# 1990–1995 Advances in Investigating the Interaction of Microwave Fields with the Nervous System

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*Abstract*—**After a short review of the nervous system and its constituents, recent data on microwave bioeffects are reviewed and evaluated, in particular, the effects on the brain and the spinal cord and under low-level irradiation. Special attention is paid to new results on the effects of modulated and pulsed waves with respect to both continuous wave (CW) irradiation, and, in particular, to the frequency of the modulation. The last section is devoted to modeling and simulation of the nervous system and nervous fibers, where significant progress has been made during the last years. Except for some tutorial aspects, the reviewed literature essentially covers the 1990–1995 period.**

## I. Introduction

FOR YEARS, data about effects of microwave radiation on the central nervous system and on behavior has been the subject of great controversy [1]. This controversy was largely due to a lack of unified methodological approaches and to an inadequate data base for selecting the most appropriate methods. Moreover, there were few attempts to verify the findings of other laboratories.

For these reasons, a formal program of cooperation between the United States and the Soviet Union, was undertaken in 1975 [2]. Concerning the biological effects of physical factors in the environment, it was concluded that duplicate projects should be initiated with the general goal of determining the most sensitive and valid test procedures for evaluating the effects of microwave radiation on the central nervous system. Male rats of the Fisher 344 strain were exposed or sham exposed to continuous wave microwave radiation at 2.45 GHz [3]. Animals were subjected to behavioral, biochemical, or electrophysiological (EEG frequency analysis) measurements during and/or immediately after exposure. Behavioral tests used were passive avoidance ("learned" behaviors) and activity in an open field ("naturalistic" behaviors).

The results of these studies are interesting. Neither group observed a significant effect of microwave irradiation on open field activity. Both groups observed changes in variability of the data obtained using the passive avoidance procedure, but not in the same parameters. The U.S. group, but not the U.S.S.R. group, found significantly less ionic activity in the microwave-exposed animals compared to the sham-exposed animals. Both groups found incidence of statistically significant effects in the power spectral analysis of EEG frequency, but not at the same frequency. The failure of both groups to observe effects in the behavioral tests attributable to microwave exposure was unexpected because previous experience with these tests, using Wistar rats [4], had detected differences between microwave-exposed and sham-exposed rats. The failure of both groups to substantiate the results of the other reinforced the contention that such duplicate projects are important and necessary.

An increasing amount of evidence, derived from in vitro and in vivo studies, now indicates that microwave fields directly affects living systems [5]. Microwave-energy absorption, in experimental animals or humans, introduces ambiguities regarding the relative contributions to physiological alterations of indirect thermal effects, microwave specific thermal effects, and possibly direct nonthermal interactions. In spite of these ambiguities, results of in vivo experiments, conducted at low specific absorption rates, indicated direct microwave effects [6]. Unambiguous evidence of direct effects of microwave fields has been provided by the results of in vitro studies. These studies were conducted under conditions of precise and accurate temperature control, revealing direct effects at various frequencies and intensities on a number of cellular endpoints, including calcium binding, proliferation, ligand-receptor-mediated events, and alteration in membrane channels [7]. Interactions occurring at the microscopic level are related to the dielectric properties of biomacromolecules and molecular asssemblages, in the form of functional units such as enzyme complexes, cell-membrane receptors, or ion channels [8].

The classical book by Michaelson and Lin [9], reviewing in 1987 the entire area of biological effects due to radio frequency radiation, is still to be read by those who want to acquire a good knowledge of the field. A more recent book by Thuery [10] reviewed, in 1992, the industrial, scientific, and medical applications of microwaves. The reader will find that there are a number of basic information sources on the interaction between microwave fields and the nervous system. A handbook by Polk and Postow [11] reviews the biological effects of electromagnetic fields. A summary of the action of microwave electromagnetic fields on the nervous system has been published recently [12].

The scope of this paper has been severely limited. It concentrates on nonionizing microwave fields and on rather recent results. The only subjects of interest are related to the nervous system, hence hyperthermia is excluded. The reader interested in a general review of European microwave bioelectromagnetic research, is referred to another paper [13]. This report is based on a systems point of view, so little will be found on isolated nerves or neurons, on cells, or

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on muscle activation. Low frequency effects, including low frequency magnetic field effects are excluded. Despite these limitations, this paper still offer the reader a respectable amount of material.

## II. Fundamentals

The nervous system is the body's main control and integration network. It serves three functions: sensing the changes both within the body, and the outside environment, interpreting and integrating these changes, and responding to the interpretion by initiating actions in the form of muscular contractions or glandular secretions.

The nervous system of vertebrae animals is composed of two primary parts: the **central nervous system**, composed of the brain and spinal cord, and the peripheral nervous system, which is composed of all nerves outside the central nervous system. The nervous sytem is further organized into sensory-motor and autonomic components.

The **sensory system** virtually has millions of sense organs, whose basic functions involve gathering information about the environment. The sensory nerves of the skin for example transmit impulses to the appropriate portions of the central nervous system, where the signals are interpreted as sensations of pressure, pain, temperature, or vibration. Other sensory receptors exist for sight, hearing, taste, and smell.

The **autonomic nervous system** has its part in the process. It operates involuntarily to control many bodily functions. It is divided into the sympathetic and parasympathetic systems. These components are usually considered to be antagonistic to each other, because they control opposite effects in various organs. They are distinguished by the anatomic distribution of their nerve fibers. One major difference between them is of prime interest in microwave bioelectromagnetics: the postganglionic fibers secrete different neurohormones. The parasympathetic system secretes substances like acetylcholine from fibers called "cholinergic," while the sympathetic system secretes epinephrine and adrenalin from fibers called "adrenergic."

Many of the functions of the autonomic system are regulated by the hypothalamus, located in the brain between the cerebrus and the mid-brain. The hypothalamus affects the cardiovascular system, the body temperature, the appetite, and the endocrine system, among its many functions. Body temperature and endocrine functions are under rather direct influence of electromagnetic fields.

The **nerve impulses** pass to or come from the brain, via twelve pairs of cranial nerves, or via the spinal cord. Among the cranial nerves, some such as the optic nerve, are sensory nerves interfacing with sense organs. Others, like the facial nerve, are motor nerves, connecting to muscles and glands. Interneurons carry impulses between the sensory and motor nerves.

In the central nervous systems, the **spinal cord**, which is continuous with the brain is the center for spinal reflexes, and is also a two-way communications system between the brain and the body. From an electrical engineering point of view, it is interesting to wonder about the equivalent electrical parameters of such a communication system.

The **neuroglials cells** are within the tissues of the brain and spinal cord. They fill in the space and support the neurons like scaffolding. Unlike neurons, neuroglials cells can reproduce.

If the electromagnetic fields are active in altering the activity and function of the central nervous system, then one may expect to see those changes reflected in the concentrations of **neurotransmitters** in various regions of the brain [13]. Hence, total or local exposure to electromagnetic fields, at levels and frequencies where the central nervous system could be influenced, will yield changes in neurotransmitter concentrations. The excitation of acupuncture points by microwaves (from 0.2 to 3 GHz) may produce a quite efficient antalgic effect, as shown by the corresponding increase in the pain threshold, measured by a dolormeter [14]. Furthermore, respective variations in pain threshold and neurotransmitter release in the center of pain reception in the brain are proportional [15].

