10

Radiofrequency Biology: *In vivo*

Masamichi Kato

When selecting papers to be summarized in this chapter, the goal was to provide a nearly comprehensive review of recent papers. The emphasis is on relatively recent (less than 10, or more typically, less than 5 years old) papers; older work is covered well in many published books and review articles.

10.1 Carcinogenesis

Carcinogenesis is a complex, multistage process. Normal cells develop into tumor cells as a result of genetic changes (initiation stage). Once a cell has been initiated, typically by the accumulation of genetic changes as a result of damage and faulty DNA repair, several kinds of chemicals and physical forces, such as ionizing radiation, can act as "promoter" (or co-promoter) to increase the rate of growth of tumor cells (promotion stage).

La Regina et al. (2003) carried out a study to determine whether chronic exposure to microwave fields from cellular phones increased incidence of spontaneous tumors in F344 rats. Eighty male and 80 female rats were randomly placed into one of three groups. The sham-exposed group received no irradiation; the Frequency Division Multiple Access (FDMA) group was exposed to 835.62 MHz, FDMA-modulated microwaves; and the Code Division Multiple Access (CDMA) group was exposed to 847.74 MHz, CDMA-modulated microwaves. Rats were exposed for 4 h/d, 5 d/w for over 2 yrs. The nominal, time-averaged brain SAR was 1.3 W/kg. There were no differences in final body weights or survival for either males or females in any group. No differences were found between treated and sham-exposed animals for any tumor in any organ. The authors conclude that chronic exposure for up to 2 years to 835.62 MHz (FDMA) or 847.74 MHz (CDMA) microwaves had no effect on the incidence of spontaneous tumors or the initiation stage of carcinogenesis.

Rat liver is the most commonly used experimental model for investigating multistage carcinogenesis in tissues. Imaida et al. (1998a) reported on a medium-term liver bioassay in which near-field exposure of F344 male rats to 900 MHz or to 1.5 GHz electromagnetic fields resulted in slightly decreased numbers and areas of

liver foci positive for glutathione S-transferase, which are pre-neoplastic liver lesions in rats. Imaida et al. (1998b) further completed an experiment in which a 929.2 MHz time division multiple access (TDMA) signal for Personal Digital Cellular (the Japanese cellular telephone standard) system was directed to rats through a quarter-wavelength monopole antenna. Maximum local SARs were 6.6 – 7.2 W/kg within the whole body and 1.7 – 2.0 W/kg within the liver, which was the target organ. Near-field exposure was for 90 min/day, 5 d/w, for 6 wks. The exposure apparatus was specially designed to allow exposure of the lateral, mid-section of the rat body to the electromagnetic field. Male F344 rats, 6 week-old, were "initiated" (at week 0) by a single dose of diethylnitrosamine (DEN). Two weeks later, exposure (n = 48) or sham-exposure (n = 48) was started. At week 3, all rats were subjected to a 2/3 partial hepatectomy, to stimulate growth of liver tissue. At week 8 (after 6 weeks exposure), the experiment was terminated. Carcinogenic potential was scored by comparing the numbers and areas of foci in the livers positive to the induced glutathione S-transferase placental form for the field-exposed and sham-exposed rats. Another group of 24 animals, given only DEN and partial hepatectomy, served as an additional control group. There were no differences between the exposed and sham-control groups. These findings showed that local body exposure has no significant promoting effect on rat liver carcinogenesis, under the experimental conditions tested.

In both experiments (Imaida et al. 1998ab), the daytime serum melatonin concentrations were increased in both 900 MHz and 1.5 GHz exposed groups as compared with sham-exposed control group values. Therefore, changes of serum melatonin levels might have modified the development of pre-neoplastic lesions in the livers of the microwave-exposed rats. Because melatonin is oncostatic, increased melatonin might have inhibited tumor development in microwave-exposed rats. (See section 2.2.2.1.3.)

In order to clarify this question, Imaida et al. (2000) analyzed the effects of different doses of melatonin in the same bioassay system employed for their previously reported EMF exposure studies. Six-week-old male F344 rats were given a single dose of DEN. Starting 2 wks later, they were treated for 6 wks with 0, 1, 5, 10 or 20 ppm melatonin in drinking water. Melatonin was provided only during the night (between 18:00 to 0:00) in order to maintain circadian rhythmicity. At wk 3, all rats were subjected to a two-thirds partial hepatectomy. At wk 8, the experiment was terminated. At this one time point, serum levels of melatonin, adrenocorticotropic hormone (ACTH), corticosterone, lutenizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone were measured. Melatonin was elevated; LH and testosterone were reduced. Although clear dose-dependence was not apparent, both numbers and areas of foci positive for the induced glutathione S-transferase placental form in the liver were decreased in the 10 ppm melatonin group. These results suggest that an increase in serum melatonin levels is a possible reason for the associated tendency for decreased pre-neoplastic hepatocyte development in microwave-exposed rats.

Bartsch et al. (2002) studied whether a signal based on the Global System for Mobile communication (GSM) could stimulate development of mammary tumors,

induced by treatment with dimethylbenzanthracene, in female Sprague Dawley (SD) rats. Exposure was at 900 MHz, pulsed at 217 Hz (pulse width 577 μsec) with a relatively low power density (100 μW/cm^2) applied continuously to freely moving animals. The average whole body SARs were 17.5–70 mW/kg. The low-level microwave exposure did not appear to possess carcinogenic or cancer-promoting effects on mammary tumors induced with dimethylbenzanthracene.

The overall result of the three studies (Imaida et al. 1998ab, Bartsch et al. 2002) was that there was no effect of microwave exposure using cell-phone signals on tumor latency and cumulative tumor incidence. These results, obtained using the animal test procedures developed to assess carcinogenicity of chemicals, show that low-level microwave exposure like that associated with mobile or cell phones does not appear to possess carcinogenic or cancer-promoting effect. Performance of a few more such experiments remains warranted. If the results continue to be negative, the answer from animal experiments will be known. However, no matter what the results of the animal experiments, human epidemiology related to the question 'do cell phones cause cancer?' undoubtedly will continue for some time.

The results also suggest that microwave electromagnetic fields might have effects on melatonin. The limited initial data from these very ambitious melatonin studies indicates a beneficial, rather than an adverse effect. Clearly, additional research on microwave (and RF) fields and melatonin is warranted.

10.2 Central Nervous System

Given its critical importance for humans, the effect of exposure to RF energy on the central nervous system (CNS) has been studied extensively. The following sections review experiments assessing brain morphology, the blood-brain barrier (BBB), electroencephalogram (EEG), evoked potentials, behavior, the hippocampus, microwave field detection, and neurotransmitters.

10.2.1 Morphology

Very few investigators have assessed the cellular morphology of brains of animals that had been exposed to microwaves. Perhaps this is because it is a daunting challenge, and perhaps because there is little reason to expect any change when the microwave doses used do not produce excessive heating.

Albert et al. (1981b) studied the effects of either 2.45 GHz (SAR of 2.8 W/kg) or 100 MHz (SAR 2 W/kg) applied to young rats. Then the histological appearance of cerebellar Purkinje cells was assessed. Environmental stress, hypoxia, alcohol or fatigue can easily damage these cells, and glia cells subsequently replace the damaged neurons. Exposure to both frequencies had similar effects, producing irreversible decreases of Purkinje cells in rats irradiated either during fetal or fetal and early postnatal periods. Decreases in the relative number of Purkinje cells were apparent in animals exposed postnatally.

Tsurita et al. (2000) investigated the effects of exposure to 1.439 GHz TDMA (Time division Multiple Access) signals on Purkinje cells in cerebellum of rats. Mature male SD rats were divided into three groups of eight. The rats in the field-exposed group, which had their heads arrayed in a circle near the central antenna of an exposure system, were exposed to microwaves for 1h/day for either 2 or 4 wks. The rats in the sham-exposed group also were placed in the exposure system, but no microwave exposure was given. The cage-control group was neither placed in the system nor exposed. The SAR for the brain was 2 W/kg; the whole body SAR was 0.25 W/kg. No morphological changes were observed in any group. The different outcomes from Albert et al. (1981b) and from Tsurita et al. (2000) might be due to the very different ages of the rats used.

Albert et al. (1981a) exposed pregnant squirrel monkeys to 2.45 GHz microwaves (SAR 3.4 W/kg) for 3 h/d, 5 d/w; post-natal exposure continued until the offspring were 9.5 months of age. They then studied the effects of microwave exposure on the density of Purkinje cells in the cerebellar uvula. In contrast to the rat data (Albert et al. 1981b), there was no effect on the monkey's Purkinje cells. Albert et al. (1981a) point out that differences in the anatomical structures of the head and in the exposure conditions (free field vs. multipath) could have contributed to the difference in results. Also, 2.45 GHz might be closer to resonant frequency of the rat than the squirrel monkey, and the depth of penetration of RF energy can be important. Further the structure of the brain in each species presents a different exposure configuration. In the rat, the cerebellum is exposed in the dorsal and posterior aspect and is covered by a thin calvaria. In the squirrel monkey, the cerebellum is overlapped by the occipital lobes, a thicker calvaria, and thick muscles in the cervical region (Albert et al. 1981a).

Based on these three studies, it is impossible to know whether or not microwave exposure can affect the microscopic anatomy of regions of the brain. However, based on the relatively low energy levels and the presumed lack of tissue heating associated with them, it is unlikely that environmental exposures produce frank brain pathology. Presumably experiments associated with ongoing research programs intended to address the safety of cell phones will produce a few more studies relevant to this specific question.

10.2.2 Blood-brain barrier

The blood-brain-barrier (BBB) maintains the homeostatic environment of the brain by regulating the entry of vital substances and nutrients into brain and the expelling of carbon dioxide and metabolic waste products out of the brain. This barrier protects the brain from foreign toxic substances but allows passage of the molecules that are necessary for metabolism.

Brain capillaries are composed of endothelial cells, pericytes, that have smooth muscle-like properties and reside adjacent to capillaries, and of astroglial processes that ensheath more than 95% of the capillary surface (Fig 10.1). Among these structures, the endothelial cells are the principal anatomic site of the BBB. The endothelial
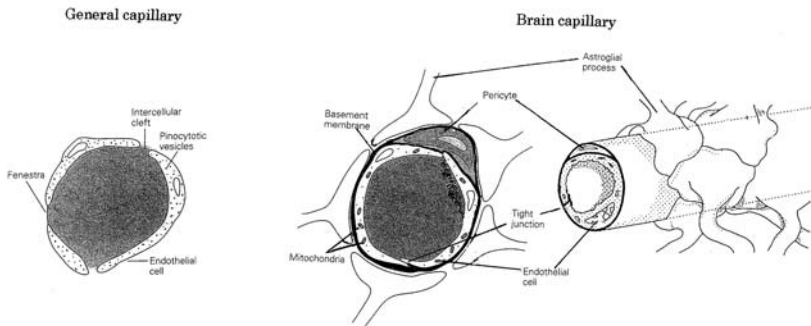
Fig. 10.1. Anatomical features of general capillaries and of brain capillaries. General capillaries have inter-endothelial clefts, fenestrae, and prominent pinocytotic vesicles. These features allow relatively non-selective diffusion across the capillary wall. Endothelial cells of the brain capillary contain an increased number of mitochondria to support energy-dependent transport systems and are inter-connected by complex, inter-endothelial "tight" junctions. These anatomical features, in conjunction with specific transport systems, result in highly selective transport of water-soluble compounds across the barrier endothelium. Astrocyte processes surround more than 95% of the brain capillaries. Functionally, this results in what is called the blood-brain barrier.

cells of the BBB are interconnected by complex arrays of "tight" junctions. These junctions block diffusion across the capillary wall.

In capillaries of other organs, and in the relatively few brain capillaries that do not form a barrier, blood-borne, polar molecules diffuse passively across vessels through "spaces" between endothelial cells, i.e., through specialized cytoplasmic fenestrations.

Normal brain function requires a large number of compounds that must be able to cross brain capillaries. Entry into the cerebrospinal fluid is achieved primarily in three ways: (1) by diffusion of lipid-soluble substances, (2) by energy-dependent, receptor-mediated transport of specific, water-soluble substances, and (3) by ion channels.

Most substances that must cross the BBB are not lipid soluble and therefore cross by specific carrier-mediated transport system. Glucose is transported through the Glut 1 system, which is not energy dependent. The net flux of glucose is driven by the relatively higher concentration of glucose in plasma. Amino acids are transported across barrier endothelial cells primarily by three distinct carrier systems: the L, and ASC systems. For further study, the readers are advised to consult with textbook of neuroscience (e.g., Kandel et al 2000)

In many diseases the BBB does not function effectively and substances that are normally excluded enter the brain. A number of causes – such as inflammation of

brain membrane (i.e., meningitis), edema, anoxia, hypertension, and ionizing radiation – have been shown to induce BBB changes, often increasing permeability of substances to the brain. Radiotracer, immunohistochemistry, or the classical staining method by Evans blue often are used to reveal permeability changes. With a functional BBB, Evans blue does not enter the brain. Thus, when areas of brain are stained blue, it indicates a breakdown of the BBB in those areas.

The existence of a microwave-induced BBB permeability increase was controversial for many years. Now most researchers believe that the permeability change is associated with an increase in temperature, and no permeability change is observed with athermal microwave exposure.

Ikeda et al. (1994) used 8 MHz RF exposure to investigate the distributions of temperature changes produced by interstitial hyperthermia in agar phantoms and in brains of dogs. The heating limits of normal dog brains were 42°C for 45 min or 43°C for 15 min; breakdown of the BBB, assessed using Evans blue, was observed with heating at 43°C for 60 min.

Ohmoto et al. (1996) used rats to investigate the temperature distribution, early histological changes, BBB disruption, and sequential changes in cerebral blood flow (CBF) following hyperthermia, ranging from 37 to 45°C, produced by RF-induced, localized cerebral hyperthermia. Histological changes and BBB disruption were observed in brain regions heated to 43°C and above.

Fritze et al. (1997) investigated the effects of GSM microwave exposure on the permeability of the BBB. Rats were restrained in a carousel of circularly arranged plastic tubes and sham-exposed or microwave irradiated at 900 MHz for 4 h at SARs of 0.3, 1.5 or 7.5 W/kg. The extravasation of protein was assessed, either at the end of exposure or 7 days later, by immunohistochemistry staining of serum albumin. An increase in serum albumin extravasation after microwave exposure was observed only in the group exposed to the highest SAR of 7.5 W/kg and the extravasation was present only immediately after exposure. Histological injury was not observed in any of the examined brains. The observed albumin extravasations were very modest and, moreover, were totally reversible.

Finnie et al. (2001) studied the effect of short-term exposure to GSM microwaves on vascular permeability in the brain. Mice (n = 30) were given a single, far-field, whole- body exposure at 898.4 MHz for 60 min at a SAR of 4 W/kg. Control mice were either sham-exposed (n = 10) or permitted free movement in a cage (n = 10) to exclude any stress-related effects. Vascular permeability changes were detected using albumin immunohistochemistry. No differences among groups were detected. Finnie et al. (2004) further studied the effect of long-term exposure to GSM fields at 900 MHz. Mice were given a 60 min, far-field, whole-body exposure 5 dy/wk for 104 wks at SARs of 0.25, 1.0, 2.0, or 4.0 W/kg. Albumin staining was used to detect increased permeability. The results suggest that prolonged exposure to mobile telephone-type radiation produced negligible disruption to BBB integrity under these experimental conditions.

Tsurita et al. (2000) investigated the effects of athermal exposure to 1.439 GHz modulated by the TDMA protocol on the permeability of the BBB. Adult male SD rats were assigned to one of three groups of eight rats. The rats in the microwave-

exposed group were exposed 1 hr/dy. The rats in the sham-exposed group were placed in the exposure system without microwave delivery. The animals in the cage control group were not placed in the exposure system. The exposure period was 2 or 4 wks. The SAR was 2 W/kg in the brain, and the whole body SAR was 0.25 W/kg. Core body temperature was measured; no increase in body temperature was detected. Changes in the BBB were sought using Evans blue injection and immunostaining of serum albumin. Microwave exposure had no effect on the BBB.

