable to account for these response differences between the sexes. However, the occurrence of leukocytosis in this investigation (in which birds were immunized when 22 weeks old) and its nonoccurrence in the previous one (Hamrick et al., 1977) (birds immunized when 5 weeks old) was attributed to the fact that the hematologic system of the adult bird is different than that of the neonatal bird.

In an abstract, Shandala et al. (1977) discussed exposure of rats to 2.375-GHz RFR at power densities of 0.01, 0.05, or 0.5 mW/cm^2, 7 hr/day for 30 days and assays of blastic transformation of lymphocytes in mitogen-stimulated cultures on days 3, 7, 10, 14, 21, and 30. They reported a downward trend in the relative numbers of transformed T lymphocytes for 0.5 mW/cm^2. For the two lower power densities, they observed initial increases followed by decreases to less than

control values. Autoallergenic activity was also reported for 0.5 mW/cm^2. Such effects are discussed in more detail in a later report (Shandala et al., 1979), which also describes the effects of RFR on the EEG of the rabbit and the behavior of rats under the same exposure conditions.

Guy et al. (1980b) sham-exposed and exposed four rabbits each to 2.45-GHz CW RFR for 23 hr/day on 180 consecutive days. The power densities at the head and body were 10 and 7 mW/cm^2, respectively; the estimated peak SAR in the head was 17 W/kg, and the average SAR of the whole body was 1.5 W/kg. The eyes were examined periodically, and no differences were found between the two groups. Hematological (as well as other physiological) parameters were also evaluated, and the results for 0, 1.5, 3, 4.5, and 6 months of exposure were presented. No significant differences in values for RFR- and sham-exposed animals were found except for a decrease in the percentage of eosinophils (a type of leukocyte) at 6 months, but the investigators noted that this parameter varies widely among animals.

McRee et al. (1980) conducted hematologic and clinical-chemistry evaluations of the same animals (in another laboratory) shortly after completion of exposure and 1 month later, at which time the animals were euthanized and necropsies were performed. Again, the eosinophil percentage at completion of exposure was lower for the RFR- than sham-exposed rabbits; however, there was no depression 1 month after exposure. Regarding clinical-chemistry values, the only statistically significant results at completion of exposure were increases in albumin and calcium. However, 1 month after completion of exposure, the total globulin percentage had increased and the albumin percentage had decreased, both nonsignificantly, but the ratio of the latter to the former showed a statistically significant decrease. At necropsy, examinations of tissues showed no lesions attributable to RFR exposure. Samples of splenic tissue were cultured; stimulated with the mitogens PHA, Con-A, or pokeweed mitogen (PMW--a mitogen that stimulates both T and B lymphocytes), each in three different concentrations; and assessed for response by the uptake of tritiated thymidine. Lower responses for the RFR-exposed animals were obtained with all three mitogens, but the differences were statistically significant only for PMW (at all three concentrations).

Guy and coworkers are conducting a study of rats exposed for 22 hr/day over their entire lifetimes to circularly polarized, pulse-modulated (8-Hz), 2.45-GHz RFR at peak and average power densities of 125 and 0.5 mW/cm^2, respectively, in individual circular waveguides under controlled environmental conditions. These exposure values were selected to simulate, by scaling considerations, chronic exposure of humans to 450-MHz RFR at an average power density of 1 mW/cm^2. The study plan is described in Guy et al. (1980a). At constant incident average power density, the SARs of rats vary with their weight and age, permitting several exposure options. The option selected (Guy et al., 1981) is to simulate, under worst-case conditions, exposure of humans

to 450-MHz RFR at SARs up to but not exceeding 0.4 W/kg (the basis for the new ANSI standard).

The initial populations consisted of 98 exposed and 98 sham-exposed specific-pathogen-free rats. The rats are monitored daily for health status, weight, and food/water intake. Oxygen consumption and carbon dioxide production are measured as an index of metabolic activity. At 6-week intervals, open field activity is assessed and blood samples are drawn and given standard blood chemistry and hematology tests. Periodic progress reports through the ninth month (Kunz et al., 1981) and the twenty-first month (Kunz et al., 1982; Johnson et al., 1982) (abstracts) of the investigation indicate no significant differences between RFR- and sham-exposed rats in T- and B-lymphocyte populations or in plaque-forming cells.

Smialowicz et al. (1981b) conducted an investigation with several biological endpoints. They exposed 20 time-bred pregnant rats to 100-MHz CW RFR in a transmission-line system at approximately 22 deg C ambient temperature and 50% relative humidity for 4 hr daily from day 6 of pregnancy to parturition. On birth, four male pups of each litter were exposed daily for 4 hr during the first 14 days at 27 deg C (approximate nest temperature), and then at 22 deg C for the remainder of the exposure regimen. Two pups of each exposed litter were removed for tests at age 20-22 days, one at 40-42 days, and the remaining pup was exposed until 97 days of age. The SARs varied with body mass, ranging from a mean of 2.02 W/kg for the pregnant dams to 2.96 W/kg for the neonatal rats, with intermediate values for the pups as they grew. Another group of 20 pregnant rats and their pups were sham-exposed but otherwise similarly treated.

Blood samples taken at ages 22 and 42 days showed no significant differences between RFR- and sham-exposed rats in erythrocyte and leukocyte counts; differential counts of lymphocytes, macrophages, and polymorphonuclear cells; hematocrit; or hemoglobin. There were also no significant differences in lymphocyte response to stimulation by T- and B-cell mitogens. The pups removed at age 22 days were immunized with purified pneumococcal polysaccharide, and blood samples taken 5 days later were assayed for serum antibody titers. No significant differences were found.

During the exposure regimen, the mean body weight of the RFR-exposed pups was consistently larger than for the sham-exposed pups at corresponding ages, but the differences were generally nonsignificant. Differences in ages for startle response and righting reflex were also nonsignificant, as were locomotor activity in a residential maze at ages 35 and 84 days. However, the mean age for complete opening of both eyes of the RFR-exposed pups was almost 1 day older than for the sham-exposed pups, a finding consonant with the larger sizes of the RFR-exposed pups.

At 90 days of age, each RFR- and sham-exposed rat (male) was mated with a pair of normal, virgin, unexposed females for 1 week. Dominant lethal assays of the females 11 days later yielded no significant differences in preimplantation loss or the number of live fetuses between the two groups, an indication that exposure of the males to the RFR was not mutagenic.

Regional brain weights of rats, determined at ages 22, 40, and 90 days, showed that the mean weight of the medulla oblongata of the RFR-exposed rats was significantly larger than for the sham-exposed rats at age 40 days but not at 22 or 90 days. No other significant regional-brain-weight differences were found. Acetylcholinesterase (AChE) activity was lower in the striatum and medulla of the 22-day-old RFR-exposed rats and in the midbrain of the 40-day-old rats, but no significant differences in AChE activity were found in any brain region of the 97-day-old rats. The authors surmise that these transient changes may be due to local alterations of cation concentrations.