Data about the effects of microwaves form a heterogeneous ensemble of facts that are not readily classified in terms of thermal versus nonthermal interactions [10]. The first category includes interactions with the peripheral nervous system and certain neurovegetative functions, alterations in EEG, changes in animal behavior, and, possibly, in the permeability of the blood-brain barrier. The second category could include membrane interactions that affect the calcium fluxes, the modulation of neuronal impulse activity, and, possibly, induced arrhythmias in isolated hearts. Also included in this category could be the somewhat confused collection of dystonias and behavioral effects that are often referred to in Eastern Europe as the microwave syndrome. It is also possible that there are some subtle very low level effects of microthermal or nonthermal origin which are masked by the more apparent thermal effects, when the power absorbed is of the same order of magnitude as the basic metabolic rate.

**Fluxes of calcium ions** have received much interest in recent years. $Ca^{++}$ ions relay electrochemical messages to the cell surface and its biochemical mechanisms. Evolution seems to have favored calcium in preference to other neighboring ions (Mg\s\up5(++), $Na^+$, $K^+$, $Cl^+$) because they are able to bond without causing deformation to either membrane proteins or to soluble proteins of cytoplasm or organelles. These proteins themselves act as intermediaries. They have several ion bonding sites, and by changing their configuration as a function of the occupied site, they excite a specific target enzyme. $Ca^{++}$ ions use special channels to cross the membrane along the concentration gradient. These voltage-gated channels are normally closed in excitable cells, but they open in response to the action potential, i.e., the transmembrane voltage pulse induced by the arrival of a messenger on the cellular surface. The membrane resting potential is $-90$ mV, but it may reach $+40$ mV. The channel opens from $-30$ mV. The phenomenon lasts for a millisecond and allows the passage of about 3000 $Ca^{++}$ ions, after which the outward migration of $K^+$ ions returns the potential to its equilibrium value. The calcium-ion flux excites the endoplasmic reticulum, which itself liberates $Ca^{++}$ ions. The evacuation of the ions must take place against the concentration gradient. It is supported by the enzyme AT-Pase, or calcium pump, which acquires the necessary energy by dissociating adenosine triphosphate (ATP) molecules [10].

The use of **weak electromagnetic fields** to study the sequence and energetics of events that couple humoral stimuli from surface receptor sites to the cell interior has identified cell membranes as a primary site of interaction with these low frequency fields in the pericellular fluid. Field modulation of cell surface chemical events indicates a major amplification of initial weak triggers associated with bindings of hormones, antibodies and neurotransmitters to their specific binding sites [16]. Calcium ions play a key role in this stimulus amplification, probably through highly cooperative alterations in binding to surface glycoproteins, with spreading waves of altered calcium binding across the membrane surface. Protein particles spanning the cell membrane form pathways for signaling and energy transfer. Fields millions of times weaker than the membrane potential gradient of $10^7$ V/m modulate cell responses to surface stimulating molecules. The evidence supports nonlinear, nonequilibrium processes at critical steps in transmembrane signal coupling. Cancer-promoting phorbol esters act at cell membranes to stimulate ornithine decarboxylase which is essential for cell growth and DNA synthesis. This response is enhanced by weak microwave fields, also acting at cell membranes. There is strong evidence [16] that cell membranes are powerful amplifiers of weak electrochemical events in their vicinity.

## III. Effect on Brain and Spinal Cord

Molecular processes involved with the **brain energy metabolism** of the rat may be affected by radiation in the radio frequency range. It has been indicated that there are 27–29 divalent iron atoms and two divalent copper atoms in the molecules of the respiratory chain [17]. Each of these is essential to the function of the respiratory chain at the molecular level. Charged particles in an electric field undergo translational motion if not otherwise constrained. Therefore, some of the divalent metal ions in these key chains could be expected to be affected by the oscillating electric field of the RF radiation, at least until the critical relaxation frequency for each structure is exceeded. This concept has been tested by examining brain metabolism during exposure to CW frequencies of 200, 591, and 2,450 MHz, and by developing dose-response relationships for the effects [18]. The presence of specific molecular interaction(s) would indeed be supported by a frequency specificity based on the macroscopic dielectric properties of biological systems. The measurement techniques included time-sharing fluorescence at the brain surface to determine relative levels of reduced nicotinamide adenine dinucleotide (NADH) and biochemical assays for adenosine triphosphate (ATP) and creatine phosphate (CP). NADH, ATP, and CP are key compounds in brain energy metabolism. ATP is a key compound in energy metabolism because it is the carrier of energy to the processes in living cells. NADH is oxidized to produce ATP in the mitochondria, while brain ATP concentration is maintained at the expense of CP. When demand for ATP is higher than the mitochondrial production capacity, CP is rapidly converted to ATP to sustain ATP levels, and significant decreases in CP levels are observed prior to any decrease in ATP.

Frequency-dependent changes have been found for all three key compounds. The measured temperature in the rat brain was essentially constant for all exposures. At 200 and 591 MHz, NADH fluorescence increased in a dose-dependent manner between approximately 1 and 10 mW/cm$^2$, then became constant at higher exposures up to at least 40 mW/cm$^2$. There was no effect at 2,450 MHz. Levels of ATP and CP were measured in whole brain after exposure. The CP levels decreased only at 591 MHz. The effect of duration of exposure (up to 5 min) was investigated for all compounds at 200 and 2,450 MHz, and exposures to 20 minutes were examined at 591 MHz.

Microwave exposures at 591 MHz resulted in a decrease in ATP levels to 75% of controls while CP levels are no lower than 60% of controls. During the 200-MHz exposures, brain ATP levels decreased to 80–90% of controls even though CP levels were not significantly decreased. These results are not consistent with normal energy metabolism where ATP levels are maintained at the expense of CP, and suggest that at 200 MHz there is RF inhibition of the reaction converting CP to ATP. Furthermore, these results occur at RF exposure levels that do not increase brain temperature, thus suggesting a direct inhibition of metabolic processes by RF radiation. The authors proposed the following speculative mechanism, which is consistent with the results obtained. RF radiation at 200 and 591 MHz inhibits specific enzymes or electron transport proteins important in maintaining the cell's ATP pool. Such inhibition can be the result of RF-radiation-induced dipole oscillation involving the divalent metal ion in the active site during catalytic or transport activity. During such oscillations, the ability of the enzyme to perform its function could be decreased. For a given molecular species, the induction of dipole oscillation and change in catalytic or transport activity would be frequency dependent and should be responsive to the local electric field, i.e., the field in the tissue. The frequency dependence would be determined by the detailed structure of the segment of the molecule and its freedom of movement in relation to the other parts of the active site. This proposed mechanism is consistent with Pethig's [19] observation that RF-induced dipole oscillations in proteins in solution are found precisely in the 30–1000 MHz frequency range. It is also consistent with the $\delta$-dispersion of the dielectric constant for proteins in solution which exists between 10 and 1000 MHz [20]. Absorption of energy from a RF-field by a dipole oscillator would be expected to give rise to such a dispersion.