Contrary to the negative findings of these five papers, two other groups have reported that non-thermal microwave irradiation did cause BBB permeability changes. Salford et al. (1994) reported that weak, non-thermal level, pulsed microwaves give rise to a significant leakage of albumin through the BBB. Salford et al. (2003) further investigated whether a pathologic leakage across the BBB might be accompanied by neuronal damage. Three groups each of eight rats were exposed for 2 hr to a GSM microwave field at whole-body SARs of 2, 20, and 200 mW/kg, all well below the level expected to produce temperature elevation. The authors found a positive relationship between SAR and number of "dark" neurons, evidence for neuronal damage, in the cortex, hippocampus, and basal ganglia of exposed rats. The authors claim that they presented, for the first time, evidence for neuronal damage caused by a nonthermal microwave exposure.

Leszczynski et al. (2002) examined whether athermal exposures of cultures of a human endothelial cell line to 900 MHz GSM radiation could activate a cellular thermal stress response. Non-thermal ($37 \pm 0.3°C$), 1 hr microwave exposure caused a transient increase in phosphorylation of heat shock protein-27. The authors hypothesized that 900 MHz GSM radiation induced activation of heat shock protein-27 to cause an increase in BBB permeability through stabilization of endothelial cell stress fibers.

Efforts to reproduce the results of Salford et al. were reported by four groups at the 2005 annual meeting of the Bioelectromagnetics Society. McQuade et al. (2005) and Haro et al. (2005) examined albumin leakage and degenerative neurons, which were originally reported by Salford's group. Both parties found no differences between the microwave-exposed and sham-control groups. Two other groups also assessed other measures in addition to albumin leakage. Shirai et al. (2005) examined alteration of BBB-related genes, such as p-glycoprotein, aquaporin-4, and claudin-5, and Masuda et al. (2005) studied microcirculation. Neither group found any differences between the irradiated and the control animals.

Combined effects of microwave irradiation and other agent(s) have been reported by two groups.

Neilly and Lin (1986) studied the combined effects of ethanol and microwaves on the BBB in male Wister rats. Anesthetized rats, each with an implanted venous cannula, were infused with 0.1, 0.3, 0.5 or 0.7 gm/kg of absolute ethanol. A control group was given 0.7 g/kg of isotonic saline. The left hemisphere of each brain was irradiated by 3.15 GHz microwave energy at 3.0 W/cm^2(rms) for 15 min. The rectal temperatures remained at 37.0°C. Immediately after irradiation, Evans blue dye was injected through the cannula. The results showed that as the quantity of alcohol was increased, the degree of staining was decreased or eliminated. The temperature of the

irradiated area of the brain increased for the first 4 to 5 min of irradiation and then stabilized for the remainder of the irradiation period. The steady-state temperature was highest in animals receiving saline or the smallest dose of alcohol. As the quantity of alcohol was increased, the steady-state temperature was reduced. These results indicate that ethanol inhibits microwave-induced permeation of the BBB through reduced heating of the brain.

There is another report which investigated combined effect of microwave exposure and virus infection. The expression of Japanese Encephalitis Virus (JEV) lethality in mice requires entry of the virus into the CNS. This entry is presumably through the capillary endothelial cells, because entry between these cells is inhibited by bands of circumferential tight-junctions. A viremic stage occurs during the first 4 to 5 days after virus administration in mice. Lange and Sedmak (1991) assessed how both microwave radiation (2.45 GHz, continuous wave, 10 min exposure) and hypercarbia (CO_2 exposure) affected capillary endothelial cells permeability to JEV in adult Swiss-Cox mice. Exposure to microwaves at very high SARS of approximately 24–98 W/kg resulted in a dose-dependent increase in JEV-induced lethality. Similarly, hypercarbia produced by exposure to 5, 10, and 20% CO_2 was observed to produce a dose-dependent increase in virus-induced lethality. Both microwave radiation and hypercarbia are thought to promote pinocytosis within capillary endothelial cells of the CNS. This may be one mechanism by which they enhance JEV-induced lethality in adult Swiss-Cox mice.

Historically, a reasonably sized set of papers has addressed the possibility that microwave exposure can diminish the effectiveness of the BBB. The pattern of results is clear. If microwave exposure produces hyperthermia, BBB integrity is diminished. If the microwave exposures used do not produce hyperthermia in the brain, i.e., if they are athermal, there is no effect.

The Salford saga appears to be a recapitulation of a process that has occurred repeatedly over the past four decades. Some group claims an "athermal" effect. Because this would be important, if true, other investigators rapidly attempt to replicate the claim. Invariably, the alleged athermal effect is not substantiated.

10.2.3 Electroencephalogram

The human EEG changes according to a 24 h circadian rhythm of behavior in response to the 24 h astronomical cycle. Sleep states lasting approximately 8 h during night form the unconscious part of that cycle. A basic principle of sleep cycle control in human has been articulated by Borbely (2001) as a "Two Process Model," in which sleep-wake state transitions result from the combined effects of circadian factors and homeostatic factors. During sleep, a third regulator, the ultradian, REM-NREM oscillator comes into play. In terms of EEG, sleep comes in two forms, rapid eye movement (REM) – when dreaming occurs – and non-REM (NREM).

10.2.3.1 Animal studies

Johnson and Guy (1972) demonstrated thermographically that metal electrodes in a cat brain increased the local SAR by 50 times. Therefore the use of metallic elec-

trodes for EEG recordings made most early results questionable. Glass electrodes filled with Ringers solution (Johnson and Guy 1972) or carbon-loaded Teflon electrodes with conductivity close to that of tissue have been used to minimize field perturbation (Chou and Guy 1979). Even with minimally field perturbing electrodes, EEG electrodes can pick up RF fields and induce current into the head, making it difficult to differentiate between the direct effect of the RF field and an effect of the induced currents in acute experiments.

Takashima et al. (1979) reported on the effects of modulated RF fields (1–30 MHz, 15 or 60 Hz modulation) on the EEGs of male rabbits following acute (2–3 h) and chronic (2 h/d for 4–6 weeks) exposures. Although acute exposure up to 500 V/m did not cause effects, chronic exposure above 90 V/m enhanced the low frequency components of the EEG and decreased high frequency activities. The acute study showed that metal electrodes caused artifacts during recording. However, the effects of chronic exposure were not due to the presence of electrodes, because electrodes were not present during RF exposure.

The effect of 40 mW/cm^2, 2.4 GHz exposure for 1 min on EEG of rabbits was described by Chizhenkova (1988). Exposure of the head increased the number of slow waves and spindle-shaped firings in the EEG. It also changed the discharge frequency of neurons in the visual cortex, producing an enhancement of the evoked response of visual cortex neurons to a light stimulus.

Thuroczy et al. (1994) reported that the total power of EEG spectra increased in rats after whole-body 2.45 GHz, continuous wave microwave exposure (30 mW/cm^2) for 10 min; changes occurred at 10 mW/cm^2. The cerebral blood flow (CBF) increased after 10 mW/cm^2. The power of EEG δ waves (0.5 – 4 Hz) was increased by thermal level of brain localized 4 GHz (continuous wave) exposure at 42 mW/g with simultaneously increase of the CBF. Vorobyov et al. (1997) analyzed average EEG frequency spectra in eight unanesthetized adult rats with chronically implanted carbon electrodes in symmetrical somesthetic areas. Microwaves of 945 MHz, at 0.1 – 0.2 mW/cm^2, amplitude modulated at 4 Hz were applied for 1 min on and 1 min off during 10 min sessions. There were no differences, other than an elevation of EEG asymmetry in the 10 – 14 Hz range observed during the first 20 sec after onset of the exposure.

In summary, it appears that ELF-modulated microwave fields produced changes in EEG patterns by enhancing the low-frequency components and decreasing high-frequency activities.

10.2.3.2 Human studies during waking state

Hietanen et al. (2000) examined the possible influence of microwave radiation on human brain function by recording EEG activity of 19 volunteers. The sources of exposure were five different cellular phones (analogue and digital models) operating at a frequency of 900 MHz or 1.80 GHz. The EEG was recorded in an awake, closed-eyes situation. Six 30 min sessions, including 1 sham exposure, were completed for each subject. The duration of the real exposure phase was 20 minutes. Exposure to

the microwave fields emitted by cellular phones had no abnormal effects on human EEG.

Kramarenko and Tan (2003) recorded EEG changes during exposure of human head mobile phone emissions. The spatial distribution of the electromagnetic field was concentrated around the ipsilateral eye adjacent to the basal surface of the brain. Slow-wave activity (2.5–6.0 Hz) appeared in the contralateral frontal and temporal areas; the activity lasted for about 1 sec and reappeared every 15–20 sec. After turning off the mobile phone, the slow-wave activity disappeared 15–20 min later. The authors interpreted these results as indicating that cellular phones might reversibly influence human brain function by inducing abnormal slow waves in the EEG of awake persons.

Krause et al. (2000a: 2000b) studied the effects of the 902 MHz microwave field emitted by one model of a cell phone on the event-related desynchronization and synchronization of the 4–6 Hz, 6–8 Hz, 8–10 Hz, and 10–12 Hz EEG frequency bands of human subjects performing either (1) an auditory memory task (Krause et al. 2000a) or (2) a visual sequential letter task with three different working memory load conditions (Krause et al. 2000b). All subjects performed the memory task both with and without exposure to EMF in counter-balanced order. The microwave exposure increased EEG power in the 8–10 Hz frequency, only when examined as a function of memory load. However, in their own replication studies, which were conducted under a double-blind procedure, Krause et al. (2004) were not able to replicate the positive finding from their own earlier studies. They mentioned that microwave-exposure effects on the EEG and on the performance on memory tasks might be variable and not easily replicable, for reasons yet to be clarified.

10.2.3.3 Human studies during sleep

Studies of sleep EEG by Mann et al. (1998a) and Wagner et al. (2000) showed no effects were produced by irradiation with a 900 MHz microwave field, pulsed at 217 Hz and with an average power density of 0.02 mW/cm^2.

During an entire night-time sleep episode, Borbely et al. (1999) exposed subjects to 900 MHz, at a maximum SAR of 1 W/kg, using an intermittent schedule consisting of alternating 15 min on and 15 min off intervals. Spectral power of the EEG increased in the 10–11 Hz and 13.5–14 Hz bands during the initial part of NREM sleep and then subsided.

Huber et al. (2002) reported that pulse-modulated, 900 MHz electromagnetic field exposure increased relative CBF (rCBF) in the dorsolateral prefrontal cortex ipsilateral to exposure. This microwave exposure also enhanced EEG power in the alpha frequency range prior to sleep onset and in the spindle frequency range during stage-2 sleep, although the effects were subtle. Huber et al. (2003) extended the analysis. Unilateral exposure during waking induced a similar effect in both hemispheres. Microwave exposure during sleep reduced waking after sleep onset and affected heart rate variability. Huber et al. (2005) observed an increase in relative rCBF in the dorsolateral prefrontal cortex on the side of exposure (ipsilateral) after 30 min of unilateral head exposure to pulse-modulated, 900 MHz microwaves EMF. Two

types of EMF exposure were applied: a 'base-station-like' and a 'handset-like' signal (SAR of 1 W/kg for both conditions). The effect depended on the special power in the amplitude modulation of the RF carrier such that only 'handset-like' exposure, with its stronger low-frequency components, but not the 'base-station-like' exposure affected rCBF. The authors stated that pulse modulation of cell phone signals is necessary to induce changes in the EEG, both waking and sleeping.

Overall, outcomes of the various human studies have been inconsistent, and comparison between individual studies is difficult. Enhanced power in the alpha band was observed in both human and some animal studies. Effects reported on sleep EEG are more likely to involve NREM alpha waves, compared to other bands, as they do in these EEG experiments on young human subjects.

10.2.3.4 Preparatory potentials

Motor actions often are self-initiated without an outside cue. Almost 1 second before a self-initiated volitional movement begins, a characteristic negative shift in cortical potentials is seen in the EEG record of medial premotor areas, where the supplementary motor area is located. This slow negative potential, referred to as the preparatory potential, signals the planning that occurs before movement is executed. The region responsible for this negative potential was localized more precisely in a study comparing increase in rCBF during simple, complex, and imagined sequences of finger movements. Complex movement sequences require more planning than do simple repetitive movements. Imagining complex movements might require the same amount of planning as real movements (Krakauer and Ghez 2000).

Freude et al. (1998) searched for effects on preparatory potentials during exposure to cell phone emissions. In the first experiment, healthy male human subjects performed simple, self-paced finger movements to elicit a preparatory potential. In the second experiment, they performed a complex and cognitively demanding visual monitoring task. Both tasks were performed with and without microwave exposure, in counter-balanced order. Exposure produced a significant decrease of preparatory potentials at central and temporo-parieto-occipital brain regions while performing the visual monitoring task. No effect on the slow potentials was seen in the simple finger movement task.

Freude et al. (2000) studied 20 healthy male subjects who were exposed to modulated 916.2 MHz microwaves (217 Hz pulse frequency, pulse width 577 μsec; 2.8 W/kg SAR) emitted near the left ear. Two experiments were completed, about 6 months apart. In the first experiment, microwave exposure produced a decrease of preparatory potential while performing a complex visual monitoring task. This effect was replicated in the second experiment. Exposure effects on preparatory potentials were analyzed further with two, less demanding tasks: a simple finger-movement task and a two-stimulus task eliciting a contingent negative variation (CNV) response. CNV was explained in Chapter 2. In comparison to the complex visual monitoring task, no effects were found with the less demanding tasks. The results suggested a selective microwave-exposure effect on particular aspects of human information processing but did not indicate any influence on human performance.

10.2.3.5 Event-related magnetic fields

Hinrichs and Heinze (2004) investigated potential effects of GSM 1800 on verbal memory encoding by recording event-related magnetic fields from the brain during subsequent memory retrieval. After encoding words from a study list presented in the first phase, the 12 subjects had to discriminate old from new words mixed together in a test list. Subjects completed two experimental sessions, one with microwave exposure during the study phase, and one without. Field exposure produced changes an early (350–400 msec), task-specific component of the event-related magnetic field. The authors suggest field exposure interfered with item encoding, although behavioral measures were not affected.

10.2.3.6 Summary

The literature on possible microwave exposure effects on the EEG is not small, and it suggests effects can be measured. Unfortunately, EEG has proven to be of limited utility as a general neurotoxicology screening measure, and the problem of suitable electrodes for recording during RF exposure is an added special difficulty. The literature does suggest that a scattering of EEG changes can be measured as a consequence of microwave exposure. It would take a considerable amount of additional research to build this hint into useful knowledge.

Exposure can produce subtle effects on human EEG. However, there is little agreement on either what mental processes are affected or the meaning of the changes reported. Most studies test of cell phone signals and human cognitive performance used only one dose, had poor dosimetry, inadequate control groups, and poor traceability. Possible interference and reflection of microwaves should be assessed in exposure setups. Boredom and heat can induce sleep, and sleep-related changes in the EEG could account for positive findings. As a result no conclusions can be drawn from the presently available research on possible effects of microwave exposure and EEG.

10.2.4 Cognitive function

In both humans and animals, microwave fields are suspected of being able to affect cognitive functions. More specifically, several studies performed in rodents have suggested that spatial learning can be impaired by electromagnetic field exposure.

A major effect of exposure to RF frequencies above 100 kHz is heating. Microwave heating is known to affect memory and learning (Saunders et al. 1991). At 2 GHz, because of the shorter wavelength, exposure is mostly superficial; the RF energy is absorbed by skin rather than the deeper tissues, as it is with the lower frequencies (longer wave lengths) of 900 and 450 MHz (Adair et al. 1999: 2001a). These frequencies are used by current mobile communication systems. Threshold SARs were estimated to be 2.5 W/kg at 225 MHz (near body resonance, for the human) and 4–5 W/kg at the higher frequencies. However, colonic temperature rose in all cases by about 1°C. The lowest SAR threshold for learning effects was found

during exposure to more deeply penetrating fields at lower frequencies, such as 225 MHz (Saunders et al. 1991). Resonant frequencies for humans and animals differ, because of their different body sizes.