Smialowicz et al. (1981d) also exposed 16 rats individually in circularly polarized waveguides to 970-MHz RFR at an SAR of 2.5 W/kg for 22 hr/day for 69-70 consecutive days. Another group of 16 rats was similarly sham-exposed. Blood samples were taken from eight rats of each group on day 69, after which the rats were euthanized and their spleens were removed. The remaining rats were treated in the same manner on day 70. There were no significant differences between RFR- and sham-exposed rats in erythrocyte count, leukocyte count, mean cell volume of erythrocytes, hematocrit, or hemoglobin concentration, or in differential leukocyte counts of lymphocytes, monocytes, eosinophils, or polymorphonuclear leukocytes. Also, spleen cells removed from the RFR- and sham-exposed rats and cultured with various mitogens showed no significant differences in responses. However, blood serum chemical analysis indicated that the levels of triglyceride, albumin, and total protein concentration were significantly higher for the RFR-exposed group. The higher levels of albumin and protein concentration were within the normal ranges for this strain of rat and were not consonant with the absence of changes in erythrocyte assays, an indication that the rats may have been dehydrated. The authors indicate that an SAR of 2.5 W/kg is approximately half the basal metabolic rate of an adult rat, and suggest that the increases in triglyceride level may have been due to thermal stress induced by the exposure to RFR.

6.8.4 In Vivo Studies: Effects of Chronic Exposures on Health and Disease

Relatively few studies have been conducted to determine whether chronic exposure to RFR alters the resistance to, or the severity of, diseases accidentally acquired or purposely given to animals. Such studies have been difficult to conduct, and reliable, consistent results have been hard to achieve. Representative examples of such investigations follow.

Prausnitz and Susskind (1962) observed that mice exposed to 9.3-GHz pulsed RFR at 100 mW/cm^2 average power density for 4.5 min/day over 59 weeks appeared to have more resistance than controls to a pneumonia infection accidentally introduced into the colony; however, this was an incidental observation, not the results of a planned experiment. (Other findings of this investigation are discussed in Section 6.2.) Similarly, Pautrizel et al. (1975) reported that exposure of mice to RFR (no frequency or intensity reported) conferred protection against an otherwise fatal challenge with Trypanosoma equiperdum.

Szmigielski et al. (1975) observed five rabbits that were experimentally infected with Staphylococcus cureus after exposure to 3-GHz RFR at 3 mW/cm^2 for 6 hr/day over 6 weeks, and five rabbits similarly treated but exposed for 12 weeks. By contrast, they reported that the animals exhibited depression of peripheral-granulocyte counts and of granulocyte reserves mobilized by subsequent injection of Staphylococcus endotoxin, and increased lysozyme activity of serum. They stated that the animals appeared "sicker."

Szmigielski et al. (1979) (abstract) also reported that exposure of mice to 2.45-GHz RFR at 20 mW/cm^2 for 2 hr/day, 6 days/week for up to 4 months and concurrent treatment with carcinogens diethylnitrosamine or 3,4-benzopyrene led to earlier appearance of tumors than in unexposed mice. However, exposure at 5 mW/cm^2 had no such "promoting" effect on carcinogenesis.

In a more detailed report, Szmigielski et al. (1980) discuss exposing mice and rabbits to 2.45-GHz pulsed or CW RFR for 2 hr/day over either 6 or 12 weeks and injecting the animals with appropriate strains of Staphylococcus after completing the exposure regimens. The average power density used was 5 or 15 mW/cm^2. Estimated SARs for the mice were 2-3 and 6-9 W/kg, respectively. No increases in rectal temperature of either species were observed during the exposures.

In the control rabbits and those exposed to RFR for 6 weeks, elevated rectal temperatures and leukocytosis (blood granulocytosis, increased release of bone-marrow granulocytes stimulated by staphylococcal alphatoxin, higher lysozyme activity) occurred during the 5-7 days after the Staphylococcus injections, with spontaneous recovery by day 10-14 and no animal deaths. By contrast, the rabbits exposed for 12 weeks and injected with Staphylococcus did not exhibit these signs of leukocytosis, a result ascribed to inhibition of granulopoiesis in these rabbits.

The dose of Staphylococcus used for the mice resulted in acute infection, and some of the exposed and control animals died within 3 days. Although the authors indicate otherwise, their Figure 4 for survival rate shows the following approximate values on day 3 in descending order: 80% for the mice exposed at 5 mW/cm^2 for 6 weeks, 60% for the control mice, 45% for those exposed at 5 mW/cm^2 for

12 weeks, 25% for the group exposed at 15 mW/cm^2 for 6 weeks, and 5% for those at 15 mW/cm^2 for 12 weeks. This figure also includes data indicating the occurrence of significantly higher phagocytosis, relative to controls, in the mice exposed at 5 mW/cm^2 for 6 weeks, and significantly lower phagocytosis in those exposed at 15 mW/cm^2 for 12 weeks. Phagocytosis was higher in the other two exposed groups, but not significantly so.

In their conclusions, the authors note that the 2-hr exposures may have been "stressogenic" on the animals, because they exhibited temporary discomfort during the exposures.

In an abstract, Majde and Lin (1979) reported exposing mice to 148-MHz RFR at either 0.5 or 30 mW/cm^2 (SARs of 0.013 or 0.75 W/kg) for 1 hr/day for 3 successive days starting 24 hr after subcutaneous immunization with human type O red blood cells. Paw challenges for hypersensitivity were performed 14 days after immunization. The authors reported a mild but significant suppression of the anaphylactic response in the mice exposed at the higher but not at the lower power density. The degree of suppression of anaphylaxis was comparable to that seen in animals exposed to cold for 1 hr on the day following immunization, an interesting observation because exposure to cold is a known producer of stress.

Liddle et al. (1980) immunized groups of mice against Streptococcus pneumoniae with a killed bacterin or with purified pneumococcal polysaccharide. Each group was then sham-exposed or exposed 2 hr/day for 5 successive days to 9-GHz pulsed RFR at an average power density of 10 mW/cm^2 (calculated SAR of 3.3-4.7 W/kg). Another group injected with saline but not exposed served as controls. On day 6 after immunization (the day after exposure), blood samples were taken for hematology and antibody titers, the mice were challenged with an LD_{50} dose (normally fatal to 50% of the mice) of virulent S. pneumoniae, and the numbers of deaths per day were noted for 10 days after challenge.

The RFR-exposed mice had significantly higher circulating antibody titers (about 28%) than the sham-exposed mice, but there were no significant differences between the groups in red and white blood cell counts, hematocrit, hemoglobin, lymphocytes, neutrophils, eosinophils, basophils, or monocytes. No antibody titers were detected in the saline-injected mice. Ten days after challenge, 25 of the 53 RFR-exposed mice and 27 of the 54 sham-exposed mice had died, a nonsignificant difference. However, the greatest number of deaths in one day in the RFR-exposed group (10) occurred on day 6, whereas 14 of the deaths in the sham-exposed group occurred on day 3. The authors suggest that the RFR caused a greater initial neutralization of the pathogens, but not enough to produce complete recovery. No saline-injected mice survived the challenge.

In a recent abstract, Liddle et al. (1982) described similar experiments with mice, in which groups of 25 each were first immunized against S. pneumoniae and then sham-exposed or exposed to 2.45-GHz CW RFR at 10 mW/cm^2 (SAR of 6.8 W/kg) in ambient temperatures of 19, 22, 25, or 28 deg C for the same durations. Survival rates were significantly higher for the RFR-exposed groups at all four ambient temperatures than for the corresponding sham-exposed groups. In addition, survival rates increased with ambient temperature in both RFR- and sham-exposed mice; the survival rate at 28 deg C was significantly higher than at 19 deg C. The authors surmise that increased heating results in higher survival, apparently by stimulation of the immune system, and that exposure to RFR further enhances the survival of the challenged mice.