The **microwave auditory phenomenon** is one of the most interesting biological effects of microwave radiation. Short rectangular microwave pulse impinging on the heads of humans and animals has been shown to produce audible sounds. When microwave radiation impinges on the head, the absorbed energy is converted into heat, which produces a small but rapid rise of temperature. This temperature rise, occurring in a very short time, generates rapid thermoelastic expansion of tissues in the head, which then launches an acoustic wave of pressure that is detected by hair cells in the cochlea. Pulsed microwaves were shown to induce acoustic pressure waves in the cat brain, which propagate with an acoustic wave velocity of 1523 m/s [21]. Cat brains were irradiated

with pulsed 2.45 GHz microwaves. Short rectangular pulses (2 $\mu$s, 15 kW peak power) were applied singly through a direct contact applicator located at the occipital pole of a cat's head. Acoustic pressure waves were detected by using a small hydrophone transducer, which was inserted stereotaxically into the brain of an anesthetized animal through a matrix of holes drilled on the skull. The mean speed of propagation was based on an ensemble of 64 measurements made at 6 different sets of distance. The amplitude attenuation experienced by the thermoelastic pressure wave in the brain follows the exponential law and has an attenuation coefficient of 0.56 per cm. Speed of propagation and attenuation are both functions of frequency and temperature.

In order to measure the relationship between pain and the release of **neurotransmitters**, a push-pull cannula has been inserted into the center of pain reception in the brain of rabbits [22]. An artificial cerebrospinal fluid was injected at a very low and very constant speed. CW Microwave stimulation at 2.45 GHz was applied by a coaxial cable in an adequate acupuncture point. The sample of fluid was collected from the pull cannula. The pain threshold was measured three times: before, during, and after each of the stimulations, using an especially designed dolormeter. The radioenzymatic assay was used to measure the levels of norepinephrine release in the sample perfusates. It was found that the respective variations in pain threshold and neurotransmitter release were proportional [15].

In an in vivo experiment set up to compare evoked potentials in both the presence and absence of microwaves irradiating directly the spinal cord, an electrical stimulus was applied on the peripheral nervous system of rabbits while the impulse response (evoked potential) was measured by an electrode in the cortex [23]. The spinal cord was irradiated at pulsed 4.2 GHz by a micro-antenna implanted in the spinal cord within the dorsal column. The purpose of the experiment was to distinguish between thermal and possible nonthermal effects. A statistical analysis of the recorded clearly pointed out a microwave effect. Power deposition was calculated and used in the bio-heat equation, which showed that the microwave effect resulted in an increased temperature within the spinal cord. No nonthermal effect was observed in this experiment.

## IV. Low-Level Irradiation

The effects of low-level radio frequency and microwave radiation on brain tissue and animal behavior were extensively reviewed in 1986 [24]. More specifically, the paper reviewed effects on the blood-brain barrier (protein permeability and saccharide permeability), on calcium ion exchange in brain tissue, and on animal behavior. Furthermore it offers a number of references and a comprehensive discussion which critically asseses the relevance of the experimental data derived from these studies to the health and safety of exposed people. Since then however, new results have been obtained.

For humans exposed to very low power densities (between a few $\mu$W/cm$^2$ and a few mW/cm$^2$), East European epidemiological studies [10], [25], [26] have revealed a variety of reversible asthenic problems that constitute the hypothetic **microwave syndrome** (headache, perspiration, emotional instability, irritability, tiredness, somnolence, sexual problems, loss of memory, concentration and decision difficulties, insomnia, and depressive hypocondriac tendencies). The evaluation of these very subjective complaints is difficult, particularly in the absence of a control group and well-established dosimetric data. Individuals suffering indeed from a variety of chronic diseases may exhibit the same dysfunctions of the central nervous and cardiovascular systems as those reported to be a result of exposure to microwaves. Thus it is extremely difficult, if not impossible, to rule out other factors in attempting to relate microwave exposure to clinical conditions. These problems may well be due to environmental factors unrelated to microwaves, but a possible nonthermal mechanism cannot be completely ruled out [27].

Exposure to **low-level pulsed-microwave radiation** has been reported to affect brain neuro-chemistry in a manner broadly consistent with responses to stress. The acute exposure of rats to pulsed 2.45 GHz (2 $\mu$s pulses; whole-body average SAR of 0.6 W/kg; specific absorption of 1.2 mJ/kg per pulse) was found to alter cholinergic activity in various regions of the forebrain [28]. Central cholinergic activity was increased after 20 min of exposure, but decreased after 45 min, and repeated exposure engendered compensatory changes in the concentration of cholinergic receptors [29]. Similar changes in central cholinergic responses can be induced by stressors such as noise and acute restraint, suggesting that low-level microwave irradiation may be a source of mild stress. Pretreatment with narcotic antagonists blocked the effects, suggesting the involvement of endogenous opioids as a mediating role in some of the neurological effects of microwaves, and that parameters of microwave exposure are important determinants of the outcome of the microwave effects. The similarity of the effects of microwaves and those of established sources of stress led to the speculation that microwave irradiation is a "stressor" [30].

The hypothesis that low-intensity microwave irradiation can be a source of **stress** has recently received an additional support by investigating effects of single and repeated exposure to low-intensity, pulsed microwaves on benzodiazepine receptors in three areas of the brain: cerebral cortex, hippocampus, and cerebellum [31]. The cerebral cortex and hippocampus are known to play significant roles in stress responses and, along with the cerebellum, contain high concentrations of benzodiazepine receptors. The authors studied the effects of single (45 min) and repeated (ten daily 45-min sessions) microwave exposures (2.45 GHz, 1 mW/cm$^2$, average whole-body SAR of 0.6 W/kg, pulsed at 500 pps with pulse width of 2 $\mu$s) on the concentration and affinity of benzodiazepine receptors in the cerebral cortex, hippocampus, and cerebellum of the rat.

Immediately after a single exposure, an increase in the concentration of receptors was observed in the cerebral cortex. The effect was brain-region selective as no significant effect was observed in the hippocampus or cerebellum after microwave exposure. No significant change in binding affinity of the receptors was observed in any of the brain-regions studied. In rats subjected to repeated exposures, no significant

change in receptor concentration was found in the cerebral cortex immediately after the last exposure, which may indicate an adaptation to repeated exposures. The data also show that handling and exposure procedures in the experiment did not significantly affect benzodiazepine repectors in the brain. Because benzodiazepine receptors in the brain are responsive to anxiety and stress, the data support the hypothesis that low-intensity microwave irradiation can be a source of stress. The mechanism however by which acute stress affects benzodiazepine receptors in the brain is not known.

A better understanding and evaluation of the possible physiological consequences of the effects of microwave irradiation on benzodiazepine receptors requires further research for the following reasons [31]: 1) the differential effects of microwave-irradiation parameters, such as power density, duration, and absorption pattern, need to be explored, because different patterns of effects can result from different parameters of irradiation; 2) the type and location in the brain of benzodiazepine receptors affected by microwaves need to be investigated, because different populations of central benzodiazepine receptors seem to serve anxiolytic, anticonvulsant, and sedative-hypnotic functions and 3) the effects of microwaves on other neurotransmitter systems in the brain also should be considered, because benzodiazepine receptors interact intensively with other neurotransmitters.