10.2.4.1 Cognitive studies with animals

Referring to body temperature changes, Yamaguchi et al. (2003) studied two behavioral tasks, using a T-maze for the assessment of memory: Subjects first performed a spatial discrimination task, being rewarded on one side in the training session; they then performed on a reversal task, being rewarded on the other side in the test session. Reversal discrimination is described by a 3-stage model. In the first stage, after the reward location has been reversed, the undoing of old habits is required. The second stage is the period when the animal responds by chance. In the third stage, the new habit is acquired. Working memory is required in the first stage, where the rats have to remember which of the two baited arms contains the food reward, whereas reference memory is involved in the following stage. SD rats were exposed daily for 1 h for either 4 days or 4 weeks. Exposure consisted of a pulsed (TDMA) 1439 MHz microwave field in a carousel-type exposure system; two different SARs were used. In one group, the SAR at the brain was 7.7 W/kg, and the whole-body SAR was 1.7 W/kg, which did not cause an increase in core body (intraperitoneal) temperature. Other subjects were exposed at the brain average SAR of 25 W/kg and the whole body average SAR of 5.7 W/kg for 45 min daily for 4 days. In this group intraperitoneal temperature began to rise soon after the beginning of exposure and rose by about 2°C within 60 minutes. The rats with a brain SAR of 25 W/kg for 4 days showed decreases in the transition in number of correct choices in the reversal task, compared to cage-control or sham-exposed subjects. However, rats exposed with a brain SAR of 7.5 W/kg, for either 4 days or for 4 weeks, showed no impairment of T-maze performance. These results suggest that the exposure to a TDMA microwave field at levels about 4-fold stronger than emitted by cellular phones does not affect the learning and memory processes when there are no thermal effects.

Wang and Lai (2000) reported that the exposure to pulsed 2.45 GHz with a whole body SAR of 1.2 W/kg for 1 h daily for 6 days caused deficits in spatial reference memory in rats using a Morris water-maze. Microwave-exposed rats were slower than sham-exposed and cage-control rats in initial learning to locate the platform. However, there was no difference in swim speed among the three groups of animals, indicating that the difference in learning was not due to a change in motor functions or motivation. During the probe trial, microwave-exposed animals spent less time in the quadrant that had contained the platform. Also, their swim patterns were different from those of the sham-exposed and cage-control animals. These observations indicated that microwave-exposed rats used a different strategy in learning the new location of the platform. The authors indicate that acute exposure to pulsed microwaves caused a deficit in spatial "reference" memory in the rat.

Lai (2004) investigated the effect of a temporally incoherent magnetic field ('noise') on microwave-induced spatial learning deficit in the rat. Rats were trained

in six sessions to locate a submerged platform in a circular water-maze. Four treatment groups of rats were studied: (1) microwave-exposure (2.45 GHz, continuous wave; whole-body SAR 1.2 W/kg), (2) magnetic field 'noise' exposure (60 mG), (3) microwave + magnetic field exposure, and (4) sham exposure. Animals were exposed to these conditions for 1 h immediately before each training session. One hour after the last training session, animals were tested in a 2 min probe trial in the maze, during which the platform was removed. The time spent the quadrant of the maze in which the platform had been located was scored. Results show that microwave-exposed rats (1) had a deficit in learning to locate the submerged platform, when compared with performance of the sham-exposed animals. Exposure to magnetic field noise alone (2) did not affect the performance of the animals. However, simultaneous exposure to magnetic field noise (3) attenuated the microwave-induced spatial learning deficit. Thus, simultaneous exposure to a temporally incoherent magnetic field attenuated microwave-induced spatial learning and memory deficits in the rat.

However, there are several reports which found no effects of microwave exposure on learning and memory tasks.

Sienkiewicz et al. (2000) studied the effect of repeated, acute exposures to a low-intensity 900 MHz microwave field pulsed at 217 Hz on a spatial learning and working memory task. Adult male C57BL/6J mice were exposed under far-field conditions in a GTEM cell for 45 min each day for 10 days at a SAR of 0.05 W/kg. Their performance in an 8-arm radial maze was compared to that of sham-exposed control animals. Animals were tested in the maze immediately following exposure or after delays of 15 or 30 min. No field-dependent effects on performance were observed in choice accuracy or in total times to complete the task.

Dubreuil et al. (2002) used a head-only exposure system emitting 900-MHz GSM microwaves, pulsed at 217 Hz, to expose rats for 45 min with SARs of either 1.0 or 3.5 W/kg. Two behavioral tasks were employed to demonstrate performance deficits in spatial learning after microwave exposure: an 8-arm radial maze and a spatial navigation task in an open-field arena, i.e., another version of the Morris water-maze. There were no differences in performance on the two spatial learning tasks among microwave-exposed, sham-exposed, and cage-control rats. Dubreuil et al. (2003) extended their study by using a more complex spatial learning task and a non-spatial object recognition task. Altogether, this set of experiments provides no evidence indicating that spatial or non-spatial memory can be affected by a 45 min, head-only exposure to a 900 MHz (GSM) microwave field.

Cobb et al. (2004) examined the possibility of changes in 'working memory' (Baddeley 1986) of rats following whole body exposure to microwave radiation. During each of 10 days, rats were exposed within circularly polarized waveguides for 45 min to pulsed (2 μsec pulses, 500 pps) 2.45 GHz fields at whole body SAR of 0.6 W/kg, followed by testing in a 12-arm radial maze. Rats received a pre-exposure injection of one of three psychoactive compounds or saline, to determine whether the drugs would interact with microwave exposure to affect maze performance. There was no evidence that exposure to pulsed 2.45 GHz microwaves caused decrements in the ability of rats to learn the spatial memory task.

Cosquer et al. (2005) studied whether whole-body exposure to 2.45 GHz electromagnetic fields affected anxiety responses of rats in a plus maze Rats were exposed for 45 min to pulsed 2.45 GHz microwaves (2 μsec pulse width, 500 pps) with a whole-body SAR of 0.6 W/kg and brain SAR of 0.9 W/kg. Exposure failed to induce any effects on anxiety responses.

D'Andrea et al. (1989) studied the effect of very high peak-power microwave pulses in the absence of whole-body heating on a time-related behavioral task. Five rhesus monkeys, *Macaca mulatta*, were exposed to peak-power densities of 131.8 W/cm^2(rms) while performing a time-related behavioral task. The task was composed of a multiple schedule of reinforcement consisting of three distinct behavioral components: inter-response time, time discrimination, and fixed interval. Trained monkeys performed the task during exposure to 1.3 GHz pulses at low pulse-repetition rates (2–32 Hz). No changes in performance were observed during field-exposure compared to sham-exposure sessions. These might be species difference between rodents and monkeys.

It is difficult to make broad generalizations about the presence or absence of microwave-exposure effects on learning and memory in animals. There are many studies reporting positive effects, but there are just as many reporting absence of effects. When attempting to compare and contrast experiments, the many differences in task, subject size, microwave exposure conditions, etc. prevent closure and produce frustration. Science would be better served if investigators stopped independently shot gunning experiments, (looking for an effect, any effect) and focused on key questions, comparing hypotheses with single experiments and conducting replicative experiments across laboratories.

10.2.4.2 Cognitive studies with humans

Koivisto et al. (2000a: 2000b) examined possible influences of a 902 MHz microwaves on cognitive function of healthy human subjects. Microwave exposure shortened response times in simple reaction time and vigilance tasks, and time to complete a mental arithmetic task was decreased (Koivisto et al. 2000a). Also, microwave exposure speeded up response times when the memory load was three items or more but had no effects with lower loads (Koivisto et al. 2000b). These results indicate that microwave exposure with a signal like that of a cell phone actually can improve human cognitive performance. However, in their own replication study, which was conducted with improved methodology including multi-center testing and a double-blind design, researchers from the same laboratory (Haarala et al. 2004) could not replicate their previous results. The authors argue that the inability to replicate previous findings could have been caused either (1) by the lack of actual effects, or (2) the magnitude of effects being at the sensitivity threshold the tests used.

Maier et al. (2004) examined effects of exposure to pulsed electromagnetic fields (GSM standard) on cognitive performance of humans by using a psychophysiological test paradigm. Eleven subjects performed an auditory discrimination task. Following a first test cycle, the volunteers relaxed for 50 min while being either field-exposed or sham-exposed. Subsequently, the test was repeated. Data acquired

before and after the resting phase were compared for both experimental conditions. Nine of the 11 test participants (81.8%) showed worse auditory discrimination performance after microwave exposure, as compared with the sham-control condition.

10.2.4.3 Human attention

Two recent papers reported facilitating effects on human attention from exposure to the microwave fields used by mobile phones.

Edelstyn and Oldershaw (2002) investigated the effects of acute mobile phone exposure on a range of tasks assessing capacity and processing speed of the attentional system. Cognitive performance was assessed at three points (prior to mobile phone exposure, and at 15 and 30 min post-exposure) using six cognitive neuropsychological tests (digit span and spatial span forwards and backwards, serial subtraction and verbal fluency). Thirty-eight subjects were assigned randomly to either an experimental group, which was exposed for 30 min to the microwaves emitted by a 900 MHz mobile phone, or to a control group in which the mobile phone was switched off. Subjects remained blind to mobile phone status throughout duration of study. Differences between the two groups were evident after 5 min on two tests of capacity (digit span forwards and spatial span backwards) and one of processing speed (serial subtraction). In all three instances, performance was facilitated following mobile phone exposure. No deficits were evident.

Lee et al. (2003) studied the relationship between the facilitating effect and the duration of exposure. Seventy-eight university students were assigned randomly to either an experimental or a control group, and then performance on the administered attention tasks was compared. Participants in the experimental group performed better on one of the two measures of attention only after they had been exposed to the electromagnetic field emitted.

In summary, the results of recent studies of cell phone effect on human cognitive performance suggest that attentional functions can be enhanced by exposure to the low-intensity microwaves emitted by mobile phones. The noting of any bioeffect is of interest, given the small amount of energy involved. The discovery of improved performance is an ironic development in a research program that is focused on hazard assessment. Note also that other research suggests cell phone use while driving is adverse, apparently because it distracts drivers from the driving task. These laboratory tasks do not duplicate all aspects of the real world situation.

10.2.5 Hippocampal slice preparation

In order to obtain some clues to help elucidate the mechanisms of microwave irradiation on the CNS, two groups have carried out experiments on hippocampal slices. The hippocampal slice preparation, in which a portion of the hippocampus is placed *in vitro* and an input pathway is stimulated and activity in an output pathway is recorded has been used extensively to study the electrophysiology and neuropharmacology of processes related to learning and memory. One classic approach is to

study long-term potentiation (LTP). The amplitude of the response gets bigger as after some initial input stimulation is applied, and the change persists over time.

Tattersall et al. (2001) reported the possibility that low-intensity microwave fields can have effects on hippocampal tissues *in vitro*. Slices of rat hippocampus were exposed to 700 MHz, continuous wave (25.2–71.0 V/m, 5–15 min exposure) microwaves in a stripline waveguide. At low field intensities, the predominant effect on the electrically evoked field potential in CA1 was a potentiation of the amplitude of the population spike by up to 20%. However, higher intensity fields could produce either increases (up to 120%) or decrease (up to 80%). To eliminate the possibility of microwave-induced artifacts associated with the use of a metal stimulating electrode, the effect of microwave exposure on spontaneous epileptiform activity induced in CA3 by 4-aminopyridine (50–100 μM) also was investigated (Tattersall et al. 2001). Exposure to a microwave field (50 V/m) reduced or abolished epileptiform bursting in 36% of the slices tested. The maximum field intensity used in these experiments, 71.0 V/m, was calculated to produce a SAR of between 0.0016 and 0.0044 W/kg in the slices. Measurements with a Luxtron fiberoptic probe confirmed that there was no detectable temperature change ($+/-0.1°$C) during a 15 min exposure to this field intensity. Furthermore, imposed temperature changes of up to 1°C failed to mimic the effects of RF exposure. The authors claim that low- intensity microwaves can modulate the excitability of hippocampal tissues *in vitro* in the absence of gross thermal effects.

Pakhomov et al. (2003) studied effects of short, extremely high-power microwave pulses on neuronal network function using electro-physiological techniques in the rat hippocampal slice model. Population spikes in the CA1 area were evoked by repeated stimulation (1 per 30 sec) of the Schaffer collateral pathway. Brief tetanic stimulation (2 sec at 5 Hz) was used to induce LTP of synaptic transmission. In three different series of experiments with a total of 160 brain slices, the extremely high-power microwave pulse irradiation was performed before, during or after the tetanus. The carrier frequency was 9.3 GHz, the pulse width was from 0.5 to 2 μsec, and the repetition rate was from 0.5 to 1 Hz. The peak SAR in brain slices reached up to 500 MW/kg. (The instantaneous power is incredible.) Microwave heating of the preparation ranged from 0.5°C (at 0.3 kW/kg) to 6°C (at 3.6 kW/kg). The experiments demonstrated that the only effect caused by extremely high peak power microwave exposure, within the studied range of parameters, was a transient and fully reversible decrease in the population spike amplitude. Recovery took no more than a few minutes after the cessation of exposure and return to the initial temperature. The effect's features were characteristic of an ordinary thermal response. Also, the effect was proportional to the temperature rise but not to any specific parameter of microwave exposure. The decrease in the amplitude of the population spike also could be induced by a continuous wave irradiation or by conventional heating. Irradiation did not affect the ability of neurons to develop LTP in response to tetanus or to retain the potentiated state that was induced before irradiation. No lasting and delayed effects were observed. The results are consistent with a thermal mechanism action for extremely high peak power microwaves, and no indication of other mechanisms on neuronal function is suggested.

In comparing Pakhomov et al. (2003) with Tatersall et al. (2001), Pakhomov et al. pointed out that of the over 400 brain slices studied to date, no positive effect could be found without a temperature increase of the preparation of at least 0.5°C, whereas Tattersall et al. elicited variable effects, comparatively, with no measurable increase in preparation temperature. Pakhomov et al. also indicated that "if the reported nonthermal effects are unambiguously replicated under artifact-free conditions, this finding could have a major impact on modern microwave biology and RF exposure safety guidelines". Further study is warranted in this area.

10.2.6 Detection of RF electromagnetic fields

10.2.6.1 Perception

Koivisto et al. (2001) studied whether healthy humans sense the presence of microwave fields from digital GSM mobile phones (902 MHz, 217 Hz pulse modulation). The subjects were assigned in two single-blind experiments. The duration of the microwave exposure was about 60 min in Experiment 1 and 30 min in Experiment 2. Each subject rated symptoms (headache, dizziness, fatigue, itching or tingling of the skin, redness on the skin, and sensations of warmth on the skin) or sensations in the beginning of the experimental session and at the end of both the exposure and the non-exposure conditions. The results did not reveal any differences between exposure and non-exposure conditions, suggesting that a 30–60 min exposure to the present microwave field for a cell phone does not produce subjective symptoms in healthy humans.

10.2.6.2 Electromagnetic hypersensitivity

Many terms are used to name hypersensitivity to electromagnetic fields; such as electromagnetic hypersensitivity, electro-hypersensitivity, hypersensitivity to electricity, hypersensitivity to electric and magnetic fields, and electrical hypersensitivity (EHS). These terms are used to describe people who claim to be sensitive to electric and magnetic fields from a variety of sources, such as power lines, mobile telephones, mobile phone base stations, household appliances, visual display monitors, and light sources (COMAR 2002). There is no independent measure for verifying this condition; currently it is totally dependent on verbal report. The COMAR report mentioned skin problems associated with visual display units in Norway (Linden and Rolfsen 1981); later reports have come from other Nordic countries, elsewhere in Europe, and North America.

Individuals claiming EHS generally report a prevalence of symptoms that are related to the nervous system, such as fatigue, stress, and sleep disturbances. The second most prevalent are skin symptoms, which include facial pricking, burning sensations, and rashes. These are followed in importance by various body symptoms (body ache and pain), eye symptoms (burning sensations), and less commonly ear, nose, throat, and digestive symptoms (COMAR, 2002). Generally, the field that elicit

EHS are reported to be very weak, well below what is known to affect normal individuals, and far below currently accepted safety standards. Nevertheless EHS is a real phenomenon which is an annoying problem for the affected persons.

The prevalence rate of self-reported EHS among the general population was studied recently in Sweden and California.

