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Review Article

Biological responses of mobile phone frequency exposure

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Existence of low level electromagnetic fields in the environment has been known since antiquity and their biological implications are noted for several decades. As such dosimetry of such field parameters and their emissions from various sources of mass utilization has been a subject of constant concern. Recent advancement in mobile communications has also drawn attention to their biological effects. Hand held children and adults alike generally use mobile sources as cordless phones in various positions with respect to the body. Further, an increasing number of mobile communication base stations have led to wide ranging concern about possible health effects of radiofrequency emissions. There are two distinct possibilities by which health could be affected as a result of radio frequency field exposure. These are thermal effects caused by holding mobile phones close to the body and extended conversations over a long period of time. Secondly, there could be possibly non thermal effects from both phones and base stations whereby the affects could also be cumulative. Some people may be adversely affected by the environmental impact of mobile phone base stations situated near their homes, schools or any other place. In addition to mobile phones, appliances like microwave oven etc are also in increasing use. Apart from the controversy over the possible health effects due to the non-thermal effect of electromagnetic fields the electromagnetic interaction of portable radio waves with human head needs to be quantitatively evaluated. Relating to this is the criteria of safe exposure to the population at large. While a lot of efforts have gone into resolving the issue, a clear picture has yet to emerge. Recent advances and the problems relating to the safety criteria are discussed.

Keywords : Electromagnetic fields, Health effects, Mobile phone

Introduction

A large number of individuals (>10^9 world wide) are exposed to the radiofrequency (RF) signals from cellular phones and other personal communication services and the number is increasing exponentially. Because the mobile phones and other wireless gadgets are held close to the body and are used frequently, these devices are potentially the most dangerous sources of electromagnetic radiation that the average person possesses. Therefore, mobile phone appears to be one of the major biological exposure[1]. This has given rise to an increasing concern for any unknown effects that may be potentially detrimental to the human health. Antennas of modern mobile telephones are located close to the head and the radiations from base stations are distributed all over in areas around it. Mobile telephones emit radiations that are intercepted in the proximity of the brain and cranial nerves. There is now an added worry if these radiations are carcinogenic or tumor promoter or have any other health implications. Keeping these in view, special attention has been drawn to the biological effects of electromagnetic fields (EMF's) in general, particularly on human nervous and reproductive system. This is largely because the positioning of the cellular phone may have proximity to one of these organs at a given instance. Reports confirming biological hazards and otherwise have been appearing and the issue appears to be far from resolved. This is largely because of different protocols, the type of input signals and the orientation and distance between electronic devise and the uncertainty involved with the subject. Cellular phones (CPs) operate at 800-900 MHz (Fig. 1). These may be classified as analog (advanced mobile phone system, AMPS). On the other hand, digital cellular phones operate under various standards such as GSM (global system for mobile communication) and digital AMPS (DAMPS). All the systems developed for cellular phones transmit encoded, digitized information using some form of phase or frequency modulation[2]. Two low frequency waves of GSM, at 8.3 and at 217 Hz, act on the composite pulsed GSM signal, in which these frequencies are present. This signal carries no power when the user is not talking or receiving but when the user communicates the power of this electromagnetic

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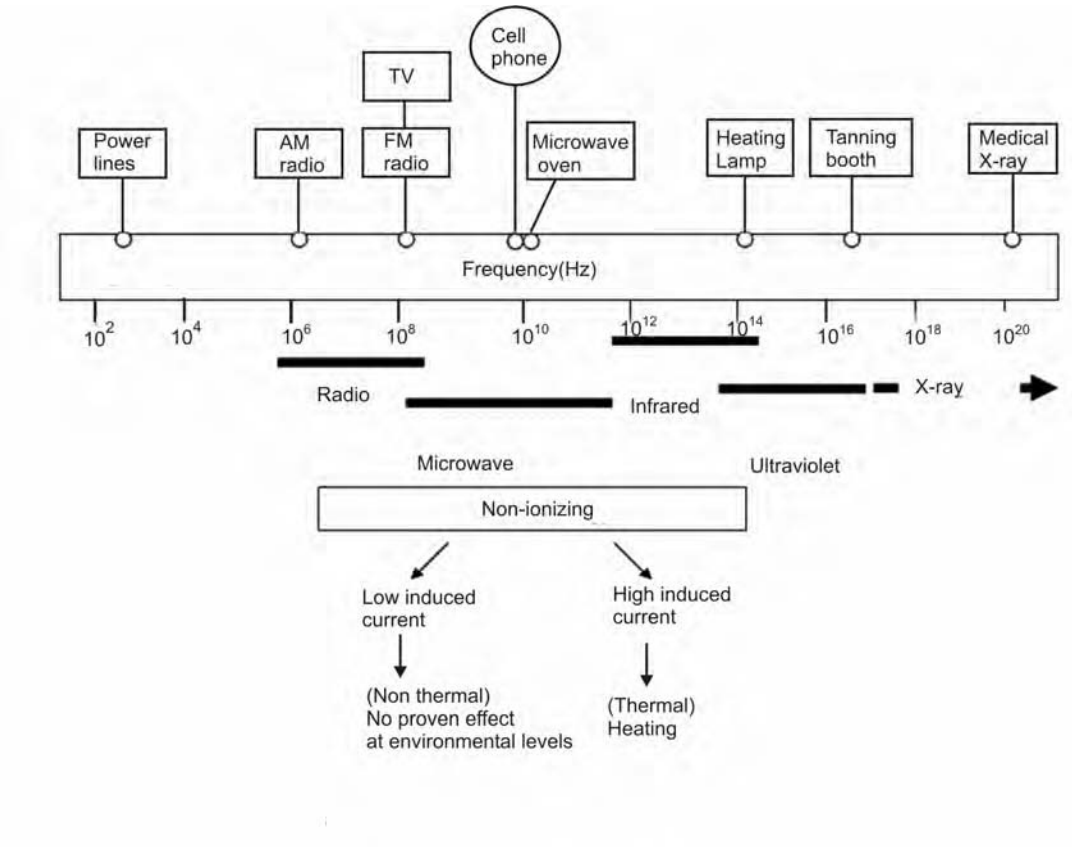

Fig. 1—In terms of the electromagnetic spectrum, cell phones fall between microwave ovens and TV transmitters. Such radiation, though non-ionizing, can induce biologically significant effects

field reaches a maximum of 250 mW[3]. The specific absorption rate of mobile phone varies in the range (0.1-2 W/kg) depending upon the manufacturing details, but the field emission is below the safety level.

The development of wireless (mobile) telephony has resulted in the transmission and propagation in the atmosphere of microwaves modulated by very specific signals. Radio waves transmitted by mobile phones of the GSM type present a characteristic pattern that results from the particular time structure of such a signal (time division multiple access, TDMA). It is an electromagnetic field (ELF) modulated pulsed microwave carrier. This is not the case for analog radio and television. One may say that digital cellular phones using the GSM system transmit information in bursts of microwaves. The presence of ELF components in the signal and the bursting activity of these waves have raised a new controversial question: can this signal structure exert a negative influence on human head tissues and more specifically on the brain by inducing nonthermal effects? This stems from the fact that modulated or pulsed radio frequency radiations are more effective in producing biological effects. They may produce a different effect when compared with continuous wave radiation of the same or different frequency. Modulated signal carries multiplicity of messages. This finding is important, because mobile telephonic radiation is modulated at low frequencies. Biological effects of low frequency (<100 Hz) electric and magnetic fields are well established. Therefore, frequency, intensity, exposure duration and the number of exposure episodes can affect the exposure to radio frequency radiations.