The research was led under the assumption that the effects of microwaves can be better understood while an animal is under the influence of a drug. It was also found that each brain region responded differently to microwave irradiation depending on exposure parameters. Effects on the frontal cortex were independent of the exposure system or the use of pulsed or CW microwaves. The hippocampus responded to pulsed but not to CW microwaves. The response of the striatal choligernic system depended on the exposure system used. Also, under the same irradiation conditions, different brain regions had different sensitivities to microwaves. Hence the areas of the brain that show changes in cholinergic activity are not correlated with localized SAR's in the brain.

An important conclusion of the investigation was that the long-term biological consequences of **repeated microwave irradiation** depend, also, on the parameters of irradiation. Further experiments showed that changes in cholinergic receptors, after repeated microwave exposure, also depended on endogenous opioids in the brain. The microwave effects could be blocked by pretreatment, before each session of daily exposure, with the narcotic antagonist naltrexone. At present, there is no convincing evidence that repeated exposure to low-level microwaves could lead to irreversible neurological effects.

From the data obtained at low-level microwave irradiation, it was concluded that endogenous **opioids** may play a mediating role in some of the neurological effects of microwaves [30], summarized as follows: 1) microwaves enhanced morphine-induced catalepsy in the rat; 2) microwaves attenuated the naloxone-induced wet-dog shake, a morphine withdrawal symptom, in morphine-dependent rats; 3) narcotic antagonist blocked a transient increase in body temperature after microwave exposure; 4) the effect of acute microwave exposure on amphetamine-induced hyperthermia; 5) microwave-induced changes in high-affinity choline uptake in the brain can be blocked by narcotic antagonists; 6) changes in concentrations of muscarinic cholinergic receptors in the brain after repeated sessions of microwave exposure can be blocked by pretreatment with narcotic antagonists before each session of microwave exposure; 7) the three major subtypes of opioid receptor, $\mu, \delta$, and $\kappa$, are involved in the effect of microwaves on hippocampal high-affinity choline uptake.

## V. Influence of Parameters of Microwave Irradiation

Parameters of the microwave irradiation are an important consideration in the production of biological effects. Different durations of acute exposure lead to different biological effects and, consequently, different long-term effects occur after repeated exposure. The waveform of the radiation is also important. This was seen in the differential effects that occur after exposure to pulsed- versus continuous-wave microwaves, and plane versus circularly polarized waves. Furthermore, the pattern of energy absorption in the body contributed to the microwave effect. These findings raise the question whether the whole-body average SAR can be used as the only determining factor in evaluating biological effects of low-level microwaves. Other features of the radiation also need to be considered [30].

The effects of **continuous-wave, sinusoidal-amplitude-modulated, and pulsed square-wave-modulated** 591-MHz microwave exposures on brain energy metabolism in male Sprague-Dawley rats (175–225 g) have been compared [32]. Brain nicotinamide adenine dinucleotide reduced form (NADH) fluorescence, adenosine triphosphate (ATP) concentration, and creatine phosphate (CP) concentration were determined as a function of modulation frequency. Brain temperatures of animals were maintained within $-0.1$ and $-0.4$°C from the preexposure temperature when subjected to as much as 20 mW/cm$^2$ (average power) CW, pulsed, or sinusoidal-amplitude-modulated 591-MHz radiation for 5 min. Sinusoidal-amplitude-modulated exposures at 16–24 Hz showed a trend toward preferential modulation frequency response in inducing increased brain NADH fluorescence. The pulse-modulated and sinusoidal-amplitude-modulated (16 Hz) microwaves were not significantly different from CW exposures in inducing increased brain NADH fluorescence and decreased ATP and CP concentrations. When the pulse-modulation frequency was decreased from 500 to 250 pulses per second the average incident power density threshold for inducing an increase in brain NADH fluorescence increased by a factor of 4, i.e., from about 0.45 to about 1.85 mW/cm$^2$. Since brain temperature did not increase, the microwave-induced increase in brain NADH and decrease in ATP and CP concentrations were not due to hyperthermia. These data suggest to the authors a direct interaction mechanism which is consistent with the hypothesis of microwave inhibition of mitochondrial electron transport chain function of ATP production.

In general, the results reported in this study have shown no substantial differences between the CW, AM, and pulsed exposures at the same average power. The apparent frequency-

dependent effect was observed in all six animals. However, no statistical significance could be obtained from the data. Since all animals showed the same trend, increasing the number of animals in the study might result in a statistically significant between the 16–24 GHz data and that for the other modulation frequencies. The increase in brain NADH fluorescence induced by 591-MHz AM microwaves was essentially the same in threshold, magnitude, and shape of curve as that observed with 591-MHz CW exposures. The NADH fluorescence response in rat brain produced by pulsed radiation varied with pulse repetition rate and duty cycle but produced qualitatively similar changes in NADH fluorescence response to those from CW and AM exposures.

Particular interest has been expressed, in recent years, in the biological effects of **pulsed-modulated RF and microwaves**. It is well established that humans can perceive pulsed-modulated radiation between 200 MHz and 6.5 GHz as a buzzing or clicking noise, depending on modulation characteristics. The effect is generally attributed to thermoelastic expansion of brain tissue, following the small but rapid increase in temperature on the absorption of the incident energy, generating a sound wave in the head which stimulates the cochlea. Some of the observed effects of pulsed radiation may relate to this phenomenon [33].

Development in **high power pulsed microwave** systems have increased their use in applications such as radar, telemetry, communications, and electronic warfare. Exposure to high-peak-power microwave pulses may cause specific behavorial responses, some of which may be related to microwave hearing [33]. Such pulses have been reported to reduce acoustic-startle responses of mice, modify the performance cognitive tasks, and evoke body movements. A startle response is a neuromuscular reflex to an intense stimulus, and exposure to a single 1 $\mu$s pulse of 1.25 GHz radiation has been shown to suppress the amplitude of these responses in rats and mice to a brief, loud noise presented 50 ms later [34]. The specific absorption was 100 mJ/kg for rats and 200 mJ/kg for mice. These values are significantly above the auditory threshold of rodents, for pulsed RF, of about 1 mJ/kg.

Furthermore, microwave **evoked body movements** are one of the biological effects associated with high peak power but low average power microwaves. Microwave evoked body movements were studied in mice [35]. A resonant cavity was used to provide head and neck exposure of the mouse to pulsed and gated CW 1.25 GHz. No difference in response to pulsed and gated CW stimuli of equal average power was found. The incidence of the microwave evoked body movement increased proportionally with specific absorption (dose) when the whole-body average specific absorption rate was at a constant level (7300 W/kg). Body movements could be evoked by a single microwave pulse. The lowest whole-body specific absorption (SA) tested was 0.18 kJ/kg, and the corresponding brain SA was 0.29 kJ/kg. Bulk heating potentials of these SA's were less than 0.1°C. For doses higher than 0.9 kJ/kg, the response incidence was also proportional to subcutaneous temperature increment and subcutaneous heating rate. The extrapolated absolute thresholds (0% incidence) were 1.21°C temperature increment and 0.24°C/s heating rate. Due to high subcutaneous heating rates, these microwaves must be perceived by the mouse as an intense thermal sensation but not a pain sensation because the temperature increment was well below the threshold for thermal pain. Results of the study could be considered in promulgation of personnel protection guideline against high peak power but low average power microwaves.