Hillert et al. (2002) analyzed a cross-sectional questionnaire completed in 1997 by 15,000 men and women between 19 and 80 years in Stockholm County. The response rate was 73%, and 1.5% of the respondents reported hypersensitivity to electric or magnetic fields. Prevalence was highest among women in the 60- to 69 year age group.

Levallois et al. (2002) completed a study based on questions regarding electromagnetic fields and chemical sensitivities that were added to the 1998 California Adult Tobacco Survey. Self-reported electric and magnetic field sensitivity was defined as "allergic or very sensitive to getting near electrical appliances, computers or power lines". Self-reported chemical sensitivity was defined as considering oneself "allergic or unusually sensitive to everyday chemicals". Among a sample of 2,072 Californians, 68 subjects (3.2%) reported to be "allergic or very sensitive" to being near electrical devices as well as to chemicals. Among the 68 subjects, 27 subjects (1.3%) reported sensitivity to electrical devices but not to chemicals.

Three sets of researchers have conducted provocation studies in which individuals claiming EHS were exposed to electric or magnetic fields in an attempt to probe any possible links between reported symptoms and exposure conditions. Researchers have tried to find objective changes, because a major problem in studying EHS is the lack of established pathophysiological markers. Several studies were performed to evaluate EHS under controlled laboratory conditions, and one provocation study was carried out under everyday conditions.

Andersson et al. (1996) tested if psychological treatment of EHS patients was effective. Seventeen patients were assigned randomly to a treatment group or to a waiting-list control group in a retest-posttest control group design. The patients also participated in double-blind provocation tests before and after the treatment. The provocation test showed that this group of EHS patients did not react to the electromagnetic fields. A 'treatment package' of cognitive-behavioral methods were used. First, information about a model for understanding of how somatic symptoms could interact with the person's interpretation of the symptoms was provided, using a 'vicious circle' model. Second, with the help of a homework assignment, each patient registered symptoms, the situations in which they occurred, and the interpretations made. With this psychological perspective, the patients could more realistically "test" the evidence. The patients in the experimental group reduced their evaluations of the disability more than the control group did, indicating that psychological approaches can be of value for these patients. Also, blood samples were analyzed for prolactin, cortisol, dehydroepiandrosterone, and cholesterol: no differences were found.

Using double-blind provocation experiments, Hietanen et al. (2002) tested the hypothesis that EHS persons can reliably report subjective symptoms from exposure to the microwaves emitted by handheld mobile phones (cellular phones). They also tested whether sensitive subjects were able to determine whether a phone was on or

off by sensing microwaves. The study group consisted of 20 volunteers (13 women and 7 men) who reported themselves as being sensitive to cellular phones. The exposure sources were one analog NMT phone (900 MHz) and two digital GSM phones (900 MHz and 1.80 GHz). The duration of a test session was 30 min, and three or four sessions were performed in random order for each subject during a single day. The subjects were asked to report symptoms or sensations as soon as they perceived any abnormal feelings. Various symptoms were reported; most of them appeared in the head region. However, the number of reported symptoms was higher during sham-exposure than during real-exposure conditions. Furthermore, none of the subject could distinguish real exposure from sham exposure. Also, blood pressure, heart rate, and respiration rate were monitored every 5 min, without finding any changes. From these results, the authors concluded that adverse subjective symptoms, though unquestionably perceived by the EHS subjects were not produced by cellular phones.

Flodin et al. (2000) carried out a provocation study in the homes or workplaces of the EHS patients; 24 hours after the test sessions, the subjects reported their symptoms and judgments as to on-off status. Fifteen subjects selected as having 'fast and distinct reactions' from electric equipment were provoked on four occasions: usually two true and two sham challenges were completed. The intervals between exposures were a few or more days, in order to provide the subjects with an opportunity to recover before the next provocation. A control group of subjects verified that the provocations were performed in a blind manner, i.e., they could not discriminate real and sham exposures. The EHS patients were no better than the control group in deciding whether or not they were exposed to electric and magnetic fields. From these data the authors concluded that exposure to electric and magnetic fields *per se* does not seem to be the cause of the symptoms experienced by this patient group.

Several groups have tried to find out indicators that might explain the complaints of EHS persons.

Sandstrom et al. (1997) hypothesized that there are other factors in the office environment that can affect the autonomic nervous system and/or CNS, resulting in the symptoms reported. Flickering light is one such factor, and it was therefore chosen as the exposure parameter in this study. Ten patients complaining of EHS and the same number of control subjects were exposed to amplitude-modulated light. The sensitivity of the brain to this type of visual stimulation was tested by means of two objective electrophysiological methods, electroretinography and visual evoked potential. A higher amplitude of brain cortical responses at all frequencies of stimulation was found when comparing EHS patients with controls. No differences in retinal responses were revealed.

Lonne-Rahm et al. (2000) assigned 24 EHS patients to one of two groups and tested them in a double-blind provocation study. These patients, who reported increased skin symptoms when exposed to electromagnetic fields, were compared with 12 controls. Both groups were exposed to 30 min periods of high- or low-stress situations, with and without simultaneous exposure to the electric and magnetic fields from a visual display unit (VDU). The matched controls were tested twice as were the patients, but the fields were turned off both times for the controls. Stress was induced by requiring the participants to act in accordance with a random sequence of flash-

ing lights while simultaneously solving complicated mathematical problems. Blood samples were analyzed for concentrations of melatonin, prolactin, ACTH, neuropeptide Y, and growth hormones, and the expression of different peptides, cellular markers, and cytokines (somatostatin, CD1, factor XIIIa, and TNF-α). Skin biopsies also were analyzed for the occurrence of mast cells. Stress provocation resulted in feelings of more intense mental stress and elevated heart rate. The EHS patients reported increased skin symptoms when they knew or believed that the VDU's "electromagnetic field" was turned on. With the blind conditions there were no differences between 'on' or 'off'. Inflammatory mediators and mast cells in the skin were not affected by the stress exposure or by exposure to electromagnetic fields. Hormones and cytokines, etc. all showed no differences among groups or conditions. The authors concluded that the patients did not react to the electric and magnetic fields associated with a VDU device.

Hillert et al. (2001) investigated the nature and possible etiology of fatigue in people claiming EHS. The aim was to test the hypotheses that perceived fatigue was due to alterations in cholinesterase activity. The rationale of the study is that fatigue has reportedly been associated with cholinesterase inhibition due to exposure to organophosphates (Markowitz 1992). Symptoms have been suggested to appear even when cholinesterase activity is near or within the range of normal or very slightly depressed (< 20%). The study group consisted of 14 people who reported a hypersensitivity to electricity, including disabling fatigue. Cholinesterase activity was assessed three times: twice based on current symptoms reported by the subjects. and once at a randomly selected time. No significant reduction in acetylcholinesterase was identified in any subject. The results do not support the hypothesis that a change in cholinesterase activity mediates fatigue in people reporting hypersensitivity to electricity.

Although not in microwave frequencies, but at 60 Hz, Lyskov et al. (2001a) performed a neurophysiological study of EHS patients by comparing visual functions, blood pressure, heart rate, electrodermal activity, respiration, EEG and visual evoked potentials. The authors found that the patients had a trend to hyper-sympathetic tone, hyper-responsiveness to sensory stimulation, and heightened arousal.

Lyskov et al. (2001b) further investigated possible neurophysiological effects of intermittent (15 sec on/off), 60 Hz, 10 μT magnetic field exposure on patients with EHS and on control subjects during rest and performance of a mental arithmetic task. EEG, visual evoked potentials, electrodermal activity, ECG, and blood pressure were recorded from 20 EHS patients and 20 control volunteers. The total duration of the test was 40 min, divided into two 10 min rest periods and two 10 min periods of mathematical performance. Magnetic field and sham exposures were presented randomly during these periods, resulting in four different conditions: Field-Rest, Sham-Rest, Field-Math, and Sham-Math. The data showed main effects of the Group factor (EHS vs. control subjects) on heart rate ($P < 0.01$), heart rate spectrum ratio, i.e., heart rate variability ($P = 0.04$); these measures were higher in the EHS group. Also, electrodermal activity was shorter in latency and higher in amplitude in the EHS group. On the other hand, EEG characteristics did not differ between groups. The Condition factor (math task vs. relaxed) showed main effects for heart rate ($P < 0.01$), heart

rate spectrum ratio (P = 0.06), electrodermal activity (P < 0.01), and alpha and theta spectrum bands of EEG. However, the Field factor (real or sham magnetic field exposure) did not affect either the autonomous functions mentioned above or the EEG variables of either group. These data do not indicate that EHS patients or controls were affected by low-level 60 Hz magnetic field exposure. However, persons reporting EHS differed from the control subjects in baseline values of several physiological characteristics.

In summary, these studies all suggest that (1) the EHS individual cannot detect electric and magnetic fields, and (2) that the symptoms reported by EHS individuals are not related to electric or magnetic field exposures. Given this, perhaps it is no surprise that, so far, researchers have not found any hormonal, immunological, or neurochemical 'markers' which are associated with EHS. However, as suggested by studies of autonomic nervous functions, such as heart rate and electrodermal activity (Lyskov et al. 2001b), or study of brain cortical responses (Sandstrom et al. 1997), it might be possible to demonstrate that EHS patients might have a physiological predisposition to hyper-sensitive responding to physical and psychological environmental stressors. EHS patients might falsely attribute their real symptoms.

10.2.7 Neurotransmitters

Because neurotransmitters are critical messenger of information within the nervous system, many researchers have focused their attention on the issue of whether microwave radiation can affect transmitter actions. (An outline of neurotransmitters is provided in section 2.1.4.)

10.2.7.1 Microwave exposure alone

Gandhi and Ross (1987) exposed rats to 700 MHz at 15 mW/cm^2, that raised the core temperature by 2.5°C. Of six brain regions investigated, only the hypothalamus showed significant changes in receptor states, confirming its pivotal role in thermoregulation. Adrenergic receptors showed a 36% decrease in binding following radiation after a 2.5°C increase in body temperature, suggesting a mechanism to facilitate noradrenaline release, which maintains thermal homeostasis by activating heat dissipation. Muscarinic cholinergic receptors showed a 65% increase in binding at the onset of radiation, which might be attributed to the release of acetylcholine (ACh) in the hypothalamus in response to heat accumulation.

Inaba et al. (1992) exposed rats to 2.45 GHz at an ambient temperature of 21–23°C. Microwave exposure at power densities of 5 and 10 mW/cm^2 increased the rectal temperature by 2.3°C and 3.4°C, respectively. The noradrenaline content in the hypothalamus was significantly reduced after microwave exposure at a power density of 10 mW/cm^2. There were no differences in the dopamine contents of any region of the brain between microwave-exposed rats and control rats. The dihydroxyphenyl acetic acid content, which is the main metabolite of dopamine was increased in the pons and medulla oblongata at a power density of 10 mW/cm^2. The dopamine turnover rates and the ratio of metabolite to dopamine in the striatum and cerebral

cortex were increased at a power density of 10 mW/cm^2. The serotonin content in all regions of the brain did not change. The 5-hydroxyindoleacetic acid content in the cerebral cortex was increased at power densities of 5 and 10 mW/cm^2. Clearly microwave exposures producing a modest rise in core body temperature produce a variety of changes in CNS neurotransmitters. The mechanisms for, and the significance of, the observed changes remains to be determined.

Mausset et al. (2001) developed a protocol of neurotransmitter detection based on immunohistochemistry and image analysis. Gamma-vinyl-GABA, an inhibitor of GABA-transaminase, was injected in rats to increase GABA concentration in the CNS. The cellular GABA contents then were revealed by immunohistochemistry and semi-quantified by image analysis using three parameters: optical density, staining area, and number of positive cells. The increase in GABA content induced by gamma-vinyl-GABA in the molecular and the granular layers of cerebellum was reflected by these three parameters. This protocol was used to investigate the effects of exposure to 900 MHz. Both pulsed microwave exposure with a SAR of 4 W/kg and continuous wave exposure with a high SAR of 32 W/kg were tested. A selective diminution of the stained processes in the Purkinje cell layer after exposure to pulsed microwaves, in addition, a decrease in optical density in the three cell layers were apparent after continuous wave exposure. Whether this effect is, at least partly, due to a local heating of the tissues is not known. Overall, it appears that microwave exposure with a relatively high SAR of 32 W/kg, one that might produce hyperthermia, induces a diminution in cellular GABA content in the cerebellum.

Testylier et al. (2002) studied ACh release in the brain of freely moving rats exposed to a 2.45 GHz continuous wave microwave field (2 or 4 mW/cm^2) or to a 800 MHz field amplitude-modulated at 32 Hz. The rats were exposed for 1 hr during the day or exposed for either 1 h or 14 h during the night. Serial neurotransmitter measurements were performed by microdialysis using a membrane implanted through the upper CA1 region of the hippocampus. After irradiation with the 2.45 GHz microwaves, at 2 mW/cm^2, rats did not show a significant modification of ACh release, whereas those exposed at 4 mW/cm^2 showed a 40% decrease in ACh release from hippocampus. This decrease was maximal at 5 h post exposure. Exposure to the 800 MHz microwaves for 1 hr do not cause any effects, but exposure for 14 hrs induced a 43% decrease in ACh release during the period 11 p.m. – 4 a.m. compared to control rats. This work indicates that neurochemical modification of the hippocampal cholinergic system can be observed during and after an exposure to a low-intensity microwave field.

Pakhomov et al. (2003) investigated the effects of high-power microwave (9.3 GHz) pulses (pulse widths from 0.5 to 2 μsec at a rate of 0.5 or 1.0 Hz) on synaptic transmission and LTP in rat hippocampal slices. (See Pakhomov et al. (2003) in section 10.2.5.1.) Microwave heating of the preparation ranged from 0.5°C (at a SAR of 0.3 kW/kg) to 6°C (at 3.6 kW/kg). The only effect produced by the high-power pulsed microwave exposure was a transient and fully reversible decrease in the population spike amplitude. Irradiation did not affect the ability of neurons to develop LTP. These results are consistent with the view that the only mechanism of action for extremely high power microwave pulses is thermal.

The available literature clearly indicates that, if the SAR is high enough, microwave exposure can alter neurotransmitter function in the CNS.

10.2.7.2 Microwaves and drug effects

Psychoactive agents affect neuronal function by modifying neurotransmitter activities, resulting in some sort of behavioral changes or altered physiological parameters, depending on the experimental conditions. If microwave irradiation caused interaction with the known effects of psychoactive agents, one could investigate, as the next step, the affected transmitter substances with established physiological and pharmacological experimental techniques.

Lai et al. (1983) studied the effects of various psychoactive drugs in rats exposed for 45 min to a circularly polarized, pulsed (2 μsec pulses, 500 pps) microwave field (2.45 GHz) at a SAR 0.6 W/kg. Apomorphine-induced hypothermia and stereotypy were enhanced by irradiation. Amphetamine-induced hyperthermia was attenuated, but stereotypy was unaffected. Morphine-induced catalepsy and lethality were enhanced by irradiation, at certain dosages of the drug. These results suggest that microwave exposure interact with certain types of psychoactive agents.

Lai et al. (1987) measured sodium-dependent, high-affinity choline uptake in various regions of the brain, including frontal cortex, hippocampus, hypothalamus, inferior colliculus and striatum, of rats irradiated for 45 min with either pulsed or continuous wave, low-level microwaves (2.45 GHz; power density, 1 mW/cm^2; average whole-body SAR 0.6 W/kg). Pulsed microwave irradiation (2 μsec pulses, 500 pps) decreased choline uptake in the hippocampus and frontal cortex. Pretreatment with a narcotic antagonist (naloxone or naltrexone; 1 mg/kg) blocked the effect of pulsed microwaves on hippocampal choline uptake but did not alter the effect on the frontal cortex. Continuous wave exposure decreased the uptake in the frontal cortex. This is the first report that microwave irradiation reduced sodium-dependent, high-affinity choline uptake, an index of cholinergic activity.