Wireless communication systems operate at several frequencies in the electromagnetic spectrum. In United States it operates at two frequencies: the old existing ones at 850 MHz and the newer personal communication services at 1900 MHz (Fig. 1). European mobile phones operate at slightly different frequencies than these. Since mobile phones are used close to the head, the emitted radiations are absorbed by the brain[4]. Microwaves in the frequency range (800-1000 MHz) can penetrate the cranium and nearly 40% of these can reach the deep brain[5-7]. Some

studies have already suggested that mobile phones affect brain functioning and behaviour[8-13]. The energy corresponding to these frequencies is insufficient to knock an electron from atoms in a living tissue and belong to the non ionizing part of the electromagnetic spectrum. A commonly occurring partial body exposure of humans to microwave radiation occurs with the use of cellular phones. Because the phone antenna is close to the head, much effort has gone into determining the dosimetry profile of microwaves in the head in various possible configurations (Fig. 2). The geometry of holding the mobile phones suggest that the exposure will be principally to the side of the head for the hand held use, or to the other parts of the body closest to the phone during hand free use. Frey[14] opined that the headache was linked to microwave emissions from cellular phones. The body of research is controversial in several respects since the experimental results as of now are, mostly understood in terms of thermal effects. The effects due to non-thermal effects are controversial and in a way not well understood. The accepted existence of non thermal phenomena in biological systems is difficult to explain within the framework of known laws of physics. This may be beyond limits set by chemical reactions in biomolecular systems.

In the mobile communication frequency range, all presently available exposure standards are based on the assumption that the incident radiations (non ionizing radiations) cause an increase in temperature (thermal effects). At the frequency range 40 MHz-6 GHz, the electromagnetic field penetrates deep into the tissue, causing an increase in the random molecular motion. This is suggestive that while defining the exposure time and the volume of the tissue over which the temperature rise is measured needs to be defined. The tissue shape is often taken as cubic, largely for geometric and numerical

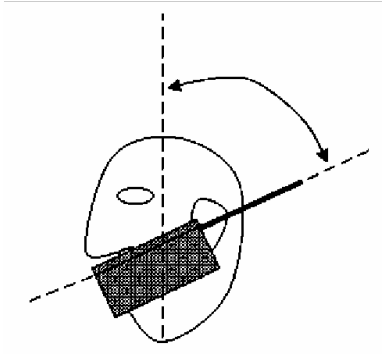

Fig. 2—A schematic diagramme of head model for calculations of induced field due to mobile phone expousre

convenience. Some people may also be adversely affected by the environmental impact of mobile phone base stations located near their homes, schools or any other place.

Partial or whole body exposure of human and animals to RF radiation as due to mobile phone use may lead to a variety of changes in tissues. Communication between brain cells is mediated by a spectrum of chemical substances that both excite and inhibit transaction and transmission of information between them. These substances act by binding to their specific receptors on cell surfaces. Changes in the different tissues may occur depending on the exposure conditions, species, and histological parameters. Penafiel *et al.*[2] have shown that the radiation from TDMA digital cellular phones can cause significant changes in ornithine decarboxylase activity (ODC), which is essential for DNA synthesis. Kolomytkin *et al.*[15] studied specific receptor binding of three neurotransmitters: gamma-aminobutyric acid (GABA), an inhibitory transmitter and acetyl choline and glutamate, both excitatory to rat brain synaptosomes. Microwave exposures used 880 or 915 MHz fields at power densities from 10 to 1500μW/cm^2. With incident field intensities of 1.5mW/cm^2, binding to GABA receptors decreased 30% at 16 pps, but differences were not significant at 3, 5, 7 or 30 pps. Conversely, 16 pps modulation induced a significant increase in glutamate receptor binding. For acetyl choline receptors, binding decreased 25% at 16pps, with similar trends at higher and lower frequencies. As a function of field intensity, sensitivities of GABA and glutamate receptors persisted for field densities as low as 50μW/cm^2 at 16 pps with 915 MHz fields.

Results of Zhao *et al.*[16] suggest that specific CNS cells may activate different genes in response to cell phone emissions, and there is variable threshold sensitivity depending on cell type. The variations in culture conditions that could contribute to the observed differences were minimized since both cells were grown in an attached manner, in the same size culture dish, and in the same volume of medium. Still, some technical differences are impossible to avoid and might create disparities in the amount of total radiation received by the two cell types. For example, the culture media for astrocytes and neurons is slightly different. Astrocytes which are highly proliferative were also plated at a lower density compared to neurons to allow for expansion of the

cell population between plating and radiofrequency/microwave (RF/MW) radiation exposure. Inherent differences in cell size and shape, composition of cell membranes, organelle distribution, junctional coupling between adjacent cells, stages of the cell cycle, and other parameters that cannot be controlled will also contribute to different amounts of energy absorption by the cells.

Definition of the problem

Using a mobile phone generate magnetic pulses that peak at several tens of micro tesla, while biological effects are reported around 0.2μT[17,18]. In the process of electromagnetic (EM) propagation, radiation falls on the population. Energy intercepted by the human body (or any other biological object) and subsequently absorbed is dependent upon several parameters viz, part body/full body exposure, l/λ (length of the body, wavelength of incident radiation), resonant absorption, deviation and signal type (pulsating sine, triangular etc), polarization of the radiation, coupling of the energy to the body and if the body is grounded or not. In the phones used the field emissions may extend over a wide range, which may have different mode of interaction. Also at any instance of time differentiation between thermal and nonthermal effect or their combination is difficult to distinguish[16]. Obviously these parameters are uncontrollable and hence the amount of energy deposited rather uncertain, which makes the estimation of effects and safe exposure criteria open for question.

When EM fields pass from one medium to another, they can be reflected, refracted, transmitted or absorbed, depending on the complex conductivity of the exposed body and the frequency of the source. Absorbed RF energy can be converted to other form of energy and cause interference with the functioning of the living system. Most of this energy is converted into heat (absorption). However, not all EM field effects can be explained in terms of energy absorption and conversion by this process. At frequencies well below 100 kHz, it has been shown that induced electric fields can stimulate nervous tissue and at the microscopic level, other interactions have been observed.

Role of ELF components—Low frequency component has been a source of signal transmission in the biological media. While estimating the biological implications, it is therefore imperative that their role may be assessed.

An *in vitro* experimental investigation was conducted to verify if pure magnetic fields at 8.3 and 217 Hz could induce any effect on the spontaneous bioelectric activity of the neurons from the brain ganglia of the snail Helix aspersa[19]. Changes have been observed, as well as the reversibility of the effects induced under exposure to magnetic fields of low magnetic flux densities in the ranges of 0.37-6.68 and 0.6-3.6 mT for 8.3 and 217 Hz, respectively. The first results indicated that, in most cases, the neurons reacted to the lowest values of applied magnetic flux density, that is, 50 μT, and that some neurons would probably react to a lower exposure level[20]. A second series of results shows the ability of the neurons to recover their spontaneous activity, after it has been modified under exposure to 8.3 and 217 Hz sinusoidal applied magnetic flux density values between 0.6 and 6.68 mT. These results show the reversibility of the bioelectric induced alterations on neurons under the specified experimental conditions[19]. These investigations are important in view of obtaining practical conclusions about sensitivity threshold and reversibility for actual mobile phone ELF magnetic field exposure.

Dosimetry—At frequencies below 100 KHz, many biological effects are quantified in terms of the current density in tissue and this parameter is most often used as a dosimetric quantity. At higher frequencies, many (but not all) interactions are due to the rate of energy deposition per unit mass. This is why the specific absorption rate (SAR) is used as the dosimetric measure. It is expressed in watts per kilogram (W/kg) and is based on absorption only. This raises questions about using this parameter for evaluating effects that may be of another nature than absorption. In this connection, the possibility of having only the SAR for evaluating all the biological effects does not seem to be suggestive.