Effects of microwave fields on the **blood-brain barrier** (BBB) have been investigated by exposing male and female Fisher 344 rats in a transverse electromagnetic line chamber to 915-GHz microwaves as continuous wave and pulse-modulated with repetition rate of 8, 16, 50, and 200 per second [36]. The specific absorption rate varied between 0.016 and 5 W/kg. The rats were not anesthetized during the 2-hour exposure. All animals were sacrificed by perfusion-fixation of the brains under chloral hydrate anesthesia about 1 hour after the exposure. The brains were perfused with saline, and fixed in 4% formaldehyde. Central coronal sections of the brains were dehydrated and embedded in paraffin. Albumin and fibrinogen were demonstrated immunohistochemically.

The results show albumin leakage in 5 of 62 of the controls and in 56 of 184 of the animals exposed to 915 MHz microwaves. Continuous wave resulted in 14 positive findings of 35, which differ significantly from the controls ($P = 0.002$). With pulsed 915 MHz microwaves with repetition rates of 200, 50, 16, and 8 per second, 42 of 149 were positive, which is highly significant at the $P = 0.001$ level. This reveals that both CW and pulsed 915 MHz microwaves have the potential to open up the BBB for albumin passage. However, there is no significant difference between continuous and pulsed 915 MHz microwaves in this respect.

The question of whether the opening of the blood-brain barrier constitutes a health hazard demands further investigation. The BBB indeed protects the mammalian brain from potentially harmful compounds in the blood. It is a selectively permeable, hydrophobic barrier that is readily crossed by small, lipid-soluble molecules. It serves not only to restrict entry of toxic polar molecules into the brain but also as a regulatory system that stabilizes and optimizes the fluid environment of the brain's intracellular compartment. A dysfunctioning BBB allows influx of normally excluded hydrophilic molecules into the brain tissue. This might lead to cerebral edema, increased intracranial pressure, and, in the worst case, irreversible brain damage.

Specific results were the following:

1) Exposed animals are at risk for opening of the BBB (odds ratio $= 3.8; P = 0.0004$).
2) The response is independent of pulse repetition rate, and the response is the same for CW as compared with pulse modulation.
3) The response is independent of SAR in the interval $0.016 < \text{SAR} < 2.5$ W/kg (odds ratio $= 3.3$), but rises for SAR $> 2.5$ W/kg.

Result 2) is especially important from our point of view in this section.

It has been found that rats acutely exposed (45 min) to pulsed 2.45 GHz (2 $\mu$s pulses, 500 pps, power density 1

mW/cm$^2$, average whole body specific absorption rate 0.6 W/kg) showed a **retarded learning** while performing in the radial-arm maze to obtain food rewards [28]. Deficits in memory functions, even transient, can lead to serious detrimental consequences. A new series of experiments was carried out to better understand this behavioral effect of microwaves and, especially, the underlying neural mechanisms involved [37]. It was shown that this behavioral deficit was reversed by treatment, before exposure, with the cholinergic agonist physostigmine or the opiate antagonist naltrexone, whereas pretreatment with the peripheral opiate antagonist naloxone methiodide showed no reversal of effect. These data indicate that both cholinergic and endogenous opioid neurotransmitter systems in the brain are involved in the microwave-induced spatial memory deficit. This would imply that reversal of cholinergic activity in the hippocampus alone is sufficient to reverse the behavioral deficit.

It has been stated that the effects of absorption of electromagnetic energy on brain tissue and cell membranes depend mostly on the frequency and type of EM fields or modulation. These effects appear to be especially important at frequency and **amplitude modulation below 300 Hz**, although few results are available which illustrate a definite effect. These modulation frequencies are comparable to the EEG wave frequency spectra. Electrical coupling of both frequencies is however unlikely [38]. Whole body irradiation at 30 mW/cm$^2$ (25 W/kg SAR) of rats caused an increase in EEG activity (sum of EEG wave frequency bands) immediately at the first stage after exposure and a slight increase in delta waves (0.5–4 Hz) of the EEG recordings [39]. Simultaneously, the rheoencephalogram increased but there was no significant change in heart rate. A 10 mW/cm$^2$ exposure with 8.4 W/kg did not cause change in any frequency bands of the EEG, however. It produced a slight temperature rise in the brain. The rheoencephalogram amplitude increased after both exposure levels, as a consequence of the increase of cerebral blood flow. The ECG records and heart rate did not show any change after the radiation exposure. Brain localized exposure showed that microwave field interactions affect not only the electrical activity of brain tissue and cerebral blood flow but also blood vessels. The recorded brain tissue impedance changes of vascular pulsation is explained as an effect not only on the cerebral blood flow and the wall of blood vessels but also on the electrical conductivity of the tissue and the rheological characteristics of the blood [40].

The **nonlinear effect of modulated waves** on chicken cerebral tissue has been demonstrated. The samples were impregnated with radioactive $^{45}Ca^{++}$ and were exposed to 0.8 mW/cm$^2$ at 147 MHz, amplitude modulated by a sinusoidal signal of 0.5–35 Hz. A statistically significant increase in net $^{45}Ca^{++}$ transport was observed for modulating frequencies of 6–16 Hz, followed by a fall in the range 20–35 Hz [41]. The existence of **frequency windows** has been confirmed [42]: for an incident power flux of 1 mW/cm$^2$, there was a positive response when the modulation lay between 6 and 12 Hz and there was little response at 0.5 and 20 Hz. A **power window** was also shown to exist at constant frequency: when the chicken cerebral tissue was submitted to a 450-MHz carrier wave modulated at 16 Hz there was a significant increase in $^{45}Ca^{++}$ transport for power levels of 0.1 and 1 mW/cm$^2$, while no effect was observed for power levels of 0.05 and 5 mW/cm$^2$. The limits of frequency and power windows seem to be 6–20 Hz and 0.1–1 mW/cm$^2$, respectively [43]. The carrier frequency should be less than 1 GHz, but itself has little effect. The optimum frequency appears to lie between 150 and 450 MHz. For example, for a 450-MHz carrier modulated by a 16-Hz sine wave with an average power density of 0.5 mW/cm$^2$, the amplitude of the phenomenon reaches 38% of its value at rest in 10 minutes [10].