Lai et al. (1992a) studied the effects of single (45 min) and repeated (ten daily 45 min sessions) pulsed (500 pps, pulse width 2 μsec) 2.45 GHz exposures (SAR of 0.6 W/kg) on the concentration and affinity of benzodiazepine receptors in the cerebral cortex, hippocampus, and cerebellum of the rat. A receptor-binding assay, with 3H-flunitrazepam as ligand, was used. Benzodiazepine receptors in the brain are responsive to anxiety and stress. Immediately after a single exposure, an increase in the concentration of receptor was observed in the cerebral cortex. However, in rats subjected to repeated exposures, no change in receptor concentration was found in the cerebral cortex immediately after the last exposure, which might indicate an adaptation to repeated exposures.

Lai et al. (1992b) performed experiments to investigate subtypes of opioid receptors in the brain involved in the effect of acute (45 min) pulsed (2 μsec pulses, 500 pps) microwave exposure (2.45 GHz; SAR 0.6 W/kg) on cholinergic activity in the rat brain. Rats were pretreated by microinjection of specific antagonists of μ, δ, and κ opioid-receptors into the lateral cerebroventricle before microwave exposure. The

data showed that all three subtypes of opioid receptors are the intermediate step in the microwave-induced decrease in cholinergic activity in the hippocampus.

Lai et al. (1994) studied effects of microwave irradiation on radial-arm-maze performance of rats. After 45 min of exposure to pulsed 2.45 GHz microwaves (2 μsec pulses, 500 pps; SAR 0.6 W/kg), rats showed retarded learning, indicating a deficit in spatial 'working memory' function. This behavioral deficit was reversed by pretreatment before exposure with the cholinergic agonist physostigmine or the opiate antagonist naltrexone. However, pretreatment with the peripheral opiate antagonist naloxone methiodide showed no reversal of the effect. These data indicate that both cholinergic and endogenous opioid neurotransmitter systems in the brain are involved in the microwave-induced spatial memory deficit.

Lai et al. (1996) reported that intra-septal microinjection of β-funaltrexamine blocked a microwave-induced decrease of hippocampal cholinergic activity in the rat after 45 min exposure to pulsed 2.45 GHz microwaves (2 μsec pulses, 500 pps; SAR 0.6 W/kg). These data indicate that μ-opioid receptors in the septum mediate a microwave-induced decrease in cholinergic activity in the hippocampus and support the hypothesis that microwaves at a whole body SAR of 0.6 W/kg can activate endogenous opioids in the brain.

10.2.7.3 Summary

Work from several investigators shows that microwave exposure can modulate brain neurotransmitter activity, especially that involve with thermoregulation. Additonally, an interesting series of papers from one laboratory clearly suggests that psychoactive agents can modulate the effects of microwave exposure on neurotransmitters (and behavior). These results indicate that (1) endogenous opioids play an important role in some of the neurological effects of microwaves, and (2) parameters of microwave exposure are important determinants of the outcome of the microwave effects. Further research in this area should be a fruitful activity, contributing to an understanding of the mechanisms connecting microwave exposure to behavior.

10.3 Peripheral Nervous System

10.3.1 Intact nerves

Yamaura and Matsumoto (1972: 1973) studied the effect of 2.45 GHz microwave irradiation on crayfish peripheral nerve. Response characteristics of discharging impulses of the slowly adapting stretch receptor were obtained by calculating the cross-correlation function between input and output of the receptor neurons. The M-sequence signal of the 2.45 GHz microwave was applied as the input. Temperature change of the receptor was measured by a thermistor. Results showed a strong correlation between the impulse frequency and temperature change. The authors concluded that the impulse frequency change was caused by the thermal change produced by the microwave irradiation.

Courtney et al. (1975) and Chou and Guy (1978) used a temperature-controlled waveguide to expose frog sciatic nerves, cat saphenous nerves, rabbit vagus nerves, and rabbit superior cervical ganglia, and rat diaphragm muscles to 2.45 GHz in either continuous wave or pulsed modes. No specific microwave effects were observed. These results show that under a constant ambient temperature, microwave effects on the selected electrically excitable tissues could not be detected. However, it was shown that a temperature rise in the solution as small as 0.2°C could induce observable effects on action potential (AP) latency or muscle contraction (Chou and Guy, 1978).

McRee and Wachtel (1986) reported that exposure to 2.45 GHz, continuous wave microwave fields (at a SAR of 10 W/kg) would consistently lower the survival time of isolated frog sciatic nerves stimulated at high repetition rates (50 pulse-pairs per sec). To assess the role that these microwaves might have on active transport of K and Na ions, McRee and Wachtel also performed a series of experiments in which the active Na-K pump was substantially blocked by ouabain prior to microwave exposure. Paired nerves were soaked for 5 min in a high concentration (10^{-3} g/liter) of ouabain to rapidly produce blockage of the Na-K pump. With stimulation at 50 pulses/sec, the 'rundown time course' was, as expected, accelerated in all ouabain-treated nerves. However, the microwave-exposed nerves showed no additional shortening of survival time. The experiments were repeated at a slower stimulation rate (5 pulses/sec) so that the survival time of the nerves more closely approximated that of nerves not treated with ouabain (1 to 2 h vs. 30 min or less for ouabain-treated nerves). Results at the lower stimulation rate also showed that there was no difference in the survival times of ouabain-treated exposed and ouabain-treated, unexposed-control nerves. These results lend support to the view that the relative loss of excitability in microwave-exposed nerves is related to an interference with or counteraction of the Na-K pump.

Pakhomov et al. (1997) studied effects of an acute, continuous wave exposure to millimeter waves (40–52 GHz) on compound action potential (CAP) conduction in an isolated frog sciatic nerve preparation. CAPs were evoked by either low-rate (4 paired pulses/sec) or high-rate (20 paired pulses/sec) electrical stimulation of the nerve. The low-rate stimulation did not alter the functional state of the nerve, and the amplitude, latency, and peak latency of CAPs could stay stable for hours. Microwave irradiation for 10–60 min at 0.24–1.5 mW/cm^2, either at various constant frequencies or with a stepwise frequency change (0.1 or 0.01 GHz/min), did not cause any detectable changes in CAP conduction or nerve refractoriness. At a higher field intensity of 2–3 mW/cm^2, a subtle and transient reduction of CAP latency and peak latency along with a rise of the test CAP amplitude were observed.

Rogers et al. (2004) used a classical electrophysiology method and preparation to assess the strength-duration (S-D) curve for the frog sciatic nerve and gastrocnemius muscle preparation. With a pulse of 1 nsec, the voltage threshold for elicitation of a muscular twitch was 4.5 kV and 35 A. The authors expressed the S-D curve in terms of all relevant units, including tissue current density, tissue electric field, calculated temperature increase in tissue, tissue SAR, external power density, and external SAR.

The computations suggest that a single 1 nsec stimulus of 35 A in tissue is athermal; the estimated temperature rise was $1.9 \times 10^{-3}\,^\circ$C.

From the experimental results presented in these five papers, it certainly appears that the effects of microwave exposure on the nerves are caused primarily by tissue heating.

10.3.2 Regenerating nerves

Kolosova et al. (1998) studied the effects of exposure to 53.57 GHz at power density 4 mW/cm^2 on the recovery of function in damaged rat sciatic nerve. Lesions were produced by nerve section followed by microsuturing. Irradiation was applied to the skin of the thigh in the area of suturing. Total number of APs recorded from the nerve was used to study the functional properties of regenerated fibers 5 mon after damage. Microwave exposure had a stimulatory effect on regeneration processes: conduction velocity increased by 25–30% with increase in total AP as compared with the sham-operated control group. It is not known whether this effect is due to local temperature changes or some other factors, such as increased local blood flow, because there is no description of temperature measurement.

The limited data available suggests RF or microwave exposure can modulate functional properties of nerves. It seems most likely that the effects are related solely to heating. Classic electrophysiology techniques applied to nerves would appear to be an excellent preparation to be used for studying microwave and RF effects and mechanisms.

10.4 Endocrinology

In many ways, the endocrine system is a key regulatory system, using diffuse chemical messages (hormones) placed into the general circulation for dispersal throughout the body. (See section 2.2 for background.)

10.4.1 Pituitary gland and its axes

The pituitary gland is the primary interface between the brain and the endocrine glands. The pituitary has been recognized as the 'master gland' for many decades. The primary targets of the hormones produce by the pituitary gland are other endocrine organs, such as adrenal or thyroid glands. A linked system, such as brain-pituitary-adrenal is called an axis.

10.4.1.1 Corticosteroids in animals

Endocrine responses can be an adaptive response to environmental stimuli; such responses are not necessarily adverse, analogous to a febrile response when there is a need for host immune defense. The adrenal is a "dual gland". ACTH acts on the cortex, i.e., the outer layer, of the adrenal gland and stimulates the secretion of steroid

hormones. Catecholamines are synthesized in the medulla, i.e., core, of the adrenal which release adrenalin and noradrenalin. Noradrenalin is a transmitter substance of sympathetic fibers, as well.

To characterize the response of the pituitary-adrenal axis to microwave exposure, Lotz and Michaelson (1978) measured plasma corticosterone and colonic temperature in unanesthetized male rats exposed to continuous wave 2.45 GHz. The rats were exposed in the far field of a horn antenna for 30 or 60 min at power densities of 0, 13, 20, 30, 40, 50 or 60 mW/cm^2. Other exposures were conducted for 120 min at 0, 13, 20, 30 or 40 mW/cm^2. The average energy absorption rate of the rats was 0.16 W/kg absorbed per mW/cm^2. Thus, for example, at 60 mW per cm^2, the SAR was about 9.6 W/kg. Colonic temperature was significantly elevated after exposures to power densities of 13 mW/cm^2 or greater, with progressively larger increase after high intensity exposures. Plasma corticosterone concentration was elevated above that of sham-exposed controls only after exposures at 50 or 60 mW/cm^2 for exposures of either 30 or 60 min. With 120 min exposures, plasma corticosterone concentration was increased at 20, 30, and 40 mW/cm^2. The relationship between the increased levels of circulating corticosterone and colonic temperature suggested that the increases in corticosterone levels reflected the level of physiological response to the body temperature elevations caused by microwave exposure. Lotz and Michaelson (1979) further studied this effect by examining the effects of acute microwave exposure of normal, hypophysectomized, or sham-hypophysectomized rats. (Hypophysectomized means the pituitary has been removed.) Plasma corticosterone levels in acutely hypophysectomized rats exposed to 60 mW/cm^2 for 60 min were below control levels, indicating that the microwave- induced corticosterone response observed in normal, intact rats is dependent on ACTH secretion by the pituitary. In other groups of rats pretreated with dexamethasone before being exposed microwaves for 60 min, the corticosterone response to a 50 mW/cm^2 exposure was completely suppressed by doses equal to greater than 3.2 μg dexamethasone/100 g body weight. However, the corticosterone response to a 70 mW/cm^2 exposure was only partially suppressed by prior administration of 3.2 or 5.6 micrograms dexamethasone/100g body weight. The evidence obtained in these experiments, combined with the results of previous report (Lotz and Michaelson, 1978), indicate that the stimulation of the adrenal axis in the microwave-exposed rat is a systemic, integrative process resulting from to general hyperthermia.

Lu et al. (1985) studied changes in thyroid stimulating hormone (TSH) concentration in unanesthetized rats exposed to 2.45 GHz, amplitude-modulated (120 Hz) microwaves in the far field for 2 or 4 h, using power densities between 0 and 55 mW/cm^2. Individual rats were exposed from 1 to 10 times to seek any possible accumulation, acclimation, or sensitization. Colonic temperature was measured using a thermistor. TSH concentration decreased in rats after microwave exposure. The influence of microwave exposure on serum TSH concentration was independent of the number of exposures, indicating absence of accumulation, acclimation, or sensitization. Decreased TSH concentration usually was accompanied by increased colonic temperature. For 4 h exposure, the lowest irradiance was 20 mW/cm^2, which produced a 0.3°C increase in colonic temperature that was independent of the number of

exposures. For 2 h exposure, the lowest irradiance was 30 mW/cm^2,which produced or a 1.1°C increase in colonic temperature, regardless of the number of exposures. The rats exposed at 10 mW/cm^2 for 2 hr had a lower TSH concentration than did sham-exposed rats. These results suggest that the microwave effect of serum TSH could be dependent on duration of exposure. None of the rats exposed at an irradiance lower than 10 mW/cm^2 had any change in TSH concentration. The effect of microwave exposure on TSH concentration was not persistent after exposure. The relation between TSH concentration and colonic temperature was curvilinear (exponential).

Imaida et al. (1998a) measured ACTH, corticosterone, and melatonin after 6 weeks of near-field exposure of F344 rats to a 929.2 MHz microwave field like that used by cellular phones. Increases occurred for all three hormones in the exposed group compared with the sham-exposed control group. Experimental conditions are described in section 10.1.1.

These examples make it clear that microwave exposure can alter hormones, when body temperature is elevated. These hormonal changes are part of the normal physiological response to hyperthermia.

10.4.1.2 Studies with humans

de Seze et al. (1998) conducted an experiment to evaluate the effect of an 800 MHz signal emitted by a GSM cell phone (217 Hz impulses, one-eight duty cycle, 2 W peak power) on endocrine function of 20 male volunteers, aged from 19 to 40. End points were serum adrenocorticotropin, thyrotropin, growth hormone, prolactin, LH, and FSH concentrations. Each subject was exposed to microwaves through the use of a cellular phone 2 h/d, 5 d/w, for 1 mon. The hormone levels were determined in weekly blood samples, obtained starting 3 weeks before the commencement of the exposure and ending 3 weeks after exposure ended. (All but one blood sample was drawn 48 h after each weekly session. The seventh drawing was performed in the morning after the last weekly exposure.) Within each individual, the pre-exposure hormone concentration was used as the control value. There was a change only in thyrotropin concentration, and it occurred only on one occasion; on the seventh sampling, a 21% decrease was found. This change recovered fully during the post-exposure period. Therefore, cell phone exposure did not induce a long-lasting effect on the hormone-secretion rate of the anterior pituitary gland in humans.

Mann et al. (1998b) investigated the influence of 900 MHz microwaves (pulsed at 217 Hz, average power density 0.02 mW/cm^2) from a circularly polarized antenna on the endocrine system in healthy humans. Nocturnal hormone profiles of growth hormone, cortisol, LH, and melatonin were determined under polysomnographic control. Only one alteration in activity of the hypothalamo-pituitary-adrenal axis was found: a slight, transient elevation in the cortisol serum level immediately after onset of field exposure, which persisted for 1 hour. For growth hormone, LH and melatonin, no effects were found on either total hormone production during the entire night or the dynamic characteristics of the secretion pattern.

Radon et al. (2001) tested 8 healthy male students to see whether or not the microwave fields used by the GSM standard have any noticeable effects on salivary melatonin, cortisol, neopterin, and immunoglobulin A levels during and several hours after exposure. In a shielded experimental chamber, the circularly polarized electromagnetic field was transmitted by an antenna position 10 cm behind the head of sitting subjects. The carrier frequency of 900 MHz was pulsed with 217 Hz, and the average power flux density was 1 W/m^2. In double blind trials, each subject received a total of 20, randomly allotted, 4 hour periods of exposure and sham exposure, equally distributed among day and night. The salivary concentrations of melatonin, cortisol, neopterin and immunoglobulin A did not differ between exposure and sham exposure.

Based on the experiments conducted with animals and humans, it appears that microwave exposure at the athermal levels produced by cell phones causes no important changes in hormones. Experiments with animals in which higher doses can be applied, resulting in increased body temperature. Under this circumstance, microwave exposure can alter hormones. These hormonal changes are part of the normal physiological response to hyperthermia.

10.4.2 Pineal gland and melatonin

There is ample experimental evidence that changes of earth-strength static magnetic fields and ELF magnetic fields can depress the nocturnally enhanced melatonin synthesis in the pineal gland of mammals, including humans. Thus, it is reasonable to ask if the electromagnetic fields associated with cell phones might also influence secretion of melatonin.

10.4.2.1 Experiments with animals

Vollrath et al. (1997) reported that exposure to 900 MHz microwaves, both continuous or pulsed at 217 Hz, for 15 min to 6 hr, at day or night, had no notable, short-term effect on pineal melatonin synthesis in male or female SD rats and Djungarian hamsters. The SARs were approximately 0.06 to 0.36 W/kg in rats and 0.04 W/kg in hamsters. Pineal synaptic ribbon profile numbers, which were studied in rats only, likewise were not affected. With such low whole-body SARs, thermal effects are very unlikely. However, brain SARs presumably were somewhat higher, and the possibility of local hot spots can not be excluded without additional study. It should be noted that much of the brain is highly vascularized, meaning high blood flow rates will dissipate heat into the large heat sink provided by the rest of the body; thus the brain is protected against local heating.