Specific absorption rate (SAR)—The time derivative (rate of the incremental energy (dW) absorbed by (dissipated in) an incremental mass (dm) contained in a volume element (dV) of a given density (ρ).

$$\text{SAR} = \frac{d}{dt}\left(\frac{dw}{dm}\right) = \frac{d}{dt}\left(\frac{(dw)}{\rho dv}\right)$$

It also refers to a volume-SAR, expressed in units of mW/cm^3, where mass density has been set to unity.

(i) SAR can be related to the E-field at a point by the relationship:

$$SAR = \frac{\sigma|E|^2}{\rho}$$

where σ = conductivity of the tissue (S/m)

ρ = mass density of the tissue (kg/m^3)

E = rms electric field strength (V/m)

(ii)- SAR can also be related to the increase in temperature at a point by

$$SAR = \frac{c\Delta T}{\Delta t}\Big|_{t=0}$$

where ΔT = change in temperature (^{o}C)

Δt = duration of exposure (s)

c = specific heat capacity (J/kg ^{o}C)

This assumes that measurements are made where no heat loss occurs by thermal diffusion, heat radiation, or thermoregulation (blood flow, sweating, etc.) With this formal definition, it is now customary to measure SAR due to mobile phone emissions and estimate its value inside the brain, using complex computation formalism.

It is said that Poynting's theorem expresses equality between the space variation of EM power and the time variation of EM energy. However, temperature is not an EM parameter: it is a consequence of energy absorption at RFs and MW frequencies. The SAR is proportional to absorption losses and there is a temperature elevation when the SAR is positive. Using EM theory, only thermal effects can be evaluated and this in principle, possibility of nonthermal effects cannot be investigated.

In the model of the mobile phone (Fig. 2), the calculated peak local SAR over 10 g is lower than the limit of 2 W/kg given by the ICNIRP. The power absorption budget by tissues indicates that more than half of the power is absorbed by the skin (absorption at 1800 MHz is more superficial than at 900 MHz). As the brain is nearer to the mobile phone in the case of the CS head, one finds that the power absorption in the brain of the CS is slightly more significant than that for the adult, while it remains at a weak level of exposure (from one third to one-half maximum) of the SAR on 10 g in the head.

Whole body exposure and mobile phone radiation

Even though the power deposited in the head is lower than that prescribed by safety considerations[21], there are reports pouring that biological effects (at times called hazards) are invariably there. This suggests that effects have nonthermal origin. These effects are caused by low intensity or ultra low intensity fields.

Based on modeling it has been estimated that SAR to head from a 900 MHz cellular telephone vary from 0.16 to 0.69W/kg and for the brain 0.06-0.41 W/kg[22]. However a similar examination by Dimbylow and Mann[23] with a vertical or a lateral antenna suggests a 3-4 W/kg averaged over 1 g. Excell[24] calculation suggested higher values upto 4.2 W/kg rising to 8.2 W/kg at 1800 MHz based on magnetic resonance imaging (MRI) and FDTD techniques. A level of 1 W/kg is expected to raise the temperature by < 0.5^{o}C.

Correspondingly non thermal effects have also been reported ranging from changes in permeability of the blood brain barrier and ocular symptoms[25,26]. Calculation of the maximum temperature rise in the head from RF exposure during mobile phone use suggest that increase of no more than about 0.1^{o}C would be expected[27]. Thus if there are health effects from RF exposure, they are unlikely to be due to any temperature rise. It is thus imperative that the non thermal effect phenomena need to be investigated. As a further indication to this DNA strand break and generation of micronuclei has been a clear indication of genotoxic effects[28-31]. Nittby *et al.*[32] reported cognitive alterations in GSM exposed animals as compared to sham exposed ones.

Research pertinent to the use of mobile phones by Sarkar *et al.*[33] and Lai and Singh[34,35] showed an increase in DNA breaks at 2.45 and 50 GHz[36]. Paulraj and Behari[31] have also obtained similar results at amplitude modulated RF signal (112 MHz – AM 16 Hz). However these findings are not supported by several other workers[37,38]. Stronati *et al.*[39] showed that 24 h of exposure to 935 MHz basic signal at 1 or 2 W/kg did not cause DNA strand breaks in human blood cells. Long term exposure of the mouse[40] showed an elevated risk of developing lymphoma in a transgenic strain. Use of phone in driving stimulator leads to negative reaction time. Evidence for a direct memory effect on brain slices from the hippocampus of rat that showed changes in long term potentiation when exposed to 915 MHz[41]. Mild *et al.*[42] looking for a subjective response, suggested increased headache or sensation of warmth when using mobile phones. Braune *et al.*[43] reported blood pressure increase (5-10 mm Hg) induced by exposure to the right side of the head. However Barker *et al.*[44] in a double blind

study reported no effect of GSM and TETRA signals on blood pressure and related physiological parameters. These authors also did not reported any significant differences between the mean concentration of adrenaline and nor adrenaline concentrations. Roschke and Mann[45] did not notice any difference in the awake electroencephalograms (EEG) of subjects exposed to radiation emitted by cellular phones.

Biological implications

The biological implications arose with the use of cell phones have been demonstrated to cause dose dependent difficulty in concentration, fatigue and headache[46] and increase in reaction time[47]. The emitted microwaves from communication devises are shown to alter cognitive functions[32,48], decrease in cholinergic activity[49], gene expression alteration in cerebellum[50], cortex and hippocampus[51]. It can be logically concluded that cells with higher metabolic rate will be more susceptible to EMF. This is because more hydrogen peroxide is generated by mitochondria to excite the reaction. The proximity of EMF to interact with iron provides a clue for more vulnerability of cell have higher content of intracellular free ions.

Blood brain barrier (BBB)—In the normal brain, the passage of compounds over the BBB is highly restricted and homeostatis within the sensitive environment of the brain parenchyma can be maintained. The BBB is formed by the vascular endothelial cells of the capillaries of the brain and the glial cells wrapped around them. The tight junctions, that seal the endothelial cells together, limit paracellular leakage of molecules. A bi-layered basal membrane supports the ablumenal side of the endothelial cells. The glial astrocytes, surrounding the surface of the basal membrane cells, are important for the maintenance, functional regulation and repair of the BBB. The protusions of the astrocytes, called end feet, cover the basal membrane on the outer endothelial surface and thus form a second barrier to hydrophilic molecules and connect the endothelium to the neurons. About 25% ablumenal membrane of the capillary surface is covered by pericytes[52], which are a type of macrophages. Seemingly, they are in the position to significantly contribute to the central nervous system (CNS) immune mechanisms[53]. Also, perivascular structures such as astrocytes and pericytes as well as a bi-layered basal membrane help maintaining the BBB[54].

In a functioning BBB, the membrane properties control the bidirectional exchange between the general circulation and the CNS. Water, most lipid soluble molecules, oxygen and carbon dioxide can diffuse from the blood to the nerve cells. The barrier is highly permeable to ions such as sodium, potassium and chloride, but large molecules, such as proteins and most water soluble, chemicals have only a poor passage. However when the barrier is damaged, in conditions such as tumors, infarcts or infections, also the normally excluded molecules can pass through, possibly bringing toxic molecules out into the brain tissue. The selective permeability is also disrupted temporally in cases of epileptic seizures[55,56].