6.8.5 Summary of Immunological Effects

In summary, RFR does appear to have effects on the immune system of mammals. Some of the reported effects were obtained at low power density levels, but most studies were performed at relatively high power densities; in some cases, effects obtained at high power densities were not found at lower power densities, suggesting the possibility that power density thresholds exist. Some of the results indicate immunosuppressive effects; some indicate immunostimulative effects; and others, both kinds of effects. Also, results from various laboratories obtained under apparently comparable conditions are sometimes contradictory, an indication of the probable presence of uncontrolled factors or subtle differences in the experimental protocols. Based on current findings, it appears that in vivo RFR-induced effects on the immune system depend to varying degrees on the ages of the experimental subjects, the frequency and average power density of the RFR (or the whole-body SAR resulting therefrom), the exposure duration and perhaps the time of day of exposure, the kind of exposure system used (which affects the internal SAR distributions within the animals), and the kind of endpoint analyses undertaken and when they are performed relative to the completion of exposures.

Reported in vivo effects on the immune systems of animals from chronic exposure to RFR at average power densities below 1 mW/cm^2 (e.g., those of Czerski, 1975; Shandala et al., 1977, 1979) are unlikely to be linked simply to temperature increases, but such results have not yet been replicated elsewhere. In most other in vivo investigations, such as those discussed herein, the exposures were at average power densities exceeding 1 mW/cm^2. The existing evidence indicates that some of the immune-system effects are probably mediated through the effect of RFR on the endocrine system, involving the general syndrome of adaptation to stress. The mechanisms and significance of such effects are not yet understood, nor have individual findings been independently verified. There is currently no evidence that reported RFR effects on the immune systems of animals at average power densities less than 1 mW/cm^2 would occur in humans chronically exposed to such RFR levels, or that such effects would be hazardous to human health.

6.9 Biochemical and Physiological Effects

The literature on biochemical and physiological effects associated with RFR is extensive. Many of the reported effects are associated with other events (e.g., changes in hormonal levels or stress adaptation), some are questionable for various reasons, and others do not have a clear medical significance.

6.9.1 In Vivo Exposure of Intact Animals

Among the relatively few investigations for possible effects of RFR on primates, and specifically with RFR in the HF range, was the study by Bollinger (1971). He exposed groups of 12 rhesus monkeys (Macaca mulatta) each to 10.5- or 26.6-MHz pulsed RFR for 1 hr at average power densities of 200 or 105 mW/cm^2, respectively, or to 19.3-MHz RFR for 14 days, 4 hr/day, at 115 mW/cm^2. For each frequency, 12 monkeys were sham-exposed to serve as controls. Hematologic and blood-chemistry analyses were performed before and after exposure. The results indicated no statistically significant differences between exposed and control monkeys for most of the cellular components of the blood. Significant differences in mean monocyte and eosinophil counts were obtained, but were ascribed to conditions not related to RFR exposure. Similar conclusions were reached regarding the blood-chemistry parameters. Gross pathological and histopathological (microscopic) examinations of these animals showed no abnormalities ascribable to RFR exposure. In another part of this study, groups of three tranquilized monkeys each were exposed for successive time intervals at increasing power densities up to 600 mW/cm^2 for the two lower frequencies, and 300 mW/cm^2 for 26.6 MHz. Deep-body (esophageal) temperatures and EKGs were taken during exposure. No obvious indications of thermal stress, increases of heart rate, or other influences on the electrical events of the heart cycle due to the RFR were found.

Frazer et al. (1976) exposed male rhesus monkeys to 26-MHz CW RFR at 500, 750, or 1,000 mW/cm^2 for 6 hr in a rectangular-coaxial-transmission-line chamber. Control monkeys were maintained just outside the exposure chamber. The ambient temperature was 22.2 deg C. Rectal and skin temperatures were measured. At the highest power density, the skin and rectal temperatures increased during the first half hour by 2.5 and 1.3 deg C, respectively, and decreased during the next hour to 1.1 and 0.7 deg C above their respective initial values. The rectal temperature remained substantially constant during the remainder of the exposure period, but the skin temperature increased again slightly until the fifth hour and then declined during the last hour to 0.1 deg C above the initial value. Similar but smaller changes were obtained at the two lower power densities. These results indicate that even at the highest power density, the monkeys were in thermal equilibrium; i.e., they were able to dissipate the additional heat induced by the RFR, and their thermoregulatory mechanisms were quite efficient in doing so. Calculations by the investigators showed that

exposure of a 3.6-kg monkey to 26-MHz RFR at 1,000 mW/cm^2 is approximately equivalent to exposing a human 1.8 m tall to this frequency at 400 mW/cm^2.

Krupp (1977b) performed similar experiments, exposing rhesus monkeys for 3 hr at frequencies of 15 and 20 MHz and power densities ranging from 760 to 1,270 mW/cm^2. The results again indicated that the additional heat induced by the RFR was readily accommodated by the thermoregulatory mechanisms of the animals. Calculations show that exposure of a monkey to 20-MHz RFR at 1,270 mW/cm^2 is equivalent to exposure of a human at 225 mW/cm^2. The equivalence for 15 MHz at 1,025 mW/cm^2 is 205 mW/cm^2.

Krupp (1978) also did a follow-up study of 18 rhesus monkeys that had been exposed 1 to 2 years previously to 15-, 20-, or 26-MHz RFR for up to 6 hr on at least two occasions at power densities in the 500 to 1,270 mW/cm^2 range. Hematological and biochemical blood parameters were measured, and physical (including ophthalmologic) examinations were performed. No variations from normal values or conditions that could be attributed to RFR exposure were found.

Adair and Adams (1980b) equilibrated squirrel monkeys for a minimum of 2 hr to constant environmental temperatures (22 to 26.5 deg C) cool enough to ensure that the cutaneous blood vessels in the tail and extremities were fully vasoconstricted (an effect produced by the thermoregulatory system to minimize heat loss). The monkeys then underwent 5-min exposures to 2.45-GHz RFR at successively higher power densities, starting at 2.5 to 4 mW/cm^2, until vasodilation in the tail occurred, as evidenced by an abrupt and rapid temperature increase for the tail skin. For example, a monkey equilibrated to 25 deg C exhibited tail vasodilation when exposed to RFR at 10 mW/cm^2 (whole-body SAR of 1.5 W/kg), whereas it did not when exposed to infrared radiation at the equivalent power density, an indication that the effect resulted from stimulation of thermosensitive elements of the thermoregulatory system by the RFR rather than from heating of the tail skin. To cause tail vasodilation in monkeys equilibrated to lower environmental temperatures required RFR exposure at higher power densities. Specifically, an increase of 3 to 4 mW/cm^2 was found necessary for every 1 deg C reduction in environmental temperature.