Hata et al. (2005) investigated the effect of 4 hour exposure during the dark to a 1.44 GHz TDMA signal on serotonin and melatonin synthesis in a total of 208 male and female SD rats. The brain SAR was 7.5 W/kg; the whole body SARs were 1.9 W/kg for the somewhat heavier males and 2.0 W/kg for the somewhat lighter females. No differences in melatonin or serotonin levels were observed among the microwave-exposed, sham-exposed, and cage-control groups.

Bakos et al. (2003) found no changes in the 6-sulfatoxymelatonin excretion of exposed Wistar rats (n = 18) compared to a sham-exposed or control group (n = 18) after exposure to 900 MHz (100 μW/cm^2) and 1.80 GHz (20 μW/cm^2), GSM-like radiation. The animals were exposed daily for 2 h, between 8:00 am and noon, during a 14 day exposure period. The exposure occurred during the morning, when melatonin production is low. One wonders what would have been found if exposure had been scheduled during the night, particularly in the earlier portion of the night when nocturnal melatonin production is rising.

Imaida et al. (1998a) mentioned increased daytime melatonin concentration after 6 weeks of near-field exposure to 929.2 MHz microwaves. (Exposure conditions were described in section 9.1.1.) It should be noted the elevation of melatonin was observed during daytime; blood samples were acquired between 9:30 a.m. and noon). A similar daytime increase after 6 weeks of exposure to a 50 Hz circularly polarized rotating magnetic fields was observed by Kato et al. (1993). (See section 3.4 for a complete review of the ELF literature.)

Stark et al. (1997) investigated the influence of 3–30 MHz RF fields on salivary melatonin concentration in dairy cattle. Two commercial dairy herds at two farms were compared. The exposed group was located at a distance of 500 m from the transmitter: the average nightly field strength was 1.59 mA/m. The control group was located at a distance of 4,000 m from the antenna: the average nightly field strength was 0.076 mA/m. At each farm, salivary melatonin concentration in five cows was monitored over a period of 10 consecutive days. Saliva samples were collected at 2 hour intervals during the dark phase of the night. As an additional intervention, the short-wave transmitter was switched off during three of the ten days (off phase). The salivary melatonin values of the two initial nights did not show a difference between exposed and unexposed cows. However, on the first night of re-exposure after the transmitter had been off for 3 days, the difference between groups (3.89 pg/ml) in salivary melatonin concentration of the two groups differed.

There are three reports which observed no effect following short-term microwave exposure (15 min, 6 hr, and 14 day) on rodents, but there is one positive result from a 6 week study. In addition, one environmental study of RF suggests a subtle effect occurred in dairy cows. In summary, the picture is suggestive, but not convincing, that microwave signals also can reduce nocturnal melatonin production. Clearly, additional research is required, particularly with longer exposure intervals.

10.4.2.2 Experiments with humans

de Seze et al. (1999) examined whether microwave fields from cell phones would alter melatonin levels in the human. Volunteers were two groups totaling 37 men, 20–32 yr old. Exposures were to commercially available cellular telephones of the GSM 900 type (900 MHz) or to the DCS type (Digital Communication System, 1.80 GHz), for 2 hr/day, 5 days/week, for 4 wks. The phones were at their maximum power. Blood samples were collected hourly during the night and every 3 hr in the daytime. Four sampling sessions were performed at 15 day intervals: before the beginning of the exposure period, at the middle and the end of the exposure period, and 15 days

later to evaluate the persistence or late appearance of potential effects. The melatonin circadian profile was not affected.

Bortkiewicz et al. (2002) evaluated the effect of cell phone on 6-hydroxymelatonin sulfate (6-OHMS) excretion of nine healthy males, aged 19–29 years. The experiment was performed under controlled lighting conditions: light intensity was 50 lx until midnight and 0 lx during the remainder of the night. Each person was sampled twice: once on a day without exposure, and once on a day with cellular phone exposure for 60 min, from 7 to 8 p.m. The phone used operated at 900 MHz, pulsed with 217 Hz (pulse width 576 μsec), and the SAR was 1.23 W/kg. The subjects did not know sham-exposed or field-exposure days. From 8 p.m. until midnight, the subjects listened to music, and then they slept till 7 a.m. Urine samples were collected at 7 p.m., at midnight, and at 7 a.m. The 6-OHMS concentration in both phone-type experiments did not differ between exposed and control sessions at any of the three time points. Circadian variation of 6-OHMS level was detected in all subjects. The results demonstrated that EMF emitted by cellular phones has no distinct influence on the melatonin level.

Jarupat et al. (2003) studied the effects of 1.9 GHz microwave fields emitted from a cellular phone on nocturnal melatonin secretion in saliva under carefully designed experimental protocol. The subjects were eight females (mean age; 27, range 16–36 years), all in the follicular phase of the menstrual cycle. The subjects had not used a cellular phone for at least one week before the experiment. A cell phone was attached to the left ear for 30 min every hour, from 19:00h to 01:00h: on one day it was on, and on the other day was off. In the within-subjects comparison, melatonin concentration on the field-exposed day was significantly ($P < 0.05$ by paired test) lower than it was on the sham-exposure day.

Santini et al. (2003) studied the effects of more than one month of exposure to VDUs (KHz frequency range) on nocturnal urinary excretion of 6-OHMS by 13 women. Six women, who worked at least 4 h/d, 5d/w, in front of a VDU, constituted the exposed group. Seven women served as the unexposed control group. The 6-OHMS concentration in urine was 54% less ($P < 0.01$) in the field-exposed group as compared with the control group.

Burch et al. (2002) evaluated the relationship between cellular telephone use and excretion of the melatonin metabolite 6-OHMS in two populations of male electric utility workers (Study 1, n = 149; Study 2, n = 77). Participants collected urine samples and recorded cellular telephone use over three consecutive workdays. Personal 60-Hz magnetic field and ambient light exposures were characterized on the same days using EMDEX II meters. No change in 6-OHMS excretion was observed among those with daily cellular telephone use >25 min in Study 1 (5 worker-days). However, in Study 2, workers with >25 min cellular telephone use per day (13 worker-days) had lower creatinine-adjusted mean nocturnal urinary 6 OHMS concentrations and lower overnight total 6-OHMS excretion, compared to subjects not using cellular telephones. There also were linear trends of decreasing nocturnal 6-OHMS/creatinine concentrations ($P = 0.02$) and total overnight 6-OHMS excretion (p = 0.08) across categories of increasing cellular telephone use. A combined effect of cellular telephone use and occupational 60 Hz magnetic field exposure also was

observed in Study 2. From these results, the authors concluded that prolonged use of cellular telephones can lead to reduced melatonin production. Furthermore, elevated 60-Hz magnetic field exposure might potentiate the effect.

10.4.2.3 Summary

Three of the four studies of microwave exposure and melatonin in animals are negative. One possibility is that the exposure durations examined were too short to detect an effect. In studies with humans, two short-term (1 hour and 2 hour) laboratory experiments with cell phone exposure during the light phase revealed no influence on melatonin rhythm in young men. Two experiments using women as subjects reported melatonin reduction. In a laboratory experiment, acute (3 hr) cell phone use was examined. In an occupation study, subacute (1 month) VDU use was examined. An additional occupational exposure study suggests melatonin reduction in men with greater cell phone use. In addition, an additive effect of 60 Hz magnetic field exposure and cell phone use was noted. Although the initial database is small, it does suggest that microwaves, like ELF electric and/or magnetic fields, can depress melatonin production.

Certainly additional studies are required. The physiological importance of melatonin and the economic importance of mobile telephony make mandatory acquisition of additional scientific knowledge.

10.5 Cardiovascular System

10.5.1 Experiments with animals

Jauchem et al. (1999) investigated the thermal distribution and cardiovascular effects produced by sustained exposure of rats to 94 GHz electromagnetic radiation. Sixteen anesthetized SD rats were exposed individually at a power density of 75 mW/cm^2 under far-field conditions in the "E" orientation. Irradiation began when colonic temperature was 37°C and continued until death. Large, immediate increases in subcutaneous temperature on the irradiated side were accompanied by more moderate, delayed increases in colonic temperature. During irradiation, arterial blood pressure initially increased and then precipitously decreased until death. The heart rate increased throughout the exposure period. The patterns of body temperature, heart-rate and blood pressure changes that occurred before death were similar at 94 GHz and 35 GHz. Because of the very short wavelength, exposure to 94 GHz produces extreme peripheral heating without similar levels of core heating, and this pattern of heat deposition can be sufficient to produce circulatory failure and subsequent death. Jauchem et al. (2000) exposed male SD rats (n = 58) individually to one of three conditions: (1) 1 GHz, (2) 10 GHz, or (3) combined 1 GHz and 10 GHz, all at an equivalent whole-body SAR of 12 W/kg. Microwave exposure was started when colonic temperature was 37.5°C, and it was continued until lethal temperatures were attained. During exposure, arterial blood pressure initially increased, but it then

decreased until death. Heart rate increased throughout the exposure period in all groups, indicating no unusual physiological responses occur during multi-frequency microwave exposure, compared with single-frequency microwave exposure. In general, the cardiovascular system is influenced by body temperature changes in the same manner, no matter how the heating is produced.

10.5.2 Experiments with humans

Mann et al. (1998a) investigated the influence of pulsed, high-frequency electromagnetic fields emitted by digital mobile radio telephones on heart rate during slow-wave as well as REM sleep in healthy humans. No significant effects were observed on heart rate and heart rate variability. The authors conclude that autonomic control of heart rate was not affected by weak, pulsed, high-frequency electromagnetic fields.

Braune et al. (2002) found no non-thermal influence of the fields emitted by mobile phones on the vascular autonomic nervous system of healthy humans. The exposure was implemented using a GSM-like signal (900 MHz, pulsed at 217 Hz; 2 W) using a mobile phone mounted on the right-hand side of the heart in a typical telephoning position. Each period of sham-exposure and of field-exposure consisted of 20 min of supine rest, 10 min of 70 degrees upright tilt on a tilt table, and another 20 min of supine rest. (Assessment cardiovascular performance with a tilt table is a standard technique in cardiovascular physiology.) Blood pressure, heart rate and cutaneous capillary perfusion were measured continuously. In addition, serum levels of norepinephrine, epinephrine, cortisol and endothelin were analyzed in venous blood samples taken every 10 min. All parameters measured showed no changes under a nonthermal electromagnetic exposure.

Tahvanainen et al. (2004) evaluated cardiovascular responses in terms of blood pressure and heart rate during controlled breathing, spontaneous breathing, head-up tilt table test, Valsalva maneuver, and deep breathing test in a randomized, double-blind, placebo-controlled cross-over trial in which 32 healthy subjects were submitted to 900 MHz (2 W), to 1.80 GHz (1 W) cellular phone exposure and to sham exposure, in separate sessions. Arterial blood pressure (arm cuff method) and heart rate were measured during and after the 3 min microwave and sham-exposure sessions. Compared to sham exposure, arterial blood pressure and heart rate did not change significantly during or after the 35 min microwave exposure at 900 MHz or 1.80 GHz

Szmigielski et al. (1998) studied the autonomic nervous system's regulation of cardiovascular function by assessing the time course of diurnal rhythms of blood pressure and heart rate in a group of workers (61 healthy workers; 30–50 years) exposed to various intensities of RF fields (0.738 – 1.50 MHz). They found a reduction in the amplitudes of blood pressure and heart rate rhythms and a shift of the acrophase to an earlier time. These changes were more pronounced among workers exposed to higher intensities of RF electromagnetic fields.

Summarizing these results from animal and humans, two primary conclusions about the data seem apparent. First, when there is no heating, there are no cardiovascular effects. Second, in animal experiments where exposure sufficient to produce

lethality from hyperthermia can be conducted, numerous, expected cardiovascular effects become manifest. These few studies are preceded by decades of work establishing the same points. Thus, one can conclude that there are no important effects on the cardiovascular system in the usual environments.

As a secondary point, it must be noted that the "engineering" aspects of these human studies often are not very good. Well-trained medical personnel who are experts in the biology of the dependent variables need to understand they must obtain engineering support to deal with independent variable issues relating to exposure, dosimetry, etc.

10.6 Ocular Responses

Studies on ocular effects from microwave exposure started with Daily et al. (1950), and many papers have been published since then, particularly in the 1970s and 1980s. Some researchers have radiated the whole body of the experimental subjects, and others have limited exposure to the eyes. Short-term (e.g., 30 minutes), repeated or chronic (e.g., several weeks or months) exposures have been used.

It has been reported that microwaves can cause a variety of ocular effects, most often cataract in the lens. However, effects on the retina, cornea, and other ocular systems also have been reported.

Cataract formation has been observed in some experimental animals when one eye was exposed to a localized, very-intense microwave field and the other eye was the sham-exposed control. Daily et al. (1950) used the dog as the experimental animal. However, the most frequently used animal has been the albino rabbit; in recent years, non-human primates also have been used. Microwaves at 2.45 GHz have been used in many recent studies, although other frequencies, such as 1.25 GHz or 94 GHz, also are used. Experimental results obtained using rabbits will be presented first; monkey and human data follow.

10.6.1 Experiments with rabbits

It is known that, under conditions of partial-body exposure to intense microwaves, significant thermal damage can occur in vulnerable tissues. Kramar et al. (1975) investigated microwave-induced (2.45 GHz) cataract formation in the rabbit eye. There was a direct relationship between maximal energy absorption and maximal temperature in the vitreous body at a point midway between the posterior surface of the lens and the retinal surface. The locus of peak energy absorption and peak temperature correlated well with cataract formation in the posterior cortical lens, after a latent period of a few days, when the microwave exposure was at or above threshold levels, e.g., 150 W/kg for 30 min and retrolental temperature above 41°C. Kramar et al. (1987) tried to explain cataractogenesis by introducing hot water into the ocular cavity of rabbit. Cataract was consistently produced by retrolental temperatures between 43°C and 45°C. The authors claim that these findings support the assumption

that microwave cataractogenesis is due to the local production of elevated temperatures.

Hirsch et al. (1977) studied effects of repeated microwave irradiation to the albino rabbit eye. They used 3.0 GHz microwaves irradiated to the eye of albino rabbits for 15 min/day for a month. Clinical examination was carried out for a period up to 1 year. No change occurred below a power density of 300 mW/cm^2. However, at and above this value, posterior subcapsular iridescence and posterior cortical cataracts were produced.

Chou et al. (1983) investigated the effects of exposure of rabbits to 0.5 and 5 mW/cm^2, 2.45 GHz continuous wave radiation for 90 days. Sixteen male New Zealand rabbits were divided into two groups: eight of them were exposed 7 hr/dy, 5 dy/wk for 13 wks; the other eight rabbits were sham exposed. Eyes were examined for cataract formation. The only difference identified was decrease of food consumption during the 5 mW/cm^2 exposure. There were no ocular differences between microwave-exposed and sham-exposed groups.

Foster et al. (1986) reported that a single, 30 min exposure to 2.45 GHz radiation, with 5.75 W being absorbed, produced a cataract in half of the exposed eyes of New Zealand white rabbits.

Saito et al. (1998) investigated the effects of acute microwave exposure at 2.45 GHz on the eye of unanesthetized rabbits, with the contralateral eye serving as the control. Nine restrained, adult Japanese white rabbits were irradiated unilaterally by 2.45 GHz continuous wave microwaves for 160 min to 240 min. Using phantom material, the estimated SAR was 26.5 W/kg. The average increment in corneal surface temperature increment was 3.0°C for 15 min. Miosis occurred in all rabbits within 15 min. Post-exposure ophthalmologic signs included 1) miosis and papillary congestion; 2) keratoleucoma and corneal edema; 3) endothelial cell detachment and floating in aqua oculi, 4) fibrogenesis in the anterior chamber, and 5) conjunctiva edema. These signs disappeared within 1 week after exposure. There was no cataract formation.