BBB has been a favorable subject of investigation due to electromagnetic field exposure[57], for even a slight variation in its permeability can lead to tissue damage[58]. Non thermal effects are identified by the leakage of albumin through the BBB[54,59]. Two hours of exposure to the radiation from a global system for mobile communications (GSM) phone at 915 MHz, at non thermal SAR values of 12mW/kg and 120mW/kg, gives rise to focal albumin extravasation and albumin uptake into neurons after 14 days exposure[60]. Significant neuronal damage is present in 28 days[60] and 50 days after exposure[61], and not after 14 days[57]. Some other investigators[62] have supported these findings.

Shivers *et al.*[63] observed that the EMF exposure of the type emitted during a MRI procedure resulted in a temporarily increased BBB permeability in the brain of rats. Through transendothelial channels, a vesicle-mediated transport of horseradish peroxidase (HRP) took place, which was replicated by Garber *et al*[64]. The work of Shivers *et al.*[63] later got quantitative support for the findings[65,66]. In rats exposed to the MRI, the BBB permeability to diethylenetriameninepentaacetic acid (DTPA) is increased. It is suggested that the increased permeability may be a stimulation of endocytosis, made possible through the time-varying magnetic fields. These findings support the observations[67] that BBB permeability to albumin was increased after exposure to MRI radiations. The most significant effect was observed after exposure to the RF part of the MRI.

Nittby *et al.*[68] reported increased permeability after mobile phone exposures which has been confirmed by others[69]. Four hours of GSM-900 MHz exposure at brain power densities ranging from 0.3 to 7.5 W/kg

resulted in significantly increased albumin extravasation both at the SAR-value of 7.5 W/kg, which is a thermal effect, but also at 0.3 and 1.3 W/kg[69]. Albumin extravasation was also seen in rats exposed for 2h to GSM-900 MHz at non thermal SAR values of 0.12, 0.5 and 2 W/kg using flourescein-labelled proteins[70]. At SAR of 2 W/kg a marked BBB permealization was observed, but also at lower SAR value of 0.5 W/kg,. However, the extravasation at 0.5 W/kg was seen at a lesser extent as compared to that seen at 2 W/kg. These authors[69,70] also concluded that an already disrupted BBB is more sensitive to the RF fields than an intact BBB.

In another study[62], increased BBB activity was seen at exposure levels of 2 W/kg and duration of 30-120 min. When the rats were pretreated with colchicines, the EMF induced rhodamine-ferritin uptake was however blocked. Colchicine is well known for its inhibition of microtublar function, which seems to play an important role for the BBB opening.

However, in other experiment no albumin extravasation was seen, neither after 2 nor 4 weeks of 1h of daily exposure (average whole body exposure at 0.25 W/kg)[71]. Kuribayashi *et al.*[72] concluded no BBB alterations after 90 min of daily EMF exposure for 1-2 weeks at SAR values of 2 or 6 W/kg. Finnie *et al.*[73] exposed mice for 1h/day at the SAR level of 4 W/kg, which is above the safe criteria for exposure. In another study Finnie *et al.*[74] exposed mice for 104 weeks at SAR values of 0.25-4 W/kg, with no alteration in BBB permeability.

It has been suggested that BBB leakage is the major reason for nerve cell injury, such as dark neurons in stroke prone spontaneously hypertensive rats[75]. Albumin leaks into the brain and neuronal degeneration is observed in areas with BBB disruption in several circumstances: after intracartoid infusion of hyperosmolar solutions in rats[76]; in the stroke prone hypertensive rat[77]; in acute hypertension by aortic compression in rats[78]. The linkage between album extravasation over the BBB and neural damage may be a potentiating effect of albumin upon the glutamate mediated neurotoxicity[79]. Indeed, both albumin and glumate induced lesions have the same histopathological appearance with invasion of macrophages and absence of neuronal cell bodies and axons in the lesion areas[77]. The glumate itself can also increase the BBB opening[80], leading to further albumin extravasation 14 days after exposure[60] and dark neurons not until after 28 days and 50 days[60,61]. It is hypothesized that albumin extravasation into the brain parenchyma, is the first observable effect of the mobile phone exposure. The albumin leakage precedes and possibly could be the cause of, the damage to the neurons seen as the dark neurons later on. In this connection it is suggested[78] that transient openings of the BBB can result in permanent tissue damage. It is apparent that cellular damage is more in the EMF exposed animals.

Developmental effects—Young laying hens, when continuously exposed to 915 MHz (CW) were exposed to incident power of 800 mW, during the first 2.5 weeks zero mW during the following week and 200mW for the rest of the experiment, the hatching was reduced by 8%. No macroscopic malformations were observed in the chick or dead embryos[81]. These authors did not mention the SAR value and the power density. Jensh *et al.*[82] irradiated pregnant Wistar albino rats at a power density level of 10 mW/cm2, at a frequency of 915 MHz (average SAR 3.57 W/kg). The animals were exposed for 6 h/day from day 1 to day 21 of gestation. No significant teratogenic signs were observed regarding the resorption rate, malformation rate, mean litter size, fetal weight and number of live and dead fetuses. The experiment was extended to include embryonic and postnatal development of offspring[83]. The authors reported no significant morphologic changes.

In another study Berman *et al.*[84] exposed (970 MHz, 22 h/day) pregnant rats (1st to 19th day). The SAR varied from 0.07, 2.4 and 4.8 W/kg. The embryo mortality, fetal weight, skeletal ossification, as well as maternal fertility were evaluated. The exposure due to (4.8 W/kg) of these caused reduced (~ 12%) fetal body weight versus the control. All the other examined parameters were not significantly different. Klug *et al.*[85] exposed rat embryos (9.5 days old) for up to 36 hr to 900 MHz. The modulation frequency was fixed at 215 Hz and the SAR values were calculated as 0.2, 1 and 5 W/kg. The end points of the experiments were crown-rump length, number of somites as well as embryonic malformations. No significant changes were observed on the growth and differentiation parameters of the embryos[86].

Reproduction pattern—Effects of radiofrequency effects on prenatal development in mice have been a favorable subject of investigation, and results have been conflicting. A study consisted of *in vivo*

experiments at several places around an "antenna park" where the frequency emission ranged from 88.5 to 950 MHz. At these locations RF power densities between 168 and 1053 nW/cm^2 were measured. These authors observed a progressive decrease in the number of new born per dam, which resulted in irreversible infertility. The prenatal development of the new born, however evaluated by the crown-rump length, the body weight, and the number of lumbar, sacral, and coccygeal vertebrae, was improved. Wistar albino rats were exposed through pregnancy (6 h/day) to 915 MHz radiation at a power density level of 10mW/cm^{2}.[87]. Teratologic evaluation included the following parameters: mean litter size, maternal organ weight and organ weight/body weight ratios of various organs (brain, liver, kidneys, and ovaries), number of resorptions and absorption rate, number of abnormalities and abnormality rate and mean term fetal weight. Mothers were rebred, and the second, unexposed litters were evaluated for teratogenic effects. Animals exposed to 915 MHz did not exhibit any constant significant alterations in any of the above parameters.

Waist pockets are the sites usually adopted by people to keep their mobile phones. Dasdag *et al.*[88] experimenting on Wistar albino rats exposed animals to mobile phone for 2 h/day for 1 month in standby position, where the SAR was 0.141 W/kg. The decrease of epididymal sperm counts in the exposed group was not found to be significant. Histological changes were observed in the testes. Seminiferious tubular diameter of rat testes in experimental group was lower than those of controls. Rectal temperature of rats in the experimental group was found to be higher than in the sham exposed group. However the same group of workers could not replicate the same results in Sprague-Dawley rats, exposed to 890-915 MHz pulsed wave (PW) daily for 20 min/day for one month (250mW radiated power, SAR=0.52 W/kg).