The oxygen-consumption rate of an animal is a direct measure of its metabolic rate. Ho and Edwards (1977) used the oxygen-consumption rate as a biological indicator of stress. They exposed mice to 2.45-GHz RFR in a waveguide system that permitted continuous monitoring of the RFR absorption rate during exposure (Ho et al., 1973). The animals were exposed under the following controlled environmental conditions: 24 deg C temperature, 55% relative humidity, and 78 ml/min airflow rate. The forward power levels ranged from 0 to 3.3 W; the corresponding range of mean SARs was 0 to 44.3 W/kg. The exposures were for 30 min, during which the oxygen-consumption and RFR absorption rates were determined at 5-min intervals; these values were converted into specific metabolic rates (SMRs) and SARs, respectively,

expressed in the same units (W/kg). The oxygen-consumption rate was also measured at 5-min intervals for 30 min before and after exposure. Sham-exposed mice served as controls. At the highest forward power used, the SAR (averaged over 16 mice) decreased during exposure from 56 to 39 W/kg, and the SMR decreased from 17.5 to 14 W/kg, thereby decreasing the total thermal burden from about 74 to 54 W/kg. (The values for individual mice varied more widely.) Apparently the mice endeavored to decrease their thermal burdens by altering their body configurations during exposure to minimize their RFR absorption rates; they also reduced their oxygen consumption. Similar but smaller changes were obtained at forward powers of 1.7 and 0.6 W (mean SARs of 23.6 and 10.4 W/kg), and insignificant changes were noted at 0.3 and 0.09 W (mean SARs of 5.5 and 1.6 W/kg). Thus, the onset of such RFR-induced thermal stresses corresponds approximately to the basal metabolic rate of the mouse (9 W/kg). Oxygen-consumption rates returned to normal after completion of the RFR exposure.

Moe et al. (1976) exposed eight rats to 918-MHz CW RFR at 10 mW/cm^2 (mean SAR about 3.6 W/kg) 10 hr/day for 3 weeks in cylindrical-waveguide chambers designed for chronic exposures under standard laboratory-maintenance conditions for rats. Eight sham-exposed rats served as controls. Physiological and behavioral comparisons between RFR- and sham-exposed rats showed no significant differences in fluid intake, body weight, rectal temperature, and corticosterone levels. However, food intake and blood glucose level were lower for the RFR-exposed animals, and their behavioral repertoires were altered, apparently to cope with the additional thermal burden imposed by the RFR.

Lovely et al. (1977) conducted a similar study but involving exposures to 918-MHz RFR at 2.5 mW/cm^2 for 10 hr/day for 13 weeks. No significant differences in behavioral repertoires, food intake, blood glucose, or most other blood-serum chemistry values were found. In another similar study by Lovely et al. (1979) (abstract), performed with 2.45-GHz RFR at 5 mW/cm^2, the results were similar to those of Moe et al. (1976). The findings of these last three investigations are consonant with one another, given the SARs involved. They indicate the existence of an SAR threshold between 0.9 and 3.6 W/kg for such effects.

Deficis et al. (1979) exposed mice continuously for nearly 60 hr to 2.45-GHz RFR, either in unstirred multimodal cavities (12 mice simultaneously per cavity, with a total of 60 mice) at an estimated power density of 3.3 mW/cm^2, or in the near field of a slotted waveguide in an anechoic chamber (usually 12 simultaneously, with a total of 94 mice) at about 4 mW/cm^2. Sham-exposed mice (126) served as controls. Means of rectal temperature and body mass after treatment did not differ significantly for sham-, cavity-RFR-, and chamber-RFR-exposed groups. However, analyses of serum triglycerides (TRG) and beta-lipoproteins (LP) 2 hr after completion of exposure showed mean TRG levels 30% higher for the mice exposed in the cavities and

55% higher for the mice exposed in the chamber than for controls, an indication of RFR-induced stress. The mean LP levels were also 40% and 51% higher, respectively, than those for controls. Both sets of results show some dose-rate dependence. These findings may be related to those of Pazderova et al. (1974), discussed under "Epidemiology," who reported that workers in television and radio transmitting stations had decreased serum albumin levels and increased serum alpha- and beta-globulin levels. The report noted that, although the changes were significant, the values were still within the normal human range and the workers appeared to be in good health.

Djordjevich et al. (1977) exposed rats for 90 days, 1 hr/day, to 2.4-GHz RFR at 5 mW/cm^2. Rectal temperatures were recorded before and after each exposure, and the animals were weighed daily. Blood samples were taken on day 10 before exposure; on days 30, 60, and 90 of the exposure period; and on day 30 after the period. These and samples from control rats were analyzed for total white cell count, erythrocytes, hematocrit, mean cell volume, and hemoglobin. Differential white cell counts for neutrophils, lymphocytes, monocytes, and eosinophils were also performed. Some rats were euthanized after the exposure period and their spleens, livers, hearts, brains, and testes were examined. No significant differences between RFR-exposed and control rats were seen for any of the analyses done or organs examined. Moderate leukocytosis was observed during the experimental period in both groups, with no significant differences between them, and the leukocyte levels returned to normal by day 30 after the exposure period. This effect was ascribed to seasonal responses by the rats.

Lin et al. (1979a) sham-exposed or exposed mice to 148-MHz RFR at 0.5 mW/cm^2 (mean SAR of 0.013 W/kg) for 1 hr/day, 5 days/week for 10 weeks, starting on the fourth to seventh day after birth. Blood samples drawn at ages 28, 70, 100, 250, 300, 360, and 600 days were analyzed for hematocrit, hemoglobin, leukocyte count, erythrocyte count, and differential blood-cell counts. The results indicated that the formed elements in the blood were not affected by exposure to the RFR. The mice were also weighed daily during the 10-week treatment period and weekly thereafter until 600 days of age. Differences in weights betweeen RFR- and sham-exposed mice at each age were not statistically significant.

D'Andrea et al. (1980) adapted rats by sham-exposing them from 0900 to 1700, 5 days/week for 8 weeks. At 1700, the rats were placed in a Wakmann rodent activity cage or tested for 1 hr on a stabilimetric platform for an alternative measurement of spontaneous locomotor activity. Two groups of 15 rats each were then selected to have equal mean activities. One group was exposed to 915-MHz RFR at 5 mW/cm^2 (SAR of 2.46 W/kg) from 0900 to 1700, 5 days/week, but for 16 weeks; the other group was similarly sham-exposed. Greater activity was seen in the RFR-exposed group, but the differences were of doubtful statistical significance. Blood samples taken under anesthesia at 2, 6, 10,

and 14 weeks of exposure showed an increase of serum sulfhydryls from baseline levels in the RFR-exposed rats at week 2, followed by return to baseline levels in succeeding weeks, but no significant differences were seen in other serum-chemistry or hematological endpoints. Also, the levels of urinary 17-ketosterones were not altered by RFR exposure. Cortical EEGs were sampled after completing the 16-week exposure regimen, and the rats were then euthanized. The EEGs of the RFR-exposed rats did not differ significantly from those of the sham-exposed rats, nor did electron micrographs of hypothalamic slices. In addition, the total body mass or the masses of the liver, heart, or adrenals were not significantly altered by the RFR exposure.