More sophisticated experimental equipment and methods have been employed in recent investigations. Kojima et al. (2004) investigated the effect of systemic anesthesia on ocular effects and temperature in rabbit eyes exposed to microwaves. One eye of male pigmented rabbits was exposed at 2.45 GHz for 20–60 min (300 mW/cm^2; 108 W/kg), either under anesthesia (ketamine hydrochloride + xylazine) or without anesthesia. Temperatures within the eye were measured during microwave exposure by a Fluoroptic thermometer. Changes in the anterior segment were evaluated by image analysis utilizing a Scheimpflug camera, specular microscopy, and a laser flare cell meter. The exposed eyes showed miosis, conjunctival congestion, corneal edema, and an increase in the light scattering of the anterior shallow cortex in the papillary area of the lens. The group under systemic anesthesia showed much stronger symptoms than those without anesthesia. The highest temperature during exposure was in the vitreous, followed by the anterior chamber, and the retrobulbar cavity of the orbit. The ocular temperatures of the rabbits under systemic anesthesia were 2 – 9°C higher than those without anesthesia. Body temperature showed an increase of 1°C during the exposure. The more pronounced ocular effects in the anesthetized rab-

bits were associated with the significantly higher ocular temperatures. The authors stressed that the influence of systemic anesthesia on ocular changes should be considered when examining microwave-induced cataract formation.

Considerable research has been done on cataractogensis in rabbit eyes exposed to microwaves. Cataracts result from excessive heating. Safe and dangerous exposure levels can be predicted.

10.6.2 Experiments with monkeys

Kramar et al. (1978) investigated possible species differences relating to cataract formation following microwave exposure. The authors irradiated both rabbits and monkeys (*Macaca mulatta*) in the near field of continuous wave 2.45 GHz to determine the cataractogenic threshold. Rabbits developed cataracts and transient changes such as miosis, dilated vessels etc. at "apparent" incident power densities of 180 mW/cm^2 or greater. Monkeys sustained facial burns, but no lens damage, even at "apparent" incident power densities of 500 mW/cm^2.

These rabbit and monkey experiments showed clearly that the same incident power density microwave exposure did not produce similar effects on the face and eye of these two experimental animals (Kramar et al. 1978). The dissimilar effects reflect the different patterns of 2.45 GHz energy absorption in the monkey and rabbit heads due to their different facial structures. Rabbit eyes protrude in comparison to monkey eyes, which are more embedded within the eye sockets. The SAR threshold for cataracts in the monkey eye might be the same as the SAR threshold for cataracts in rabbit eyes. These results showed that cataractogenic power density levels in rabbit and dogs should not be directly extrapolated to primates, including human beings.

Kues et al. (1999) examined ocular effects associated with exposure to 60 GHz waves on rabbits and monkeys (*Macaca mulatta*). An antenna that produced a uniform energy distribution was used at an incident power density of 10 mW/cm^2. Acute exposure of both rabbits and monkeys consisted of a single, 8 h exposure; the repeated exposure protocol consisted of five separate 4 h exposures on consecutive days. One eye was exposed, and the contralateral eye served as the sham-exposed control. After post-exposure diagnostic examinations, ocular tissue was examined by both light and transmission electron microscopy. No ocular changes were found in either rabbits or monkeys that could be attributed to millimeter-wave exposure at 10 mW/cm^2. As mentioned above, Kramar et al. (1978) also saw no cataracts in microwave-exposed monkeys.

McAfee et al. (1979) trained unrestrained monkeys (*Macaca mulatta*) to expose their own face and eyes to pulsed microwave radiation at a frequency of 9.31 GHz and an average power density of 150 mW/cm^2. Twelve monkeys were individually irradiated during for periods of 30 to 40 days, for 294 to 665 minutes each day. The subjects then were observed for a period of one year. No deleterious effects, such as cataracts, were been observed. McAfee et al. (1983) further reported the outcome of microwave irradiation of rhesus monkeys' eyes at 9.31 GHz over 34 months and 2.45 GHz for 4 months at average power density of 150 mW/cm^2. Irradiation of 17 monkeys (*Macaca mulatta*) was accomplished without restraint or anesthesia by training

the monkeys to irradiate themselves. No cataracts, no effects on cornea, aqueous and vitreous humors or retina, and no loss of visual capability were found.

Lu et al. (2000) studied the effects of 1.25 GHz, high-peak power microwaves on retina in rhesus monkeys. Pre-exposure fundus photographs, retinal angiograms, and electroretinograms (ERG) were obtained to screen for normal ocular structure and function. Seventeen monkeys were randomly assigned to receive either sham or pulsed microwave exposure. The pulse characteristics were 1.04 MW (approximately 1.30 MW/kg, temporal peak retinal SAR), 5.59 μsec pulse length at pulses repetition rates of 0, 0.59, 1.18, and 2.79 Hz. (These are extremely high power values, but the pulses are very short.) Microwaves were delivered to the face with retinal SARs of 0, 4.3, 8.4, or 20.2 W/kg. Nine exposures were given at 4 hr/dy, 3 dy/wk for 3 weeks. Pre-exposure and post-exposure fundus pictures and angiograms all were within normal limits. The response of cone photoreceptors to light flash was enhanced in monkeys exposed at 8.4 or 20.2 W/kg, but not in monkeys exposed at 4.3 W/kg. Enhanced cone photoreceptor b-wave responses were observed in a SAR-dependent manner; these could be an early indicator of mild injury. However, no evidence of degenerative change or ERG depression was seen. From these results, retinal injury is very unlikely at 4 W/kg delivered to the retina. Functional changes probably were reversible, because no evidence of histopathologic correlation with ERG changes was observed.

Chalfin et al. (2002) evaluated anterior segment bioeffects of pulsed, 35 GHz and 94 GHz microwave exposure in the nonhuman primate eye. Five juvenile rhesus monkeys (*Macaca mulatta*) underwent baseline anterior segment ocular assessment consisting of slit lamp examination, corneal topography, specular microscopy, and pachymetry. These studies were repeated after exposure of one eye to pulsed 35 GHz or 94 GHz microwaves at varied fluences, with the other eye serving as a control. The fluence required to produce a threshold corneal lesion, i.e., faint epithelial edema and fluorescein staining, was 7.5 J/cm^2 at 35 GHz and 5.0 J/cm^2 at 94 GHz. Transient changes in corneal topography and pachymetry were noted at these fluences. Endothelial cell counts remained unchanged. Threshold corneal injury from 35 GHz and 94 GHz microwave exposure is produced at fluences below those previously reported for CO_2 laser radiation. These data might help elucidate the mechanism of thermal injury to the cornea.

10.6.3 Magnetic resonance imaging

Magnetic resonance imaging (MRI) has been widely used worldwide since 1980. High-field-strength/high-frequency MRI systems can cause tissue heating. The eye is particularly susceptible to temperature elevations because of its relatively poor blood supply. Shellock and Crues (1988a) and Shellock and Schatz (1992) measured corneal temperatures in 33 patients immediately before and after MRI performed with a 1.5 T, 64 MHz imager and a transmit/receive head coil; estimated peak SARs ranged from 2.54 to 3.05 W/kg. There was an increase in the average corneal temperature: 32.7 ± 0.7°C before imaging and 33.2 ± 0.5°C after. The changes in corneal

temperature ranged from 0.0°C to 1.8°C (mean 0.5°C), and the highest corneal temperature measured after imaging was 34.4°C. In animal models, the eye temperature threshold for microwave-induced cataractogenesis is between 41°C and 55°C. From these results, it was concluded that clinical MRI with use of a head coil delivering microwaves at the SARs studied causes relatively minor increases in corneal temperature that do not appear to pose any thermal hazard to ocular tissue.

From the results described above, one can conclude that microwave-induced cataracts are caused by an elevation in corneal temperature. Whole body (or far-field) exposure studies show that cataracts do not form in rabbit eyes unless intense microwave fields, at or near lethal levels, are applied.

Because microwave-induced cataracts and other ocular changes have been reported in experimental animals, especially rabbits, several researchers have been concerned with human eyes. Dozens of papers, referring to communication facilities and equipment, were published during 1960s and 1980s. However, cataracts caused by microwave exposure have not been reported in humans. Accidental exposures have produced either sub-clinical changes to the lens or no ocular effects (Elder 2003).

In summary, experimentally induced cataracts have been reported in rabbits, but not monkeys following microwave exposure. The presumed mechanism for cataract initiation is hyperthermia. At frequencies of about 100 kHz or greater, the dominant interaction mechanism in biological tissues is heating. At lower frequencies, the dominant interaction mechanism in biological tissues is induced current. The photon energy of microwave radiation is far too low to affect chemical bonding directly. The electric fields induced in tissues by RF radiation result in energy absorption due to the polarization of electrically charged structures and the flow of ions. It is assumed that the increase in linear and rotational energy is rapidly dissipated by molecular collision, resulting in generalized heating.

10.7 Auditory Responses

Investigations on auditory responses to microwaves can be classified into two categories. One is perception, i.e., hearing of microwaves, and the other is any possible effects on the auditory pathway.

10.7.1 Sensation and perception

Audible frequency ranges for sound waves are 10 Hz to 20,000 Hz in humans; 15 Hz to 50,000 Hz in dogs; and 1 kHz to 120 kHz in bats. The receptor cells for hearing are the inner and outer hair cells in the organ of Corti of the cochlea within the inner ear. Both hair cells and the auditory nerve fibers are tonotopically organized; at any position, they are most responsive to a particular frequency. The tectorial membrane arises from the organ of Corti. The longest stereocilia of the outer hair cells are tightly attached to the lower surface of the tectorial membrane. When the basilar

membrane vibrates in response to a sound, the organ of Corti and the overlying tectorial membrane are carried mechanically with it. Because the basilar and tectorial membranes pivot about different lines of insertion, their oscillating displacements are accompanied by back-and-forth shearing motions between the upper surface of the organ of Corti and the lower surface of the tectorial membrane. The mechanical deflection of the hair cell bundle is the proximate stimulus that excites each hair cells of the cochlea. This deflection is transduced into a receptor potential. The receptor potentials trigger APs that eventually are transmitted to the cortical auditory areas, which are responsible for perception of sound.

The localization of sound sources sets stringent limits on the speed of direct mechano-electrical transduction of hair cells. If a sound source lies directly to one side of an animal, an emitted sound will reach the nearer ear somewhat sooner than the farther ear. For a human, this delay is at most 700 μsec. Both humans and owls can locate sound sources on the basis of much smaller temporal delays, about 10 μsec. For this to occur, hair cells must be capable of detecting acoustical waveforms with microsecond-level resolution (Hudspeth 2000). At 1 MHz, the wave duration is 1 μsec. Any frequencies higher than 1 MHz are therefore "out of limit" for activation of hair cells in the organ of Corti. Indeed, there are no known reports of continuous wave signals causing microwave-induced sound in humans or microwave-induced auditory responses in experimental animals (Elder and Chou 2003).

10.7.2 RF hearing

10.7.2.1 Basic phenomenon

All the reports on 'hearing' of radiofrequency deal with auditory response to pulsed (27 to around 1,000 Hz) microwaves, which commonly is called radiofrequency hearing. The 'sound was something like that of a bee buzzing on a window, but with, perhaps, more high frequencies' (Ingalls 1967). It also has been reported to be similar to other common sounds, such as a click, hiss, knock ,or chirp. A quiet environment is required for the MF hearing, because the normal noise levels in outdoor or laboratory settings mask the hearing of microwave sounds. The necessary condition for hearing the radiofrequency-induced sound is the ability to hear audio frequencies above approximately 5 kHz and bone conduction hearing at lower acoustic frequencies.

10.7.2.2 Mechanisms for RF hearing

Cochlear microphonics are the alternating potential changes which follow the stimulus frequency. Microphonics are recorded from near the cochlea and are mainly composed of receptor potentials from outer hair cells. Chou *et al*. (1975) recorded cochlear microphonics that were similar to those evoked by acoustic stimuli, from the round window of guinea pigs during irradiation by pulsed 918 MHz (repletion rate 100 Hz) microwaves. Recording of cochlear microphonics demonstrated that the microwave auditory effect was due to mechanical distortion of the cilia of cochlear hair

cells. These experiments indicate that the primary site of transduction of microwave energy is outside or at the cochlea.

Chou and Galambos (1979) recorded the brain-stem evoked response from guinea pigs stimulated at various intensities by acoustic pulses. Either blocking of the external ear or destruction of the middle-ear produced little change in the brain-stem evoked responses elicited by microwave pulses. From these results, it was suggested that conduction of pressure waves through the bones appear to be the mechanism responsible in perception of pulsed microwaves.

Using conventional glass microelectrodes, Seaman and Lebovitz (1989) recorded extracellular APs of neurons in cat dorsal and postventral cochlear nuclei while the head of the cat was exposed to microwave pulses at 915 MHz. Response thresholds to acoustic tones, acoustic clicks, and microwave pulses were determined for auditory units with characteristic frequencies from 278 Hz to 39.2 kHz. The midline brainstem SAR threshold was as small as 11.1 mW/g/pulse, and specific absorption threshold was as small as 0.6 μJ/g/pulse. Microwave thresholds were generally lower for characteristic frequency less than 9 kHz, as were most acoustic thresholds. These results show that microwave pulses directly stimulated cochlea, then the evoked APs propagated along the normal auditory system, i.e., eighth cranial nerve, medial geniculate nucleus, and primary auditory cortex.

Foster and Finch (1974) proposed thermoelastic expansion as a mechanism for RF hearing. They conducted experiments in water and in KCl solution exposed to microwave pulses similar to those that produce sounds in humans. They showed that pressure changes would result from the absorption of microwave pulses that could produce significant acoustic energy in the solution. Thus, they concluded that audible sounds were produced, via bone conduction, by rapid thermal expansion caused by absorption of the energy in the microwave pulses.

10.7.3 Effects on auditory pathway

10.7.3.1 Experimental data

Arai et al. (2003) investigated whether the pulsed microwaves emitted by a mobile phone have short-term, adverse effects on the human central auditory system. Using 15 volunteers with normal hearing, the auditory brainstem response (ABR), the ABR recovery function, and the middle latency response were recorded before and after using a mobile phone for 30 min. None of the three measures were affected by exposure to the field for 30 min.

Bak et al. (2003) reported no effects of microwave exposure at 450 MHz, 935 MHz, or 1.80 GHz on ABR during and after exposure for 20 min. The subjects were 45 young, healthy volunteers of both sexes. The ABR evaluation was performed before, during, and immediately after the exposure, and the latencies of waves I, III, and V, and inter-waves I-V were analyzed. The authors concluded that brief mobile phone use does not affect propagation of electrical stimuli along the auditory nerve to auditory brainstem centers.

Ozturan et al. (2002) studied the effects of mobile phone use for 10 minutes on human hearing. Using 30 volunteers with normal hearing, evoked otoacoustic emissions (OAEs) were measured before and after cell phone exposure. No measurable changes in evoked OAEs were detected, and none of the subjects reported a deterioration in hearing level. The authors concluded that a 10 min exposure to the microwaves emitted by a mobile telephone had no effect on hearing, a least at outer ear, middle ear, and cochlea. Then the same group (Kizilay et al. 2003) studied the effects of chronic exposure to the microwaves emitted by a mobile phone on the inner ear of adult and developing rats using distortion-product OAEs. Seven of 14 adult rats and four newborn rats were exposed 1 hr/day for 30 days; the other seven adult rats were assigned to control group. No measurable difference in distortion-product OAEs were found between exposed and control groups, and no changes were found in developing rats. It was concluded that 30 days of exposure at 1 hr/dy did not cause any hearing deterioration in either adult or developing rats.

The RF hearing effect occurs because the ELF-modulated pulses stimulate the cochlea, which then responds in the normal manner. Apparently the cochlea is stimulated via bone conduction caused by rapid thermal expansion resulting from the absorption of the energy in the microwave pulses.

These available data from animals and humans suggest that the microwave fields associated with cell phones have no effect on the auditory pathway. However, the data base is small, and the durations of experimental exposure are short, especially in humans. Because so many people already make extensive use of their cell phones, finding unexposed (or not recently exposed) subject will become increasingly difficult. Perhaps laboratory tests show no differences, because the auditory system has been affected before the subject arrives at the laboratory.