Aitken *et al.*[89] assessed the testis of mice irradiated with 900 MHz in a wave guide, for 7 days (12 h/day, SAR=90mw/kg) and reported no abnormalities in sperm count, morphology and vitality. However, they reported significant damage to the mitochondrial genome as well as to the nuclear globin locus. Ozguner *et al.*[90] have not reported any adverse affect on rats due to 900 MHz CW microwave exposure (1±0.4 mW/cm^2). The parameters they considered were weight of testis, testicular biopsy score count and the percentage of interstitial tissue. However the exposed group showed a decrease in height of germinal epithelium.

Forgacs *et al.*[91] repeatedly exposed male mice to 1800MHz GSM like microwave radiation at 0.018-0.023 W/kg whole body SAR. A two week exposure (2 h/day) was resulted no morphological alterations in testis, epididymus and prostate. In another study Ribeiro *et al.*[92] exposed male rats to RF emitted from a conventional cell phone on their testicular function (1835-1850 MHz, 0.04-1.4 mW/cm^2). These authors have reported that total body weight and absolute and relative testicular and epididymal weights did not change significantly, and so the epididymal sperm count. Yan *et al.*[93] exposed (800 MHz digital and 800 MHz analog) cell phones to rats for a period of 3h-30 min rest-3 h) for 18 weeks, for SAR of 0.9 to 1.8 W/kg. The authors analyzed the morphology of the sperm cells from epididymis of rats and found no significant difference in the deformities among the experimental and control group of animals. Yilmaz *et al.*[94] reported that rats exposed to 900 MHz radiation (SAR 0.87 W/kg) 20 min/day for a period of one month did not alter the anti-apoptotic protein in the testes of rats. Also Dasdag *et al.*[95] reported that 2hr/day (7 days a week) exposure to rats for a period of 10 months did not affect the active caspase-3 level in testes of rats.

Oral *et al.*[96] exposed 16 weeks female rats to 900 MHz radiation (30 min/day for 30 days). The animals were exposed at 1±04 mW/cm^2 (SAR 0.016-4 W/kg) and experimental group fed vitamin C and E. They found endometrium apoptosis in exposed group. Guney *et al.*[97] repeating the same set of experiments (with the inclusion of control group) reported histological changes in endometrium, diffuse and severe apoptosis in the endometrial surface, epithelial and glandular cells in the group exposed to EMF. Also, eosinophilic leucocytes and lymphocyte infiltration were seen in the endometrial stroma.

Wistar rats were continuously exposed[98] during pregnancy to a low level of 0.1mw/cm2 (900 MHz, 217 Hz pulse modulated EMF). Whole body average SAR values for the freely roaming, pregnant animals were measured in models; they ranged between 17.5 and 75 mW/kg. No differences between exposed and sham exposed dams or offspring were recorded in terms of litter size, evolution of body mass and developmental landmarks of litter mates.

Dasdag *et al.*[99] examined the effect of microwaves emitted by cellular phones on males and females (915 MHz, SAR 0.155 W/kg). These authors observed no difference in the rectal temperature between the experimental and control group. The birth weight of offspring in the experimental group was significantly lower than in the sham exposed group. However in the next generation of rats the parameters under investigation showed no difference. Cobb *et al.*[100] exposed pregnant rats to ultra wide band (UVB) 0.1-1 GHz radiation. In order to determine if teratological changes occur in rat pups as a result of (i) daily UWB exposures during gestation days 3±1.8, or (ii) as a result of both prenatal and postnatal (10 days) exposures, dams were exposed either to (a) UWB irradiation with average whole body specific absorption rate 45 mW/kg (b) sham irradiation or (c) a positive control. Offsprings were examined regarding litter size, sex ratios, weights, coat appearance, and tooth eruption. The pups postnatally exposed were examined for hippocampal morphology. Generally, no significant differences were found between the exposed and sham group. The medial to lateral length of the hippocampus was significantly longer in the UWB-exposed pups than in the sham exposed animals but could not be correlated with neurological dysfunction. The male offspring exposed *in utero* to UWB mated significantly less frequently than sham exposed males, but when they did mate there was no difference in fertilization and offspring numbers from the sham group.

Chicken embryos were exposed to EMF from GSM mobile phone during the embryonic development. The embryo mortality rate in the incubation period increased to 75% versus 16% in control group[101].

Ingole and Ghosh[102] studied the developmental effects on the avian kidney of radiation, from a cell phone handset (900 MHz frequency, power of 2W and SAR of 0.37 W/kg). The authors reported morphological alterations on the epithelium of the renal tubules as well as the renal corpuscles and chicken embryos.

Kumlin *et al.*[12] examined the effect of 900 MHz for 2h/day (5 day/week) on the development of the nervous system of Wistar rats. After five weeks of exposure no degenerative morphological changes were found.

Batellier *et al.*[103] exposed fertilized chicken eggs to a mobile phone over the entire period of incubation. The cell phone in call position was placed at a distance of <25 cm from the eggs, where in the sham position the cell phone in the off position was kept at a distance of 1.5 m away from the exposed group. A significantly higher percentage of embryo mortality was observed in the experimental group compared to the sham.

Agarwal *et al.*[104] in an epidemiological study has concluded that the use of mobile phone adversely affected the quality of semen by decreasing the sperm count, motility, viability and morphology. These parameters were found to be lower in mobile user group. In another study conducted on 37 men, the duration of possession and daily transmission time of cell phones correlated negatively with the proportion of rapidly progressive mobile spermatozoa, suggesting that the prolonged use of cell phone have negative result on sperm motility[105]. Davoudi *et al.*[106] involving 13 men with normal semen analysis, also concluded that using GSM phones for 6 h a day for 5 days decreased the rapid progressive motility of spermatozoa. Similarly, Erogul *et al.*[107] found a decrease in sperm motility in semen samples of 27 men exposed to 900 MHz cell phone for 5 min. Kilgallon and Simmons[108] found a decrease in sperm concentration in subjects using mobile phone. Inspite of consistency in these data, the variability in the life style and possible impact of emitted radiation from other sources are the major instance of uncertainty.

Brain function—Exposure of brain to mobile phone is maximum, hence the possibility of EMF induced genetic damage in brain cells is of particular importance. These cells have high level of iron. Nerve cells have low capacity of DNA repair and hence such damages could accumulate. The presence of magnetic particles could enhance free radical activity in cell. Thus the effect of EMF on DNA is more significant on nerve cells than on other type of cells in the body. Since nerve cells do not repair, they may undergo apoptosis or accelerate the process of neuro degeneration. Double strand breaks if not properly repaired, are known to lead to cell death[109]. However another type of brain cells (glial cells), can become cancerous as a result of DNA damage.

Preece *et al.*[47] studied the effect of a 915 MHz simulated mobile phone signal on cognitive function in man. They reported evidence of an increase in responsiveness, strongly in the analogue and less in the digital simulation, in reaction time. They further concluded that this could be associated with mild localized heating, or possibly a non-thermal response.

Lai *et al.*[110] have reported that different areas of the brain have different sensitivities to radiofrequency radiations. Chou *et al.*[111], measuring energy absorption (SAR's), have shown that brain regions less than 1 mm apart can have more than two fold difference in SAR. The situation is more complicated if the animal was moving. Ray and Behari[112] have also computed different values of relaxation time in grey and white matter of rat brain, thus confirming these findings.