Phillips et al. (1975) exposed rats to 2.45-GHz RFR at SARs of 0, 4.5, 6.5, or 11.1 W/kg for 30 min in a microwave cavity. Colonic temperatures were measured immediately after exposure, and measurements of colonic and skin temperatures, oxygen consumption, carbon dioxide production, respiratory quotient, and heart rate were recorded continuously for 5 hr, starting 10 min after exposure. Control rats were sham-exposed. The mean colonic temperature of the control rats immediately after sham exposure was 38.6 deg C, and it diminished gradually over the test period to a final value of about 38.0 deg C. For the rats exposed at 4.5 W/kg, there was an initial elevation of colonic temperature to 40.0 deg C, followed by a decrease to mean control values in 20 min and continuation at such levels for the remainder of the period. For those exposed at 6.5 W/kg, the initial colonic temperature increase was slightly larger (to 40.5 deg C) and was followed by a rapid decrease to levels significantly below control values that persisted for the remainder of the period. For the rats exposed at 11.1 W/kg, the initial colonic temperature was much higher (42.4 deg C), but it diminished more slowly to values well below those for the 6.5-W/kg group by 3 hr after exposure; it then increased again to essentially control value by the end of the 5-hr period. Dose-rate-dependent elevations of skin temperature were observed shortly after exposure; temperatures diminished to normal values within 50 min. For the rats exposed to 4.5 and 6.5 W/kg, normal values persisted for the remainder of the period. However, for the group exposed at 11.1 W/kg, skin temperature continued to decrease during the next hour, finally leveling off at well below control values for the rest of the period. Oxygen consumption and carbon dioxide production by the 4.5-W/kg group were comparable to control values, but they were lower for the two groups exposed at the higher levels. Last, statistically insignificant bradycardia (lower heart rate) was observed in the 4.5-W/kg group; mild but statistically significant bradycardia developed within 20 min for the 6.5-W/kg group, which recovered within about 2 hr; pronounced bradycardia developed abruptly for the 11.1-W/kg group, after which heart rates increased to values well above those of controls (tachycardia) and persisted at these levels to the end of the test period. Irregular heart rhythms accompanied bradycardia, and incomplete heart block was evident for most of the rats exposed at the highest level, but the animals recovered within 60 min after cessation of exposure.

Such heart block was surmised to be caused by the release of toxic materials, by elevated serum potassium, or by myocardial ischemia, all from excessive heat.

Chou et al. (1980b) exposed three rabbits dorsally or ventrally 20 min/day for 10 days to 2.45-GHz RFR, CW or pulsed (1-microsecond pulses, 700 pps), at an average power density of 5 mW/cm^2. For dorsal exposure at this power density, the maximum SARs were 0.86 W/kg in the brain and 0.09 W/kg in the heart; for ventral exposure, the corresponding values were 0.24 and 0.30 W/kg. The same animals were also exposed dorsally to 10-microsecond pulses, at a pulse power density of 13,700 mW/cm^2, that were synchronized to the heart rate with 0-, 0.1-, or 0.2-s delay times relative to the R wave of the EKG (which was measured with carbon-loaded Teflon electrodes; see Chou and Guy, 1979a). Before the experiments, the rabbits were acclimated for several weeks, and for at least 15 min before and after exposure. No significant differences were observed between heart rates during the periods of exposure and nonexposure to RFR. In addition, no cumulative effects on heart rate were observed over 4 months of such exposures. The rabbits were also exposed at 80 mW/cm^2 CW RFR, which disturbed them sufficiently, because of the heat stress, to render heart-rate recording difficult. For this exposure, however, the heart rate increased, then returned to normal about 20 min after termination of exposure.

In an abstract, Galvin and McRee (1981b) described the sham exposure or exposure of anesthetized rats to 2.45-GHz CW RFR for 4 hr at 10 mW/cm^2 in an anechoic box maintained at 23 deg C, 50% relative humidity, and 70-dB noise level. In the sham-exposed rats, the mean arterial blood pressure, heart rate, and colonic temperature were 120 mmHg, 300 beats per minute, and 37.5 deg C, respectively, and the exposure to RFR had no influence on these parameters. In addition, there were no significant differences between the two groups in numbers of white and red cells, hematocrit, or plasma protein.

6.9.2 In Vivo and In Vitro Exposure of Specific Tissues

McArthur et al. (1977) suspended post-pyloric segments of rat gut in Ringer's solution, permitted them to stabilize for 25 to 40 min at 28.5 deg C, then exposed them to 960-MHz RFR for 10 min at SARs of 1.5 to 5.5 W/kg. The waveform of peristaltic pressure of these smooth-muscle segments was monitored during stabilization and exposure, and for 30 to 45 min after exposure. Other similarly prepared segments were monitored while being maintained (without RFR exposure) in Ringer's solution with atropine as an additive, and still others were monitored during treatment with both atropine and RFR. Control segments were monitored for 90 to 120 min without either treatment. The results shown in Table 1 of the paper indicate that exposure to RFR alone significantly increased the rate of muscle contraction, whereas treatment with atropine alone caused a slight but nonsignificant decrease in peristaltic rate. Treatment with both atropine and RFR significantly decreased the peristaltic rate.

Whitcomb et al. (1979) suspended segments of rat gut in a modified Ringer's solution, permitted them to equilibrate for 1 hr at 7 deg C and for an additional hour at 36 deg C, then exposed them to 1-GHz RFR at SARs of 1.2, 2.3, or 6.9 W/kg. In contrast with the results of McArthur et al. (1977), exposure to RFR did not affect the rate of contraction. Differences in preparation and treatment methods may account for such contrary findings.

Lords et al. (1973) submerged isolated turtle hearts in Ringer's solution and exposed them to 960-MHz CW RFR, typically for 30 min, in a capacitor exposure system at applied powers in the range from 0 to 500 mW. Bradycardia was observed for the range from about 50 to 200 mW, and tachycardia at higher powers. They estimated that about 3.3% of the applied power was absorbed by the heart, and that the temperature increase in the heart at 100 mW was about 0.2 deg C. These investigators also found that heating the solution (without RFR) produced tachycardia, so they hypothesized that the bradycardia observed in the lower power range resulted from RFR-induced neurotransmitter release by the remnants of the sympathetic and parasympathetic nervous systems in the heart preparation. In a later paper, Tinney et al. (1976) presented confirmation of this hypothesis. They showed that when propranolol hydrochloride (which blocks the sympathetic system) or atropine (which blocks the parasympathetic system) was added to the Ringer's solution, exposure to RFR did not produce bradycardia. Reed et al. (1977) produced bradycardia in isolated rat hearts exposed to the same frequency for 10 min in the SAR range from 1.5 to 2.5 W/kg; no bradycardia was observed when the same blocking agents were used.

In an abstract, Chalker et al. (1981) reported that RFR exposure altered the beat rate of the isolated frog heart. Their technique was to remove the heart and perfuse it with oxygenated Ringer's solution to keep it cool and maintain an isotonic environment. Light from a low-power laser was bounced off the heart as a means for remotely detecting heartbeats. They exposed the heart to 2.45-GHz RFR at an SAR of about 100 W/kg for an unstated duration in a TEM stripline arrangement; they reported changes in the heartbeat rate, but did not indicate the directions of such changes. They did state that the onset of such changes was fast relative to the thermal time constant and that the effects were similar to those obtained with microelectrodes in neuronal pacemaker cells, in support of the conclusion that the microelectrodes were not the cause of the effect.

Galvin and McRee (1981a) investigated the influence of exposure to RFR on the functioning of the intact heart of the cat with and without myocardial ischemia (MI). MI was induced in two groups of cats by occluding the left anterior descending coronary artery. With a dielectrically loaded waveguide applicator, the hearts of one group were exposed to 2.45-GHz CW RFR for 5 hr at an SAR of 30 W/kg, and the hearts of the other group were sham-exposed for the same duration. For comparisons, the coronary artery of two other groups were isolated but not occluded, and the hearts were similarly RFR- or sham-exposed.