**Low-level effects** are thought to be due to the direct interaction between neuron membranes and the local electric field. In the vicinity of a membrane, the local field is not very different from its value in free space which gives 61 and 194 V/m for 0.1 and 1 mW/cm$^2$, respectively. This field is negligible in comparison with the figure of $2 \times 10^7$ V/m characterizing the static transmembrane potential (90 mV accross 4 nm), but is nevertheless large in comparison with slow brain waves (1 V/m) or with terrestrial ELF fields (from $10^{-3}$ to $10^{-6}$ V/m) picked up by fish, birds, and mammals and used by them for navigation, the detection of prey, and the regulation of the circadian rhythm. A model examines the possibility of induced transmembrane potential on the order of 10–100 mV [44]. Other studies [45] have shown that, because of the spike or edge effect, the interface field may locally exceed the macroscopic field by up to two orders of magnitude, which is sufficient to reduce by a factor of $10^4$ the threshold of sensivity to the electromagnetic flux. This phenomenon is confined to a very narrow ELF modulation band and is believed unlikely to cause any damage. The ANSI subcommittee in charge of the revision of the American safety standards did not judge it necessary to take this effect into account [10].

Frequency and intensity windows of $Ca^{++}$ have been observed in the presence of weak extremely low frequency electromagnetic fields below 100 Hz, similar to the ELF modulated radio frequency fields [46]. These findings suggest further interactions, resulting in specific EEG changes which are affected by modulated RF fields. Furthermore, different effects of modulated and CW microwave irradiation were found on morphology and cell surface negative charges [47]. As results from static experimental models (i.e., biochemicals models) do not give information about the **transient effects** and functional changes induced by exposure to electromagnetic fields, especially in the nervous system, an electrophysiological approach and time series analysis with multichannel signal processing and statistics are more appropriate to explain the phenomena in the central nervous system (CNS).

Such experiments [39] were performed on F1-hybrid male anesthetized rats, and addressed to the following questions: 1) Does a weak modulated field cause measurable effects on systemic and/or localized regulation mechanisms in the CNS? 2) Is there any correlation between the field activated systemic and/or localized regulatory mechanisms and the changes in CNS activity? 3) Does evaluation of measured biopotentials (i.e., quantitative polygraphy) provide more information about the effects on the CNS of modulated and CW electromagnetic

field exposure? In two series of experiments on 40 anesthetized rats 1) before and after 10 min whole-body exposures to 2.45-GHz CW microwaves, and 2) during 30 min exposure to 4-GHz amplitude modulated (AM, 16 Hz) microwaves, the effects on the CNS were observed simultaneously with those of the cardiovascular system by quantitative polygraphic measurement.

Experimental data were obtained 3, 20, and 30 min before (control, baseline data), and 1, 10, 20, and 30 min after exposure. Forty seconds of polygraph recordings were processed on each animal. Transient effects of absorbed microwave CW and modulated radiation in the brain were examined in order to clarify the involvement of physiological modalities during local and/or systemic irradiation. The local cerebral physiological modalities (EEG, REG, dc impedance and brain temperature) were recorded simultaneously with the systemic regulation modalities, ECG, respiration and rectal temperature. Slight changes in cerebral metabolism and cerebral blood were observed during microwave irradiation. These transient alterations did not exceed the range of normal physiological variations, although various compensating factors with different speeds were involved.

The total power of EEG spectra increased after whole-body 30 mW/cm$^2$ 2.45-GHz CW exposure. No changes occurred at 10 mW/cm$^2$. The cerebral blood flow (CBF) increased after 10 mW/cm$^2$. The power of EEG delta (0.5–4 Hz) was increased by brain localized 4-GHz CW exposure at 42 W/kg specific absorption rate (SAR) simultaneously with the REG amplitude as an index of CBF. Amplitude modulation at 16 Hz and 8.4 W/kg SAR was associated with increased power of EEG beta (14.5–30 Hz) waves but changes in the CBF were not observed. CW radiation at 8.4 W/kg increased the CBF, but did not change EEG spectra. Thus, the **correlations between physiological modalities** in either microwave field-activated systemic or localized regulatory mechanisms, and changes in the central nervous system do not seem to be identical. It has not been clarified whether the mechanisms of the observed changes induced by microwaves are due to energy absorption in the brain.

The necessity of quantitative evaluation of these phenomena concerning central nervous system functions is obvious.

## VI. Modeling the Nervous System and Simulation

Models and computer simulations of nervous fibers and of the nervous system have developed rather recently. A first step in computer simulation of neural reactions to electrical stimuli was introduced by McNeal in 1976, who introduced a popular spatial model consisting in a network of lumped circuit models [47]. An excellent discussion of various models is found in [48].

The **propagation of neural activity** in an axon is a consequence of the electric properties of the axonal cell membrane. A small segment of the membrane can be modeled by an electric circuit consisting of a capacitance, a voltage source, and nonlinear resistances, which represent the gating of the ionic channels. Potentials within and on the surface of a finite cylindrical volume conductor due to a single fiber along its center have been calculated by solving Laplace's equation using a relaxation model [49]. The results have enabled the variation of the single fiber surface potential (SFSP) that would be recorded from a surface electrode to be estimated for differing nerve depths and conduction velocities. The transmembrane current waveform was taken from measurements made in 1947 by Lorente de no. A conduction velocity of 60 m/s was chosen, which results in an instantaneous active length of 30 mm on the fiber and the model length was chosen as 150 mm to reduce end effects. The model radius was taken as 10 mm which corresponds to the approximate depth of the ulnar nerve at superficial sites such as the elbow and axilla. Results are that the SFSP is more elongated than the transmembrane current waveform, and that the relative amplitude of its first positive phase is considerably decreased. The waveshape changes are slight when modeling an inner concentric cylinder, radius 2.5 mm, of different conductivity from the remainder of the 10 mm radius model, despite a conductivity ratio varying between 0.1 and 1.0 to a first approximation, the SFSP waveshape is independent of fiber velocity and its amplitude is proportional to the velocity squared.

The effect of electrical stimulation with several electrode combinations on nerve fibers with different orientations in the spinal cord was investigated by computing the steady-state **field potentials and activating functions** [50]. The model comprises gray matter, white matter, cerebrospinal fluid (CSF), epidural fat, and a low conductivity layer around the epidural space. This layer represents the peripheral parts, like the vertebral bone, muscle, fat, and skin. Dura mater, pia mater, and arachnoid were not incorporated in the model, because of the estimation that these membranes have only negligible influence on the field potential distribution in the spinal cord [51].