Several researchers have showed non thermal bioeffects of mobile phones[9,113-115]. Some of these have used evoked potentials as one kind of objective analysis of human brain exposure. Arai *et al.*[114] have shown that no short term adverse affects of 30 min of mobile phone exposure on auditory brain stem responses (ABRs), middle latency responses (MLRs) or somatosensory evoked potentials (SEPs)[116]. Other groups have employed visual evoked potentials (VEPs) to investigate possible bioeffects of mobile phone exposure[117] and showed no significant effects. The reaction times were not affected by the mobile phone exposure[118]. Even though transcranial magnetic stimulation (TMS) is very useful in investigating motor cortex physiology in humans, there have been no reports of effects of mobile phones on human motor cortex using (TMS).

Exposure due to mobile phone frequencies has been found to have an impact on brain EEG activity[119]. This also affects the synchronization of cerebral rhythms. These findings suggest that prolonged exposure to mobile phone emissions affect cortical activity and the speed of neural synchronization by inter hemispherical functional coupling of EEG rhythms.

This may also point to the possibility of desynchronizing the rhythms between two halves of the brain by deregulating the normal alpha wave 2 (8-10 Hz) and alpha 3 (10-12 Hz) bands. This may affect the brain-immune system. Also human brain EEG beta rhythms energies are reported to be increased by exposure to 450 MHz modulated at different low wave frequencies[120]. Frequency and intensity windows of Ca^{2+} have been observed in the presence of weak fields below 100 Hz, similar to the ELF modulated RF fields[121,122]. These findings suggest further interactions, resulting in specific EEG changes that are affected by modulated RF fields. Further, different effects of modulated and CW microwave exposure were found on morphology and cell surface negative charges. As static experimental models (i.e., biochemical models) do not give information about the transient effects and functional changes induced by EM exposure, especially in the nervous system, an electro physiological approach is more appropriate to explain the phenomena in the CNS.

GSM radiation does seem to affect a variety of brain functions (including the neuroencocrine system) and health problems reportedly happen to be neurological. It may be pointed out that mobile phone frequency has two components: one CW and other in the extremely low frequency range (8.3 Hz and 8.34 Hz) respectively. These are close to delta and alpha range of brain wave frequencies, having similarity in the oscillatory behavior. Salford *et al.*[61] reported neuronal damage caused by nonthermal microwave exposure. The cortex as well as the hippocampus and the basal ganglia in the brains of exposed rats contain dark neurons.

A study undertaken in Australia on transgenic mice due to exposure of 918 MHz (repeated at 217 Hz) for 30 min a day for 18 months, showed incidences of lymphomas length in exposed (53%) than in sham exposed (22%). In these experiments pulse width was 0.6 ms. the average incident power density and SAR were 2.6 to 13W/m^2 and 0.13 to 1.4W/kg, respectively. However, in this study since the transgenic mice were free to move around, a wide venation in SAR, value has been reported to occur. It is possible that the incidence of lymphomas might have occurred due to the high value of SAR. The study has however several dosimetric and experimental problems[123].

In a double blind study Utteridge *et al.*[124] carried out study on mice for two years to a exposure of GSM-mobile phone radiation, where the animals were exposed for one hour a day. These authors reported no significant effects when compared to sham-irradiated animals. Oberto *et al.*[125] carried out investigations on 500 transgenic mice (250 female/250 male) and SAR levels varied between 0.5–4.0 W/kg. The exposure was performed 1 hr/day seven days a week, for a period of 18 months. These authors reported different results on six animals. The incidence in female being two to three times higher than males. These authors have reported that there was no significant difference in the number of animals with incidence of tumors, regardless of malignancy. However, the incidence was reduced by 34% at 4.0 W/kg for females. Further in female, there was reduction in the time in death at 0.5 W/kg.

Brain tumor formation—The animal research that has followed provides possible importance of localized exposures and the occurrence consequence impact on biological objects. Development of brain cancer takes years or may be decades to develop and in view of the difficulty in controlling the exposure parameters over a long period of time is difficult to arrive at any definite conclusion. Exposing rats to pulse modulated 837 MHz RF energy similar to that emitted by some digital cell phones does not cause any promotion of brain cancer[126]. Adey[126] reported the same finding for continuous wave RF, such as those emitted by analog cell phones. Most studies performed so far have reported conflicting findings, varying from no major effect to severe health risk.

Evidence of brain tumor promotion from exposure to TDMA fields has been sought in rats exposed to a single dose of the short-lived carcinogen ENU (ethyl nitrosourea) *in utero*, and thereafter, intermittently exposed to digital phone fields for 243 months[127]. The mean life span of rats used in this study was 26 months. A low dose of ENU (4mg/kg) on day of promotion, animals was exposed by phone fields over the life time of the animals. Far field irradiation with an 836 MHz circularly polarized field began on day 19 and continued after parturition until weaning of offspring at 23 days of age. Near field exposure of offspring began at 35 days, and continued for the next 22 months, 4 days weekly. Exposures were for 2 h daily, field on and off for 7.5 min. Modeled far-field time averaged SAR were: pregnant dam (uterus) 0.3 W/kg; fetus (brain) 0.29 W/kg isolated pup (brain) 0.035 W/kg; young rat (brain) 0.13 W/kg). Time averaged near field thermographic SARs were: larger males 0.75 W/kg (localized maximum 1.0 W/kg); smaller females 0.58 W/kg (localized maximum 0.75 W/kg).

Genotoxic effects are thought to be significant contributors to and/or initiators of carcinogenesis. Among the potentially genotoxic effects reported are that 2450 MHz radiations can cause DNA damage in rat brain cells exposed *in vivo*[31,34,35,28,129], though this has not been confirmed by other workers[37,130,131]. Similarly, reports that RF radiations in 800-900 MHz range cause DNA damage *in vitro*[132] has not being confirmed by other workers[133]. Work reporting that RF radiations with modulations relevant to mobile phones at high SARs (10 W/kg) in human lymphocytes induce micronuclei after 24 hr exposure[134] or to 5 W/kg 1.748 GHz GSMK for 15 min[135] are in contrast to reports that 24 h exposures to either 835.62 MHz FDMA or 847.74 MHz CDMA at 5 W/kg did not induce micronuclei[136].

The TDMA field had no enhancing effect on incidence, type or location of spontaneous nervous system tumors. On termination of experiments, the TDMA field appeared to reduce incidence of malignant glial cell tumors in rats that received the ENU drug when compared with rats receiving ENU and no field exposure (4 vs. 13). The TDMA field also appeared to reduce the incidence of spontaneous glial tumors occurring in rats not receiving the ENU drug when they were compared with control animals (2 vs. 7). Tumors in exposed rats were smaller in volume. There were no gender differences in tumor incidence. In rats not surviving to experiment termination (n=54, 22%), the TDMA field appeared to prolong latency of appearance of both spontaneous and ENU induced glial cell tumors, but did not alter histological criteria of tumor types. Consistent non significant differences in survival rates were noted between the four rat groups, with higher death rates in a progression: sham/field; sham/sham; ENU/field; ENU/sham.