At this SAR, the heart temperature of dead cats increased at an initial rate of 0.43 deg C per min. However, no increases in aortic blood temperature occurred in the live cats during RFR exposure. The mean arterial blood pressure, cardiac output, heart rate, and EKG were measured before and during the 5-hr period. Arterial blood samples were drawn just prior to occlusion or isolation and hourly afterward, and assayed for plasma protein concentration and creatine phosphokinase (CPK) activity. After the 5-hr period, the hearts were excised. The left ventricle of the cats with occluded artery was divided into ischemic-myocardium (IM), and nonischemic-myocardium (NIM) parts. Anatomically equivalent tissue samples were derived from the hearts of other cats. The heart samples were assayed for tissue CPK activity, expressed as the ratio of CPK activity in the first part to that in the second part of each heart.

In both the ischemic and nonischemic cats, the results showed no significant differences in mean arterial blood pressure, cardiac output, or heart rate between RFR- and sham-exposed groups, and no synergism of ischemia and RFR exposure for these cardiovascular indices. The EKG of the IM groups showed significant elevation of the S-T segment during the 5 hr, which did not occur for the NIM groups, but there were no significant differences in each case between RFR- and sham-exposed groups. In addition, plasma CPK activity in the IM groups increased about ninefold in the 5-hr period, whereas it increased only about threefold in the NIM groups, but again, the differences between RFR- and sham-exposed groups were nonsignificant. Last, the ratio of tissue (myocardial) CPK activity in the two heart parts was about 0.8 for the ischemic RFR- and sham-exposed hearts and about unity for the nonischemic RFR- and sham-exposed hearts. These results indicate that local exposure of either the undamaged or the ischemic heart to CW RFR in vivo has no effect on the myocardium or its neural components. These findings are at variance with those obtained from isolated hearts exposed to RFR in vitro.

Recently, Galvin et al. (1982) isolated atria of spontaneously beating rat hearts, suspended the atria in glass tubes continuously perfused with aerated Krebs Henseleit solution, and exposed the specimens individually for 30 min to 2.45-GHz CW RFR at an SAR of 2 or 10 W/kg in a special water-filled-waveguide system at 37 or 22 deg C. The impedance of the waveguide was matched to that of free space by a quarter-wavelength dielectric plate, and the specimen to be exposed was placed against the immersed surface of the plate. For a control, another similarly prepared specimen was concurrently mounted in the waveguide at 9.5 cm from that surface of the plate, and thus received essentially no RFR because of the attenuation by the intervening water. The atria were equilibrated for 30 min prior to exposure and allowed to recover for 30 min after exposure.

Contractile force and beat rate were recorded with a cardiotachometer periodically before, during, and after exposure. At 37 deg C, the average beat rate for both exposed and control atria was 230 beats

per minute for 2 W/kg and 215 beats per minute for 10 W/kg. However, the beat rate of each specimen expressed as a percentage of its own rate at the start of exposure was not significantly different from 100%. The average contractile force at 37 deg C was 640 mg for the control atria and those exposed at 2 and 10 W/kg. At 22 deg C, the average beat rates at 2 and 10 W/kg were 102 and 106 beats per minute, respectively, and there were no significant differences between these values and their corresponding control values expressed as percentages of initial rates. The average contractile force at 22 deg C was 1,200 mg. These findings for isolated heart atria support the conclusion of Galvin and McRee (1981a) that in vivo exposure of intact animals to CW RFR at the indicated power densities or SARs has no influence on the myocardium or its neural components.

Frey and Seifert (1968) exposed isolated frog hearts to 1.425-GHz pulsed RFR at a peak power density of 60 mW/cm^2 and a pulse duration of 0.01 ms. The pulses were triggered at the peak of the P wave of the EKG and at 100 and 200 ms after the peak, so the average power density was negligible. The results were inconclusive for the 0- and 100-ms delays, but showed significant tachycardia for the 200-ms delay.

Clapman and Cain (1975) exposed 14 groups of isolated frog hearts for 1 min each to 1.42- or 3-GHz pulsed RFR. A fifteenth group served as controls. Three of the groups were exposed to 1.42-GHz, 0.01-ms pulses at a peak power density of 60 mW/cm^2 and triggered at 0, 100, or 200 ms relative to the P wave (i.e., the same values used by Frey and Seifert, 1968, but each group was exposed at only one of the delays). Three other groups were similarly exposed, but with 0.15-ms instead of 0.01-ms pulses. The other eight groups were exposed to 3-GHz RFR at a peak power density of 5,500 mW/cm^2. For three of these, 0.01-ms pulses were used, and 0.002-ms pulses were used for another three. For one of the remaining groups, 0.002-ms pulses were triggered at the initial rise of the QRS complex of the EKG. The last group was exposed to unsynchronized 0.002-ms pulses at 500 pps, yielding an average power density of 5.5 mW/cm^2. The results showed no significant differences in heart rate between the control group and any of the groups exposed to RFR.

Liu et al. (1976) also endeavored to obtain effects similar to those of Frey and Seifert (1968). In one set of experiments, frog hearts were isolated and exposed to 0.1-ms pulses of 1.42-GHz RFR triggered either by the P wave to begin 200-250 ms after the P-wave peak or by the R wave without significant delay. The time intervals between successive P-wave peaks were determined in the former, and the intervals between successive R-wave peaks in the latter. The results for both showed no significant variations in time intervals. In the other set of experiments, the thorax of the frog was opened, and the heart was exposed in situ to 0.1-ms pulses of either 1.42- or 10-GHz RFR. Again, negative results were obtained.

6.9.3 In Vitro Cellular Effects

Guy (1977) has described the development and characteristics of a transmission line cell-culture sample holder suitable for use in exposing a sample of cells in a culture medium for short periods to controlled broadband radiofrequency fields and controlled temperatures. Guy indicates that:

> In analyzing the data of many earlier experiments involving the effects of EM fields on cell cultures, blood samples and solutions containing microorganisms, one can raise questions concerning the exact magnitude of the fields and the temperatures of solutions during exposure... Samples are often placed in fields of known strength and power density, but, due to the complex shape of vessels that hold the samples, the actual fields acting on the cells and the temperature in the sample are unknown. These unknowns make it difficult in many cases to determine whether observed effects are due specifically to the fields, or simply to a rise in temperature. (Guy, 1977)

These comments are relevant to evaluating the results and conclusions of the several papers reported in this and other sections.

Michaelson (1970) made similar points with regard to evaluating studies on isolated cell systems, emphasizing that the interpretation of the biological results (e.g., cytogenetic effects) is difficult and does not necessarily lead to meaningful conclusions because of the many variables in tissue culture technique (e.g., influence of heat, viruses, and chemicals) that must be considered. In his recent reviews, Michaelson (1978, 1980) has again emphasized the problems of interpreting in vitro cellular studies.