10.8 Thermoregulatory Responses

It is essentially important for the existence of animals or humans to maintain body temperature within a certain limited range, while living environments of diverse and varying temperatures. Said the most basic level, the maintenance of body temperature is achieved by balancing heat production within the body and heat loss to the surroundings.

10.8.1 Regulation of body temperature

Change of body temperature is detected, especially externally at the skin and internally by a specialized region of the brain. The information is integrated in the CNS, and regulation is achieved by autonomic and behavioral thermoregulatory reactions (Fig 10.2). These reactions act to overcome the thermal load for maintaining the normal body temperature.

The balance of body temperature is expressed by the following equation;
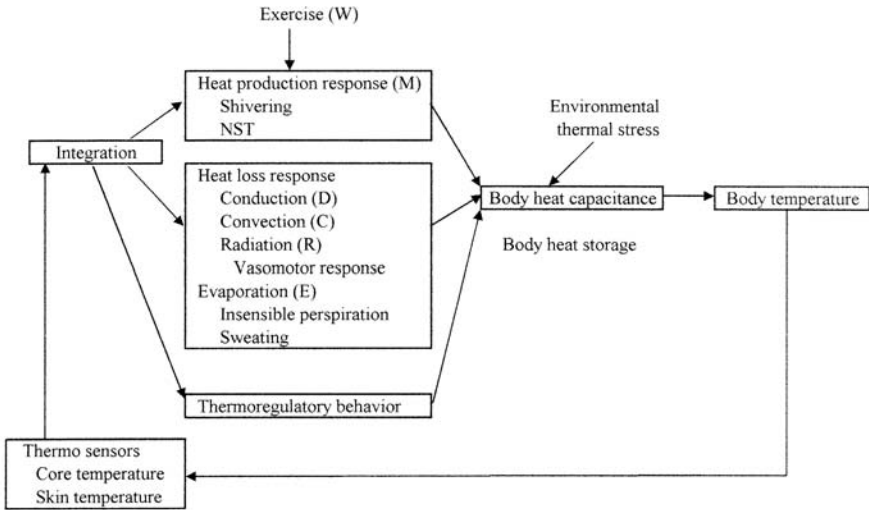
$$M \pm W = E \pm R \pm C \pm D \pm S$$

Fig. 10.2. Block diagram of thermoregulation. The system has two groups of sensors, cutaneous and internal detectors.

where M is the rate at which thermal energy is produced through metabolic processes; W is the rate at which work is produced; E is the rate of heat exchange with the surroundings via evaporation; R is the rate of heat exchange with the surroundings via radiation; C is the rate of heat exchange with the environment via convection; D is the rate of heat exchange with the surroundings via conduction; and S is the rate of body heat storage.

Heat production is achieved by non-shivering thermogenesis (NST) and shivering heat production. The basal metabolic rate, a part of NST, is the heat production of a resting human being in a thermo-neutral condition ($20-27°C$) at a time exceeding 12 hours from the last meal. NST consists of both basic NST, which is related to energy demand of the body, and thermoregulatory NST, which takes place during cold exposure. Body tissues that produce thermogenesis are skeletal muscles, thoracic and abdominal organs (such as heart, liver, and alimentary canal), brain, and brown adipose tissues. NST is humorally controlled by β-adrenergic activity.

Shivering is non-voluntary contraction of skeletal muscles that occurs simultaneously on both flexor and extensor muscles at 9–11 Hz. The produced heat is conducted by blood flow throughout the body.

Heat exchange between body and the surroundings is achieved by heat loss responses and evaporation.

Thermosensors are located under the skin and deep inside the body. The deep sensors are mainly located in medial preoptic/anterior hypothalamic region. However, some additional thermosensors are found in medulla oblongata, spinal cord, and deep abdominal organs. Among these receptors, the skin sensors are the most impor-

tant, but medial preoptic/anterior hypothalamic receptors also contribute greatly to production of thermoregulatory responses.

Integration of temperature information from these sensors takes place in hypothalamus. The thermoregulatory system can be described as a "closed loop, with negative feedback", as are other biological regulatory systems, like endocrine system.

Exposure to RF at frequencies above 100 kHz, i.e., exposure to microwaves, generates heat in body tissues. The sensation of tissue warming is necessary to initiate appropriate behavioral action, although physiological responses such as sweating and peripheral circulation changes also can be initiated automatically and autonomously by thermal stimuli. Therefore, any microwave experiments should be planned and interpreted vis-à-vis thermoregulatory mechanisms.

10.8.2 Experiments with animals

Spiers et al. (1989) reported neonatal rats (6–7 days of age) showed a 1.7°C increase in the colonic temperature at the end of a 60 min continuous wave exposure to 2.45 GHz microwaves (5 mW/cm^2, SAR = 3 W/kg) at cold ambient temperature of 25°C, without any change in metabolic heat production. Colonic temperature was increased by 3.4°C after exposure to 20 mW/cm^2 for 60 min. The results indicate that the hypothermic rat pup can be effectively warmed by low-level microwave irradiation. Furthermore, the pup is capable of altering metabolism in response to such heating.

Adair et al. (1985) studied changes in thermoregulatory physiological responses and behaviors in squirrel monkeys chronically exposed to continuous wave, 2.45 GHz microwaves, for 40 hr/wk for 15 wk at power densities of 1 or 5 mW/cm^2. The whole body SAR was 0.16 W/kg per mW/cm^2. Three different, controlled environmental temperatures, 25, 30 or 35°C, were used. Most previous studies paid no attention to the factor of environmental temperature. Physiological responses were measured three times: (1) during a pre-exposure phase of 8–12 weeks, (2) during a 15-week exposure period, and (3) during a post-exposure period of 4–8 weeks. Variables measured were body mass, blood properties, metabolic heat production, sweating, skin temperature, deep body temperature and behavioral responses by which the monkeys selected a preferred environmental temperature. Results showed no reliable alteration of metabolic rate, internal body temperature, blood indices, or thermoregulatory behavior. An increase in sweating rate occurred in the 35°C environment. Skin temperature, reflecting vasomotor state, was reliably influenced by both ambient temperature and microwaves. The most robust consequence of microwave exposure was a reduction in body mass.

Adair et al. (1992) studied whether exposure to microwave fields at the resonant frequency generated heat deep within the body. Adult male squirrel monkeys, held in the far field of an antenna within an anechoic chamber, were exposed (10 min or 90 min) to either resonant 450 MHz or supra-resonant 2.45 MHz continuous wave fields (E polarization) in cool environments. Whole-body SARs ranged from 0–6 W/kg (450 MHz) and 0–9 W/kg (2,450 MHz). Colonic and several skin temperatures, metabolic heat production, and evaporative heat loss were monitored continuously. During brief microwave exposures in the cold, the reduction of metabolic heat

production was directly proportional to the SAR, but 2,450 MHz energy was a more efficient stimulus than was the resonant frequency (450 MHz). Detailed analyses of the data indicate that temperature changes in the skin were the primary source of the neural signal for a change in physiological interaction processes during microwave exposure in the cold.

The essential message from these experiment is that microwave irradiation is just another source of heat, which the body can deal with by the normal processes of the thermoregulatory system. Microwaves are not an extraordinary, highly-dangerous stimulus that is beyond the body's coping mechanisms. Microwaves are just a heat source, like a heat lamp or hot air. However, too much heat, like a very high SAR or a forest fire, is a serious threat to existence.

10.8.3 Experiments with humans

Adair et al. (1998) measured thermoregulatory responses of heat production and heat loss in seven adult volunteers (4 women and 3 men, aged 21–57 years) during 45 min dorsal exposures of the whole body to continuous wave, 450 MHz microwaves. Two exposure levels, SARs of 5.76 or 7.68 W/kg, were tested in each of three ambient temperatures (24, 28 and 31°C). No changes in metabolic heat production occurred under any of the exposure conditions. Vigorous increases in sweating rate on back and chest, directly related to both ambient temperature and power densities, cooled the skin and ensured efficient regulation of the deep body (esophageal) temperature to within 0.1°C of the normal level. These results indicate that dorsal exposures of humans to microwaves at the supra-resonant frequency of 450 MHz, at local peak SAR up to 7.68 W/kg, are mildly thermogenic and are counteracted efficiently by normal thermophysiologic heat loss mechanisms, principally sweating. Adair et al. (1999) further measured thermoregulatory responses of heat production and heat loss in two different groups of seven adult volunteers (males and females) during 45 min dorsal exposures of the whole body to continuous wave 450 MHz or 2.45 GHz microwave fields. At each frequency, two power densities were tested at each of three ambient temperatures [T(a)] = 24, 28 and 31°C) plus T(a) controls (no RF). The normalized peak SAR was the same for comparable power densities at both frequencies, i.e. peak surface SAR = 6.0 and 7.7 W/kg. No change in metabolic heat production occurred under any exposure conditions at either frequency. The magnitude of increase in those skin temperatures under direct irradiation was directly related to frequency, but local sweating rates on back and chest were related more to T(a) and SAR. Both efficient sweating and increased local blood flow contributed to the regulation of the deep body (esophageal) temperature to within 0.1°C of the baseline level, which agreed with the previous study.

Many reports present data showing that continuous wave and pulsed microwave fields, at the same frequency and average power density, produce similar responses in the exposed organism. During whole-body exposure of squirrel monkeys at 2.45 GHz using either continuous wave or pulsed fields, heat production and heat loss responses were nearly identical. To explore this question in humans, Adair et al.

(2001a) exposed two different groups of volunteers to 2.45 GHz using either continuous wave (two females, five males) and pulsed (65 μsec pulse width; three females, three males) microwave fields. Thermophysiological responses of heat production and heat loss were measured under a standardized protocol (30 min pre-exposure baseline, 45 min field or sham exposure, 10 min post-exposure baseline), conducted in three T(a) levels: 24, 28, and 31°C. At each T(a), the SARs were 0, 5.94 and 7.7 W/kg. Data for each group showed minimal changes in core temperature and metabolic heat production for all test conditions. Local skin temperatures showed similar patterns for continuous wave vs. pulsed exposure; skin temperature depended only on SAR. However, there was one reliable difference between continuous wave and pulsed exposure. Only the skin temperature of the upper back (i.e., the area facing the antenna) showed a greater increase during pulsed exposure than during continuous exposure. For all other measurements, no clear evidence for a differential response to continuous vs. pulsed microwave fields was found.

Adair et al. (2001b) studied thermoregulatory responses of human beings following partial body exposure to 2.45 GHz continuous wave microwaves at higher peak power densities of 50 and 70 mW/cm^2. Seven volunteers (four males and three females) were tested at each power density at three T(a) values: 24, 28 and 31°C. The lab's standard protocol of 30 min baseline, 45 min exposure, and 10 min baseline was used. Esophageal and six skin temperatures, metabolic heat production, local sweating rate, and local skin blood flow were measured. No change in esophageal temperature or metabolic heat production was recorded at any power density at any T(a). At peak density of 70 mW/cm^2, skin temperature on the upper back (irradiated directly) increased 4.0°C with T(a) at 24°C; 2.6°C with T(a) at 28°C, and 1.8°C with T(a) at 31°C. These differences were due primarily to increases in local sweating rate, which was greatest in ambient temperature at 31°C. Also at peak power density at 70 mW/cm^2, local skin blood flow on the back increased 65% over baseline level with T(a) at 31°C; the increase was only 40% at a T(a) of 24°C. Vigorous heat loss responses of blood flow and sweating maintain thermal homeostasis efficiently.

Adair et al. (2003) measured thermophysiological responses of heat production and heat loss in seven adult volunteers (six males and one female, aged 31–74 years) during 45 min dorsal exposures of the whole body to a 100 MHz (continuous wave) microwave field. SARs of 0.27, 0.41 and 0.54 W/kg were tested in each of three T(a) (24, 28, and 31°C), along with sham exposure. A standardized protocol consisting of 30 min pre-exposure baseline, 45 min microwave or sham exposure, and 10 min post-exposure baseline was used. Measured responses included esophageal and skin temperatures at seven locations, metabolic heat production, local sweating rate, and local skin blood flow. No changes in metabolic heat production occurred under any test condition. Unlike published results of similar exposure at 450 MHz and 2.45 GHz, local skin temperatures, even those on the back that were irradiated directly, changed little or not at all during 100 MHz exposures. During the 45 min microwave exposure, esophageal temperature showed modest changes (range = −0.15 to 0.13°C) and never exceeded 37.2°C. Thermoregulation principally was controlled by appropriate increases in evaporative heat loss (sweating) and, to a lesser extent, by changes in skin blood flow. Because of the relatively deep penetration of microwave

energy at this frequency, effectively bypassing the skin, these changes must have been stimulated by thermal receptors deep in the body, rather than by those located in the skin. From these results, the authors argued that continuous microwave radiation with an intensity less than 10 mW/cm^2 is unlikely to affect physiology significantly through athermal mechanisms.

Walters et al. (2004) studied the role of baseline skin blood flow on the rate of cutaneous heating induced by 94 GHz microwave energy in humans (3 female, 3 male). Exposure intensities were high power, 1 W/cm^2 for 4 sec, and low power, 175 mW/cm^2 for 180 sec. At the time of exposure, skin blood flow was (a) normal, (b) eliminated using a blood pressure cuff to occlude forearm blood flow, or (c) elevated by heating the skin prior to irradiation. Results showed that only a two-fold elevation in baseline skin blood flow had a profound impact on the subsequent rate of heating, resulting in a substantially lower rate of heating. Occlusion to block increased blood flow to the skin reversed this lower rate of heating. These results demonstrate that relatively small changes in skin blood flow can produce substantial alterations in the rate of skin heating during prolonged 94 GHz exposure.

In summary, results from humans tell the same story as experiments with animals. Microwaves produce tissue heating, and the body uses its thermoregulatory system in the usual manner to deal with the added heat load. The strong implication is that microwaves and RF are not hazardous, so long as they do not exceed the thermoregulatory capacity of the body.

10.8.4 Magnetic resonance imaging

For clinical investigation of patients, MRI devices are used widely. The primary concern about this technology is the possibility of tissue heating caused by microwave exposure. Shellock and Crues (1988b) measured body and skin temperatures in 35 patients immediately before and after clinical MRI. MRI was performed with a 1.5 T system using a 28 cm, open-bore microwave transmit/receive head coil specifically designed for examination of the brain. Body temperature did not change. However, forehead skin temperature and outer canthus skin temperature increased by 0.2°C and 0.6°C, respectively. Shellock et al. (1994) further studied physiological responses to an MRI procedure performed at a SAR of 6.0 W/kg at 1.5 T, 64 MHz. Assessment was made before, during a 16 min MRI procedure, and immediately after MRI. Statistically significant ($P < 0.005$) increases in temperature of the tympanic membrane, the skin of the chest, abdomen, upper arm, hand and thigh, plus increases in heart rate and cutaneous blood flow, were associated with exposure to high SAR. However, these small changes all are well within the limits that can be tolerated by persons with normal thermoregulatory function.

10.8.5 Conclusions

Mammals have evolved elaborate systems for regulating optimal body temperature in hot or cold environments. Experiments with animals show that microwaves are just another heat source, like hot air or an infrared heat lamp. If heat load produced by

microwave (or RF) exposure is small, the thermoregulatory system adjusts and there are no adverse effects. However, if the heat load applied is too great, lethality can result. Experiments with humans, including those with MRI, are directly in agreement with the viewpoint based on animal experiments. However, with humans, only low SARs can be used. Many details enter the story, such as differences in penetration depth of different wavelengths (i.e., frequencies), but the big picture is clear.

Biological systems are fundamentally noisy – on the molecular scale as a consequence of thermal agitation – and macroscopically – as a consequence of physiological functions and animal behavior. If electromagnetic fields are to significantly affect physiology, their direct physical effect must be greater than that from the ubiquitous, endogenous noise. Thermal noise is an essential attribute of living systems, and the lack of thermal noise means death.

One of the classic problems in bioelectromagnetics has been the 'needle in the haystack' problem. How can an imposed stimulus producing tiny energy effects have any influence under conditions where the noise is many orders of magnitude bigger than the signal? Scientists have offered theoretical formulations by which the signal/noise ratio could be overcome, but it has been very difficult to illustrate the workings of such theoretical mechanisms in data from real biological systems.

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