Free radical generation and oxidative stress

There are regular media reports of an unusually high incidence of cancer in the vicinity of mobile phone base stations. Because there are several hundred thousand base stations operating all over the world some must coincide by chance with a high local cancer incidence. Regionally cancer incidence has a distribution due to variations in the age and gender. Therefore, a much higher number of cases than expected from average incidences can occur by chance. Unfortunately there are no multi regional systematic investigations of cancer incidence related to mobile phone base stations available to date. Only studies in a single community, one in Bavaria[137] and one in Israel[138], have been published that reported a significantly increased incidence in an area of 400 and 350 m around a base station, respectively. Although incidence in proximity to the base station strongly exceeded the expected values and was significant even considering over dispersion in the case of the Neila study in Bavaria, still no far reaching conclusions can be drawn due to the ecological nature of the studies. However, both studies underline the urgent need to investigate this problem with an appropriate design. Neubauer *et al.*[139] have recommended focusing initially on short term effects

and 'soft' outcomes given the problems of exposure assessment. However, as has been mentioned previously, the problems of exposure assessment are less profound as often assumed. A similar approach as chosen in the study of leukemia around nuclear power plants[140] could be applied also for studying cancer in relation to base station exposure. Such a case control design within areas around a sufficiently large sample of base stations would provide answers to the questions raised by the studies of Eger *et al.*[137] and Wolf and Wolf[138].

Water chemistry—Mobile phone frequency exposure on humans is considered important from the health point of view, because of its large water content.

The vast majority of biological molecules are present in an aqueous medium. When water is exposed to radiation, the water absorbs energy, and as a results forms chemically reactive species that can interact with dissolved substances (solutes). Water is ionized to form a solvated electron and H_2O^+, the H_2O^+ cation can react with water to form a hydrated proton (H_3O+) and a hydroxyl radical (HO). Furthermore, the solvated electron can recombine with the H_2O+ cation to form an excited state of the water. This excited state than discomposes to its species as hydroxyl radicals (HO), hydrogen atoms (H) and oxygen atoms (O). Finally, the solvated electron can react with solutes such as solvated protons or oxygen molecules to form respectively hydrogen atoms and dioxygen radical anions.

The fact that oxygen changes the radiation chemistry may be one reason why oxygenated tissues are more sensitive to irradiation than the deoxygenated tissue at the centre of a tumor. The free radicals, such as the hydroxyl radical, chemically modified biomolecules such as DNA leads to damage such as breaks in the DNA strands. Some substances can protect against radiation induced damage by reacting with the reactive species generated by the irradiation of water.

While *in vitro* data are available these are often not confirmative because of the fact that *in vivo* there is a mechanism of defense built into the system which is not available in the former. Microwave frequency exposure effects on humans are divided into two parts: thermal and nonthermal. Mobile phone exposures are likely to produce mainly non thermal effects. Blood brain barrier[141] and ocular effects[142] have been reported, but are mainly due to power exposure in the thermal range.

Water is a wide band attenuator of microwaves and hence this property is utilized for cooking in microwave ovens. The amount of energy deposited inside the body to produce heating is invariably dependent on its frequency, its orientation and the electrical properties of the tissue. When the intensity increases above the level to maintain homeostates, it starts affecting the biosystems, when the temperature exceeds 1^{o}C. There is a preferential heating near a frequency close to the resonance level. The organs of the body, having reduced blood supply are more prone to this leading to cataract formation and reduction in sperm counts (tests), due to acute microwaves exposure.

While *in vivo* exposure of Wistar albino rats[143] imply an induction of oxidative stress or an interaction with antioxidant cellular activity, *in vitro* experiments[144] found no indication of cellular stress in human glioblastoma cells and fibroblasts. One of the major molecular effects of magnetic fields is their influence on nuclear spins of paramagnetic molecules[145]. Results of experimental data *in vitro*[146,145], revealed that intracellular processes occurring under the influence of a power line magnetic field related to free radicals and signal transmission, may determine its biological effects. An uncontrolled free oxygen radical release, termed oxidative stress, may cause protein oxidation, enzyme inactivation and lipid peroxidation within the cellular membranes, resulting in structural and functional abnormalities as well as in oxidative damage to the DNA and RNA may lead to increased mutation frequency and correspondingly triggering of carcinogenesis[147].

Mitochondrial respiratory chain is the major site for the generation of superoxide radicals (O_2, H_2O_2). It is possible that EMR may affect the mitochondrial membranes to produce large amounts of radicals ROS under experimental conditions. It has been pointed out by Iuleis *et al.*[148] that when SAR increased (0.4-27.5 W/Kg), human spermatozoa motility and vitality significantly reduced after the EMR exposure at 1800 MHz, while the mitochondrial generation of ROS and DNA fragmentation significantly increased.

Superoxide dismutase (SOD) plays a key role in the system protecting the body from destructive free radical activity. Its absence or decreased activity may have noxious metabolic outcomes. Hydrogen superoxide, a product of SOD activity, is also a strong inhibitor of this enzyme[149]. That is why the effective detoxication of active oxygen forms takes place with concordant SOD and CAT action.

SOD activity decreases due to the effect of electromagnetic field exposure and CAT activity increases. Glutathione peroxidase (GSH-P_X) inactivates hydrogen superoxide and organic hydroxides together with glutathione raductase and glucose-6–dehydrogenase with reduced glutathione. The oxidized glutathione generated is then reduced again by NADPH dependent glutathione reductase, in the process that maintains the peroxidation continuity[150].

A significant red blood cell GSH-P_X activity decrease shows a tendency of abnormal function of the antioxidative system caused by the electromagnetic field. Exposure to electromagnetic fields had lower ceruloplasmin activity, which seems to indicate that the free copper plasma concentration increases. However, mechanism of interaction is unclear. In young individuals, cellular defenses against the radicals induced protein oxidation by antioxidant enzymes are likely in prime shape and the proteases and protein synthesis machinery are fully functional. Thus there is no change in the level of protein carbonyl during the first 45 years. However after attaining the age of 45 years, enzymes including proteases and antioxidant proteins, and smaller antioxidant molecules in the individual become progressively inactivated due to the failure of the antioxidant systems to overcome the constant influx of ROS. Consequently, the accumulation of free radical induced carbonylated proteins accelerates, indicating the age when cells in the individual become increasingly more susceptible to ROS-mediated damage. Cumulated oxidative stress in brain cells can lead to neurodegenerative diseases and an excess of free radicals in cells has been suggested to be the cause of various human diseases (e.g. Parkinson, Alzheimer, amyotrophic lateral sclerosis, etc).

An enzymatic cascade is initiated within cells when glutamate receptors are activated, leading to the synthesis of nitric oxide (NO). Receptor activation initiates an influx of calcium, triggering the enzyme nitric oxide synthase to produce nitric oxide from the amino acid arginine. It has been identified as a widely distributed neuoregulator and neurotransmitter in many body tissues[151].

Oxidative damage has been reported in brain tissues[152,61]. Spermatozoa are known to be susceptible to damage induced by oxidative stress: however whether RF radiation is capable of inducing oxidative stress is still debatable. Conflicting results have been reported regarding the effect of electromagnetic waves exposure on the secretion of an antioxidant melatonin[153-155]. Studies analyzing the effect of RF radiation on apoptosis have failed to find any significant effect. An exposure of 1800 MHz signal for 12 h failed to induce apoptosis is human mono Mac 6 cells[156]. No evidence of apoptosis have been detected after exposing human leukemia cells *in vitro* to RF waves 25 times higher than the reference levels set by the International Commissions Non-Ionising Radiation Protection (ICNIRP), However, this view has been recently revised by results from this laboratory where RF radiations have been found to increase apoptosis[157,158] have examined classical contact energy reactions, such as chromate allergy. These authors described the clinical characteristics and results of patch tests in eight patients with contact dermatitis possibly caused by handling a cellular phone. A possible mechanistic pathway is shown in Fig. 3.