Baranski et al. (1974) reported increases in membrane permeability of rabbit erythrocytes and granulocytes during in vitro exposure for up to 3 hr to 1-GHz RFR at power densities of 1 to 10 mW/cm^2. Peterson et al. (1978) (abstract) exposed rabbit and human erythrocyte cultures to RFR at 2.45 GHz or at swept frequencies of 12.5 to 13.0 GHz or 17.5 to 18.0 GHz. They found no significant differences in membrane permeability between cultures exposed at 10 mW/cm^2 and control cultures held at room temperature. However, comparable increases in permeability were obtained for cultures heated for 45 min with and without RFR to 37 deg C, indicating that such increases were thermally induced. Liu et al. (1979) obtained similar results. They exposed suspensions of rabbit, human, and dog erythrocytes for 3 hr to 2.45-, 3.0-, or 3.95-GHz RFR in a waveguide system at various SARs; the resulting temperatures ranged from 25 to 44 deg C. They also heated suspensions in a water bath to comparable temperatures. As a representative result, they found no significant differences in membrane permeability between suspensions exposed to 3.0-GHz RFR at about 200 W/kg (which corresponds to an equivalent plane-wave power density of about 42 mW/cm^2 at the center of the waveguide) and suspensions

heated by water bath to the same temperature (44 deg C). Likewise, Janiak and Szmigielski (1977) (abstract) reported no significant differences in the sequence and time course of mouse fibroblast cells heated to 43 deg C in a water bath or by exposure to 2.45-GHz RFR.

Corelli et al. (1977) investigated the effects of 2.6- to 4.0-GHz RFR on the colony-forming ability (CFA) and the molecular structure (determined by infrared spectroscopy) of Escherichia coli B bacterial cells in aqueous suspension. Cells were exposed for 10 hr at an SAR of 20 W/kg (estimated to be approximately equivalent to 50 mW/cm^2 plane-wave exposure). No RFR-induced effects on either CFA or molecular structure were observed.

Riley et al. (1979) (abstract) developed an experimental method for detecting "intrinsic" (as opposed to hyperthermic) effects of RFR on neoplastic (cancer) cells exposed in culture. They sham-exposed or exposed mouse lymphosarcoma cells to 30-MHz RFR at 100, 500, or 1,000 V/m (SARs or 31, 352, or 1,805 W/kg) in a Guy cell-culture system. Such cells were then implanted subcutaneously in mice of a specially selected immunocompetent strain. Tumors were produced with both RFR- and sham-exposed cells. However, a large percentage of the tumors derived from RFR-exposed cells subsequently regressed, resulting in host survival, whereas a large percentage of the tumors produced by the sham-exposed cells continued to grow, becoming lethal.

Other reported effects of in vitro exposure of cells to RFR are the calcium-efflux phenomenon; alterations of the blood-brain barrier; and changes in leukocyte proliferation, differentiation, and functional capacity. These topics are discussed in Sections 6.5.2, 6.5.3, and 6.8, respectively.

6.9.4 Summary of Biochemical and Physiological Effects

The thermal basis for most of the reported physiological and biochemical effects of in vivo exposure of intact animals to RFR is evident. Most significant with respect to possible hazards of human exposure to RFR are the investigations with nonhuman primates because their anatomies and physiological characteristics are closer to those of humans than are those of other experimental animals. The results of Bollinger (1971), Frazer et al. (1976), and Krupp (1977b) with rhesus monkeys showed that exposure to RFR at frequencies in the HF range at average power densities of the order of 100 mW/cm^2 were well within the thermoregulatory capabilities of this species. Also noteworthy were the negative findings of the blood-chemistry assays performed on rhesus monkeys 1-2 years after exposures to such high power densities (Krupp, 1978). In a similar vein, the work of Adair and Adams (1980b) showed that exposure of squirrel monkeys to 2.45-GHz RFR at 8 mW/cm^2 in an ambient temperature of 26 deg C is equivalent to about 20% of their resting metabolic rate and does not increase their deep body temperature. In addition, squirrel monkeys can readily compensate, by thermoregulation, to higher power densities at lower ambient temperatures.

The investigations involving exposure of intact, smaller species of mammals to RFR have yielded a variety of positive and negative results. Some of the positive findings are also clearly due to the additional thermal burden imposed by the RFR, such as the results of Ho and Edwards (1977) on increased oxygen consumption and of Deficis et al. (1979) on higher levels of serum triglycerides in mice exposed to 2.45-GHz RFR. Other results, such as those of Moe et al. (1976) on decreased food intake and lower blood glucose levels in rats exposed to 918-MHz RFR at 10 mW/cm^2 and of Lovely et al. (1977) at 2.5 mW/cm^2 in which these effects were absent, indicate the existence of an SAR threshold of about 1 W/kg or higher for such effects. Still other investigators obtained negative results (Djordjevich et al., 1977; Lin et al., 1979a; Galvin and McRee, 1981b), or negative results for some biological endpoints and positive results for others (D'Andrea et al., 1980).

One physiological aspect of concern is whether exposure of humans to RFR can affect their heart function. In early work on this subject with excised turtle, frog, or rat hearts, various investigators (Lords et al., 1973; Tinney et al., 1976; Reed et al., 1977) reported RFR-induced bradycardia, tachycardia, or both (depending on average power densities, with bradycardia for the lower range of power densities used). The lowest SAR at which bradycardia was observed in the isolated turtle heart was 1.5 W/kg (Reed et al., 1977). Coincidentally, this was also the lowest value at which McArthur et al. (1977) induced increases in the contraction rate of isolated muscle segments (a finding not confirmed by Whitcomb et al., 1979, for SARs up to 6.9 W/kg). More recently, Galvin et al. (1982) found no RFR-induced changes in beat rate or contractile force in isolated atria of rat hearts exposed to 2.45-GHz CW RFR at 2 or 10 W/kg.

The possibility that pulsed RFR at pulse rates that are synchronous with various periodic characteristics of the EKG may alter the heart rate was also investigated. Frey and Seifert (1968) reported significant tachycardia in isolated frog hearts by 1.42-GHz pulses triggered about 200 ms after the peak of the P wave. The peak power density used was 60 mW/cm^2 and the average power density was negligible. However, Clapman and Cain (1975) could not confirm this finding at the same or considerably higher peak power density (5,500 mW/cm^2), and Liu et al. (1976) were also unable to reproduce this effect.

Changes in heartbeat rate in intact animals were also reported. Phillips et al. (1975) found that rats exposed to 2.45-GHz RFR exhibited bradycardia that was not significant (relative to controls) at 4.5 W/kg, significant at 6.5 W/kg, and pronounced at 11.1 W/kg. On the other hand, Chou et al. (1980b) found no changes of heart rate in rabbits exposed to either CW or pulsed RFR at an average power density of 5 mW/cm^2 (SAR of 0.86 W/kg in the brain and 0.009 W/kg in the heart), a result that is not inconsistent with the SAR-dependent results of Phillips et al. (1975). However, Chou et al. (1980b) saw

no changes in heart rate when the pulses at a peak power density of 13,700 mW/cm^2 were synchronized to the EKG, a finding again at variance with that of Frey and Seifert (1968).

Galvin and McRee (1981b) found no significant changes in the mean arterial blood pressure, heart rate, and colonic temperature of unanesthetized rats exposed to CW RFR at 10 mW/cm^2, and no differences in numbers of white and red cells, hematocrit, or plasma protein. Galvin and McRee (1981a) also compared the results of in situ RFR exposure of the hearts of cats with and without myocardial ischemia, and found no significant differences ascribable to the RFR, an indication that RFR at the levels used does not affect the functioning of already damaged hearts.