At first an infinite homogeneous model was used, solving Laplace's equation. Secondly the spinal cord and its surroundings tissues were modeled as an inhomogeneous anisotropic volume conductor, using a variational principle by which a functional representing the power dissipation of the potential fields must be minimized to obtain the solution. Applying this method, inhomogeneities, anisotropy, and various boundary conditions can easily be incorporated and only first order derivatives are used, while in direct discretization methods of Laplace's equation second-order derivatives appear. The effect on spinal nerve fibers was approximated using the activating function which, for myelinated fibers, is the second order difference of the extracellular potentials along the fiber. The effect of mediodorsal epidural stimulation was calculated. It was concluded that with cathodal simulation, mediodorsally in the epidural space, longitudinal fibers are depolarized, while dorsoventral ones are hyperpolarized. With anodal stimulation the opposite occurs. It was found that parameters substantially affecting the potential distribution in the dorsal column are the conductivity of the white matter and the width and the conductivity of the CSF layer. The CSF has a major influence on the potential distribution on the spinal cord. Although limited to the analysis of electrode configurations and to design alternative electrodes for dc spinal cord stimulation, these

TABLE I
SUMMARY OF EXPERIMENTAL DATA

| Type of irradiation | Effects ? | Measured effect | Reference(s) |
|---|---|---|---|
| CW - 200 MHz (up to 5 min.) | Yes | brain metabolism of rats (NADH, ATP, CP) | [18] Sanders, 84 |
| CW - 591 MHz (up to 20 min.) | Yes | brain metabolism of rats (NADH, ATP, CP) | [18] Sanders, 84 |
| CW - 591 MHz (5 min.) | Yes | brain metabolism of rats (NADH, ATP, CP) | [32] Sanders, 85 |
| CW - 2,450 MHz ( up to 5 min.) | No | brain metabolism of rats (NADH, ATP, CP) | [18] Sanders, 84 |
| CW - 2,450 MHz (30 $mW/m^2$, 10 min.) | Yes | EEG spectra (rats) | [39] Thuroczy, 94 |
| CW - 2,450 MHz (10 $mW/m^2$, 10 min.) | No | EEG spectra (rats) | [39] Thuroczy, 94 |
| CW - 2,450 MHz (30 $mW/m^2$, 10 min.) | Yes | CBF (rats) | [39] Thuroczy, 94 |
| CW - 2,450 MHz (10 $mW/m^2$, 10 min.) | No | CBF (rats) | [39] Thuroczy, 94 |
| CW - 4 GHz (42 mW/kg SAR, 30 min.) | Yes | EEG delta, REG ,and CBF (rats) | [39] Thuroczy, 94 |
| CW - 4 GHz (8.4 mW/kg SAR, 30 min.) | No | EEG spectra (rats) | [39] Thuroczy, 94 |
| CW - 4 GHz (8.4 mW/kg SAR, 30 min.) | Yes | CBF (rats) | [39] Thuroczy, 94 |
| CW - 0.2 to 3.0 GHz | Yes | pain threshold and neurotransmitter release (rabbits) | [22] Teng, 91 |
| CW - 1.25 GHz high peak power but low power average | No | head and neck of a mouse | [35] Brown, 94 |
| CW - 915 MHz | Yes | BBB | [36] Salford, 94 |
| Low power densities ($mW/cm^2$ to $mW/cm^2$) | Yes | human's bodies | [10] Thuery, 92<br>[25] Presman, 70<br>[26] Marha, 71 |
| AMW - 4 GHz (amplitude modulated at 16 Hz and 8.4 mW/kg SAR, 30 min.) | Yes | EEG beta | [39] Thuroczy, 94 |
| AMW - 4 GHz (amplitude modulated at 16 Hz and 8.4 mW/kg SAR, 30 min.) | No | CBF | [39] Thuroczy, 94 |
| AMW - 591 MHz (amplitude modulated at 16 -24 Hz, 5 min.) | Yes | brain metabolism of rats (NADH, ATP, CP) | [32] Sanders, 85 |
| PW - 2,450 MHz (2 ms, 15 kW peak power) | Yes | microwave auditory system (cat) | [21] Lin, 88 |
| PW - 2,450 MHz (pulsed 500 pps with pulse width of 2 ms, average whole-body SAR of 0.6 W/kg, 1 $mW/cm^2$) | Yes | brain: cholinergic activity | [28] Lai, 89<br>[37] Lai, 94 |
| PW - 2,450 MHz (pulsed 500 pps with pulse width of 2 ms, average whole-body SAR of 0.6 W/kg, 1 $mW/cm^2$, 45 min.) | No | brain: hippocampus, cerebellum (rats) | [31] Lai, 92 |
| PW - 2,450 MHz (pulsed 500 pps with pulse width of 2 ms, average whole-body SAR of 0.6 W/kg, 1 $mW/cm^2$, 45 min.) | Yes | brain: cerebral cortex, | [31] Lai, 92 |
| PW - 2,450 MHz (pulsed 500 pps with pulse width of 2 ms, average whole-body SAR of 0.6 W/kg, 1 $mW/cm^2$ 10 daily 45-min. sessions) | No | brain: cerebral cortex, hippocampus, cerebellum (rats) | [31] Lai, 92 |
| PW - 4,2 GHz | No | evoked potentiels (rabbits) | [23] Teng, 96 |
| PW - 2,450 MHz (2 ms pulses, average whole-body SAR of 0.6 W/kg, 1.2 mJ/kg per pulse) | Yes (>20 min.)<br>No (>45 min) | brain: cerebral cholinergic activity (rats) | [29] Lai, 91 |
| PW - 1.25 GHz high power | Yes | bodies responses of rats and mice | [34] Seaman, 92 |
| PW - 1.25 GHz high peak power but low power average | Yes | head and neck of a mouse | [35] Brown, 94 |
| PMW - 591 MHz (amplitude modulated at 16 -24 Hz 500 and 250 pulses per second) | Yes | brain metabolism (NADH, ATP, CP) (rats) | [32] Sanders, 85 |
| PMW - 200 MHz to 6.5 GHz | Yes | microwave auditory system | [33] Sienkiewicz, 93 |
| PMW - 915 MHz (repetition rate of 8, 16, 50, 200 per second) | Yes | BBB (rats) | [35] Salford, 94 |
| PMW - 147 MHz (amplitude modulated by a sinusoidal signal of 6 - 16 Hz). | Yes | chicken cerebral tissue | [41] Bawin, 78 |
| PMW - ? MHz (amplitude modulated by a sinusoidal signal of 6 - 12 Hz and 20 - 35 Hz). | Yes | chicken cerebral tissue | [42] Blackman, 79 |
| PMW - 450 MHz (amplitude modulated at 16 Hz and power levels of 0.1 and 1 $mW/cm^2$) | Yes | chicken cerebral tissue | [43] Gandhi, 82 |
| PMW - 450 MHz (amplitude modulated at 16 Hz with an average power density of 0.5 mW/cm2° | Yes | chicken cerebral tissue | [10] Thuery, 92 |

CW: continuous wave; AMW: amplitude modulated wave; PW: pulsed wave; PMW: pulsed modulated wave

results are important in that they give an insight on the field potential distribution in the dorsal column.

Interest in **neural excitation by electromagnetic induction** has grown in recent years, to stimulate both the central and peripheral nervous system. Magnetic stimulation of the central nervous system is indeed a painless alternative to electrical stimulation, and is finding increasing use. The spatial distribution of induced currents from the stimulating coil has been calculated from a computer model [52]. Two configurations of a plane circular coil were considered: parallel to the tissue surface and perpendicular to the surface. The surface was assumed planar and infinite in extent. The tissue was modeled as a uniform, isotropic volume conductor. A quasistatic approximation was made in calculating the electric field. The current density was mapped as a function of position, including depth. In both configurations, it was always parallel to the surface, and maximum at the surface. There was no perpendicular (vertical) current. The stimulation of a nerve fiber requires that the component of surrounding electric field, and hence bulk current flow, is parallel to the fiber and should exceed a particular threshold value. These results suggest that nerve fibers running parallel to the skin surface are more likely to be stimulated than those running obliquely, and that it is extremely difficult to stimulate nerve fibers running perpendicularly. On the other hand, it was found that, for a given coil, the current density at a particular point in the tissue is only dependent on its distance from the coil. This current density is independent of the point's distance below the tissue surface, and of the distance of the coil from the tissue surface. In this analysis the magnetic field produced by the induced current in the tissue has been ignored, because it is much less than that produced by the primary current in the coil. The frequency components of the coil current waveform are at about 10 kHz; at this frequency the skin depth is approximately 10 m, i.e., much larger than the object.