Thus, the preponderance of results indicates that pulsed RFR synchronized with elements of the EKG does not alter the heartbeat rate. Some of the results indicate that CW RFR does not alter heart function, and others that it does. However, most of the results, both positive and negative, support the conclusion that the effects occur at relatively high average power densities (above 1 mW/cm^2) or SAR values (above 1 W/kg). The same conclusion is applicable to the in vitro cellular effects discussed above, which were obtained at much higher SARs than those in the tissue preparations.

7 MISCONCEPTIONS

Several misconceptions regarding the bioeffects of RFR continue to be expressed in popular accounts outside peer-reviewed scientific publications on the subject. Those accounts tend to be sources of some confusion for the nonspecialist. The following are representative examples.

The distinction between RFR and ionizing radiation is often not made; consequently, the known hazards of ionizing radiation are linked--by implication--with exposure to RFR. In essence, ionizing radiation (which includes ultraviolet light, X-rays, and the emissions from radioactive materials) has sufficient quantum energy (see Section 5.1) to expel an electron from a molecule, leaving the molecule positively charged and thereby strongly affecting its interactions with neighboring molecules. Ionization can alter the functions of biological molecules fundamentally and often irreversibly.

By contrast, the quantum energies of RFR are so much smaller that their primary effect is to agitate molecules rather than to ionize them. (The possibility of long-range quantum interactions, discussed in Section 5.1.3, is not excluded; however, evidence of their occurrence in live animals is sparse as yet, and there is no evidence that such effects would be harmful if they do occur.) Also, RFR-induced agitation ceases as soon as exposure to RFR is halted. At low RFR intensities, the heat that such agitation represents is well accommodated by the normal thermoregulatory capabilities of the biological entity exposed, and therefore such effects are generally reversible. At high RFR intensities, the thermoregulatory capabilities may be inadequate to compensate for such effects, and exposure at such intensities may lead to thermal distress or even irreversible thermal damage. In short, a single quantum of ionizing radiation that is absorbed by a molecule alters the properties of that molecule, and exposure to such radiation may thereby profoundly affect the function of the biological constituent involved, whereas the concurrent absorption of many quanta of RFR is necessary to cause biologically significant effects.

Even if an effect is produced by RFR, that effect may not necessarily be deleterious to the entity involved. As an example of a nonhazardous biological effect, the absorption of visible light (a form of electromagnetic radiation having quantum energies above those of RFR but below those of the ionizing radiations mentioned previously) in the eyes is necessary for vision. Light is also absorbed by the skin and at normal levels is converted into harmless heat. One reason that the levels of allowable exposure of humans to RFR are generally lower in Eastern European countries than they are in the West is the philosophically based assumption that even small RFR-induced effects are potentially harmful--a view not generally shared in Western countries.

Concerned people often ask whether guarantees can be offered that chronic exposure to low levels of an agent such as RFR will have no deleterious effects many years in the future. To obtain data on which a guarantee of absolute safety can be based is scientifically impossible. However, the large body of experimental data on the bioeffects of RFR indicates that, unlike the ingestion of certain substances in small quantities that can accumulate into a potentially harmful dose, RFR energy continually absorbed at low incident power densities (dose rates) is readily dissipated and does not accumulate in the body toward the equivalent of RFR energy absorbed at high incident power densities. This is one of the basic reasons for the existence of threshold power densities for the various RFR bioeffects.

8 UNRESOLVED ISSUES

The potential biological effects of RFR at frequencies up to 300 GHz have been assessed from existing studies. Based on the studies evaluated, with recognition that the negative findings reported in some studies may have been obtained because the experiments had been poorly conducted, there is no reliable evidence to indicate that chronic exposure to RFR at incident average power densities below 1 mW/cm^2 or at SARs below 0.4 W/kg are hazardous to human health. However, certain gaps remain in our knowledge of the biological effects of RFR. These gaps may be identified as follows:

(1) Epidemiologic Studies. Epidemiologic studies of effects of exposure of humans to RFR, in which the actual frequencies, levels, and durations of exposure are accurately known and quantified, are lacking. Existing epidemiologic studies, although extensive and reasonably well done, are subject to inherent defects, such as imprecise classification of the individuals with regard to RFR exposure and unavailability of complete sets of medical records, death certificates, or health questionnaires.

(2) Extrapolation of Findings on Animals to Humans. The most directly applicable experimental evidence relative to possible bioeffects of exposure to the RFR from any specific system would be from studies in which humans were exposed to the frequencies and waveform characteristics of that kind of system for appropriate durations at the pulse and average power densities likely to be encountered. Further, quantitative evaluation of many biological endpoints would be necessary. Such data, of course, do not exist. Instead, data are obtained from laboratory animals (mostly small rodents) used as surrogates for humans, a standard practice for investigating the effects of other agents. Because of the biological differences among species, a basic uncertainty is the degree of validity of this practice, which depends in part on the species used, the nature of the agent and its quantitative aspects, and the biological endpoints studied. In investigations of RFR bioeffects, much progress has been achieved in quantifying exposures in terms of whole-body SARs and internal SAR distributions in animal carcasses and in physical and mathematical models of various species (including humans). For example, such data can be used to determine what the whole-body SARs would be in humans at a given system frequency if, say, laboratory rats are exposed to RFR of another frequency (usually close to their whole-body resonance) at prespecified power densities. Nevertheless, there are significant gaps in knowledge regarding internal SAR distributions in humans. Moreover, most such interspecies calculations do not try to account for the

roles of blood flow and other factors in determining heat flow patterns or of thermoregulatory mechanisms in mammals that maintain constant body temperatures.

(3) Thresholds and Long-Term, Low-Level Studies. Most experimental data indicating the existence of threshold power densities for various RFR bioeffects were obtained from exposures for relatively short durations. Although it is difficult to conceive of mechanisms whereby RFR exposures at well below threshold values over a long time could result in cumulative effects deleterious to health, there have been very few investigations involving exposure of animals to low-level RFR over a large fraction of their lifetime.

(4) Differential Bioeffects of Pulsed Versus CW RFR. Questions of quantitative and/or qualitative differences in bioeffects induced by pulsed versus CW RFR at equivalent average power densities cannot be resolved fully from current knowledge (i.e., some investigators have found no significant differences, whereas others have). Also, it should be noted that although the permissible average power densities in most current and proposed safety guidelines are applicable to both pulsed and CW RFR, these guidelines do not include maximum allowable pulse power densities per se.

In the light of these gaps, the possibility that new information would reveal a significant hazard from chronic exposure to low levels of RFR cannot be dismissed, but is judged to be relatively low.

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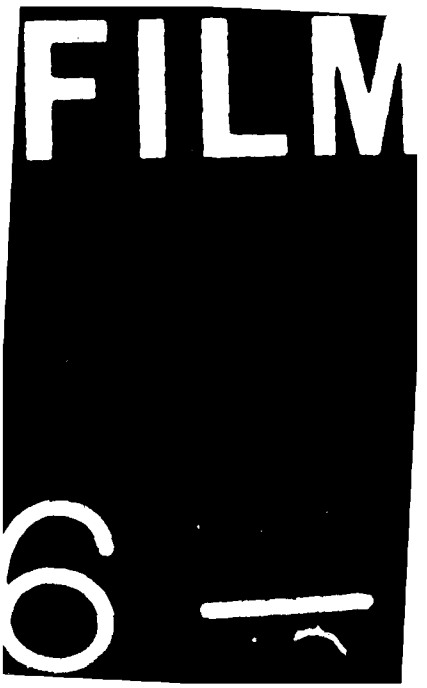
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