A model of magnetic stimulation of an unmyelinated nerve fiber that predicts where and when excitation occurs has been proposed [53]. It consisted of a one-dimensional (1-D) **cable equation** that is forced by a term that is analogous to the activating function for electrical stimulation with extracellular electrodes. While neural stimulation is caused by a three-dimensional (3-D) electric field distribution, the response is generally described by a 1-D cable model. The activation function in the 1-D cable equation should represent the action of this applied electric field. These 1- and 3-D representations of nerve stimulation have been reconciled [54], and an activating function for magnetic stimulation was derived, which was consistent with both. From a 3-D volume conductor model of magnetic stimulation, the induced electric field and its resultant transmembrane potential distribution along an axon was derived analytically. This model validated several simplified assumptions on which the 1-D was based: 1) the electric field within the axon is axial, 2) the field in the membrane is radial, 3) the electric field in the membrane due to induction is negligible compared to the electric field due to charge separation, and 4) the extracellular potential is negligible, so that transmembrane potential equals intracellular potential.

Those linear models assume infinitely long fibers, i.e., a fiber whose length is large relative to the distance separating it from the electrode. In a number of usual applications, this condition does not apply and it is necessary to consider the **termination conditions of fibers** in the field of a focal electrode. An analytical model of a fiber terminal in the field of a monopolar, time-varying, spherical or point source has been presented, and the effects of the termination impedance of an axon on the membrane polarization induced by extracellular stimuli have been shown [55]. The significance of any termination current is determined by the ratio of the termination impedance and the axon's input impedance. If this ratio is large, the fiber is effectively "sealed" and the termination current is insignificant. If it is small, the fiber is "unsealed" and the membrane potential at the terminal is zero. If the ratio is of the order of 1, there is significant termination current and the fiber is in an intermediate state between "sealed" and "unsealed." For a myelinated fiber terminating with nodal membrane, this latter situation appears to apply. An important feature of end-structure stimulation is its time constant.

An analysis of magnetic stimulation of finite length neuronal structures has been performed, using computer simulations [56]. Models of finite neuronal structures in the presence of extrinsically applied electric fields indicate that excitation can be characterized by two driving functions: one due to field gradients and the other due to fields at the boundaries of neuronal structures. It was found that **boundary field driving functions** play an important role in governing excitation characteristics during magnetic stimulation. Simulations indicated that axons whose length are short compared to the spatial extent of the induced field are easier to excite than longer axons of the same diameter, and also that independent cellular dendritic processes are probably not excited during magnetic stimulation. Analysis of the temporal distribution of induced fields indicated that the temporal shape of the stimulus waveform modulates excitation thresholds and propagation of action potentials. Those results are based on simulations only, and need to be confirmed by experimental results.

As mentioned earlier in this section, an excellent **discussion of various models** appeared recently [48], discussing work by Hodgkin–Huxley, Frankenhaeuser–Huxley, Chiu–Ritchie–Rogert–Staff–Stagg, and Schwarz–Eikhof. Among others results, it showed that great differences in model behavior are obvious for strong signals. Besides the local modal data, the results depend also on fiber parameters, the influence of myelin, irregularities, branching, electrode geometry, etc., in order to determine which of the models reflects best the dynamics in special applications of functional electrical nerve stimulation.

A new model of the neuronal membrane electrical activity was presented in 1994 [57]. The main differences with respect to previous models consist both in taking into account the temperature dependence of the various parameters, and in inserting the synaptic inputs described as ionic channels. The model consists of two interconnected schemes: a circuital model, representing the ionic currents crossing the membranes, and a block model, representing the intracellular calcium concentration dynamics. It provides **a deterministic and a sto-**

**chastic analysis**. In the deterministic model the time course of the membrane voltage and the firing frequency are univocally determined once given the initial conditions. The insertion of the synaptic inputs in the model causes stochastic time fluctuations of the instantaneous membrane voltage and of the interspike interval, without inducing variations in the spike's shape. The model yields a good simulation of some known responses of the membrane in terms of its firing frequency and resistance, validated by experimental results. It can be used in a variety of applications, and may be particularly promising in the study of interaction between electromagnetic fields and neuronal membrane activity for the comprehension of the interaction mechanisms. The field-induced modifications of the membrane stochastic behavior can be simulated by suitable alterations of specific model parameters according to the type of the stimulus (frequency, waveshape, incident energy, etc.). A number of experimental results have been simulated with accuracy.

## VII. Conclusion

The variety of irradiation schemes, experiments, and models do not presently yield definite conclusions. Table I summarizes the experimental data. Type of irradiation, existence of an effect, short characterization of the effect, and main references are distinguished as separate columns. On the other hand, the type of irradiation and the measured effect are distinguished as separate lines. The irradiation parameters are separated into continuous wave, amplitude modulated wave, pulsed wave, and pulse modulated wave. As can be seen, it is very difficult to draw conclusions. The number however of experimental results has increased significantly.

A number of questions remain unanswered. There is a lack of quantitative results illustrating the significant differences, if any, between continuous wave excitation, pulsed microwaves, and very low frequency modulated waves. Systematic experiments are necessary to illustrate possible significant differences at different frequencies. Little information is available about the quantitative effects of millimeter waves either on the nervous system or on its constituents, although there might be fundamental differences between microwave excitation and millimeter wave excitation. Millimeter waves, whose wavelength is much smaller, may be of a similar order of magnitude to some constituents of the nervous system and hence cause resonance effects. The microwave syndrome, if it exists, needs clarification and experimental validation. Some experiments on animals need a more precise comparison between actual and sham irradiation. More direct experiments on the brain and/or the spinal cord should be welcome to distinguish between thermal, microthermal and possible nonthermal effects. Much care should be given to microthermal effects to avoid any erroneous conclusion about possible nonthermal effects. In a number of calculations related to the link between the nervous system and fields of mobilophony, one should go beyond the calculation of the deposited power and use the bioheat equation to calculate the actual temperature elevation. With this in view, low-level irradiation should be looked at very carefully.

From the literature, two main conclusions seem to be drawn. One is that the parameters of irradiation should be more carefully controlled. As an example, in some experiments, a comparison is made between continuous wave irradiation at some power level and pulsed wave or modulated wave irradiation at another power level. Naturally, such a change of too many parameters should be avoided. The other conclusion is that for the last years there has been, and still is, an impressive amount of active research involving setting up experiments, building up theory, and establishing models. Such ongoing activity is extremely encouraging.

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