Electromagnetic fields and DNA

DNA damage caused by any endogenous and exogenous factors is under a constant repair process. Any imbalance or mistakes in damage and repair result in accumulation of former, causing apoptosis, ageing or promotion of cancer. One of the markers of this is the strand break mostly caused by endogenous process causing free radical generation by mitochondrial respiration and metabolism. This may also be caused by exogenous agents e.g. UV radiation, ionizing, non ionizing radiation and chemicals[109]. Phillips *et al.*[132] were the first to study the effects of two forms of cellular phones signal known as TDMA and IDEN on DNA damage in molt-4 human lymphoblastoid cells using the comet assay, using low intensity of field (2.4-2.6 μW/kg). Diem *et al.*[159] exposed human fibroblast and rat granulosa cells to cell phones signal (1800 MHz, SAR 1.2 or 2 W/kg; different modulation, for 4, 6 and 24 h; intermittent 5 min on/10 min off or continuous). Intermittent exposure caused a significant stronger effect than continuous exposure. Gandhi and Anita[160] reported increase in DNA strand breaks and micro-nucleation in lymphocytes obtained from cell phones user. Markova *et al.*[161] reported that GSM signals affected chromatin conformation and Y-H2AX foci that co-localized in distinct foci with DNA double strand breaks in mouse embryonic cells after acute exposure to a 1.7 GHz field. Sun *et al.*[162] reported that DNA damage caused by the field at 4 W/kg was

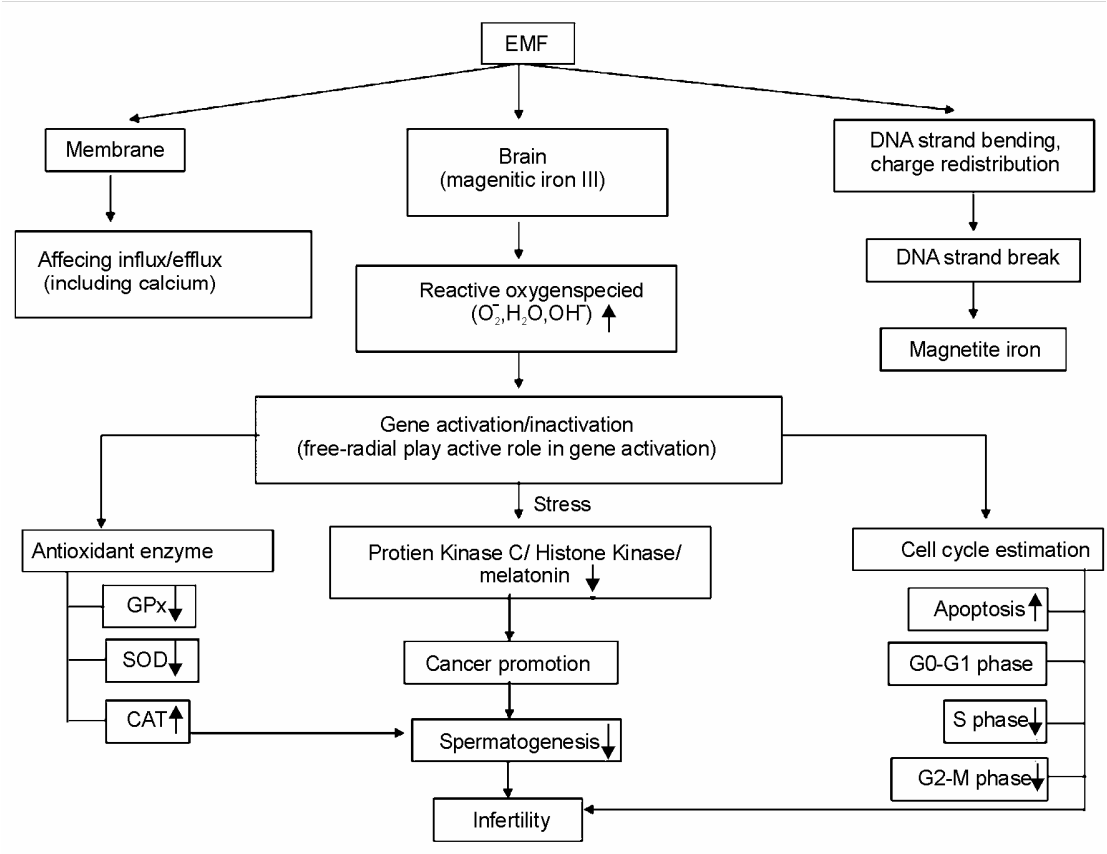

Fig. 3—A suggestive mechanistic pathway of EMF field expression on biological systems.

irreversible. Zhang *et al.*[163] also reported that an 1800 MHz field at 3.0 W/kg induced DNA damage. Erogul *et al.*[107] reported changes in morphology and decreased motility in isolated sperm cells, exposed to cell phone radiations[93] and cell phone users[105]. Some of these *in vivo* effects caused by hormonal changes[164,90]. Stronati *et al.*[39] showed that 24 h of exposure to 935MHz GSM base signal at 1 or 2 W/kg did not cause DNA strand break. Similarly, Verschaeve *et al.*[165] did not observe significant affect of DNA strand break to long term (2 h/day, 5 days/week for 2 years) to 900 MHz GSM signal.

However, there have also been reports regarding the effects on DNA damage in cells (C3H10T) exposed to radiofrequency radiations[133]. Hook *et al.*[166] showed that a 24 h exposure of Molt-4 cells to CDMA, FDMA, IDEN or TDMA-modulated RFR did not significantly alter the level of DNA damage. Lagroye *et al.*[167,168] also reported no significant change in DNA strand breaks, DNA-protein cross links and DNA-DNA cross links in cells exposed to 2450 MHz RFR. In line with these Vijayalaxmi *et al.*[169] reported no increase in DNA strand breaks in human lymphocytes exposed *in vitro* to 2450 MHz RFR at 2.135 W/kg for 2 h.

EMR and melatonin

The melatonin/serotonin cycle is a primary physiological driver of the daily metabolic, awake/sleep cycle. Melatonin is a vital part of many of the body's biochemical systems, including sleep and learning and is free radical scavenging in all cells and hence is a potent antioxidant with anti-aging and anti-cancer properties. It helps to protect embryonic fetuses. Through regulation of the cyclic AMP (cAMP) pathway, the serotonin/melatonin transformation is controlled. A key element of the cAMP pathway is calcium ions. Substances that can alter cellular calcium ions at many levels involving many cell receptors and cellular processes. Calcium ion efflux from the pinealocytes has the effect of reducing melatonin through reducing the cAMP.

Radon *et al.*[170] showed that pulsed RF electromagnetic fields (900 MHz carrier frequency pulsed with 217 Hz) similar to those emitted from mobile radio telephones had no short term or medium term effects on salivary melatonin, cortisol, neopterin

and sIgA concentrations. These authors also confirmed the observation that nocturnal melatonin levels are not affected by exposure to RF electromagnetic fields[171]. The findings are in confirmation with the data showing that day time melatonin levels are unaffected by exposure to RF electromagnetic fields of 900 and 1800 MHz[153]. Also no effect was noted on melatonin synthesis and excretion in humans exposed to 50 Hz magnetic fields of 10 μT[172]. Vollrath *et al.*[173] have also reported that day as well as night melatonin levels were unaffected.

EMR alters calcium ion homeostasis—Rosen *et al.*[174] mentioned suppression of nighttime rise in pineal melatonin production in laboratory animals. The show that a 50 mT, 60 Hz field with a 0.066mT DC field, over 10 experiments, averages a 46%, reduction in melatonin production from pinealocytes. Yaga *et al.*[175] showed that rat pineal response to ELF pulsed magnetic fields varied significantly during the light-dark cycle. They found that the rate-limiting enzyme in melatonin synthesis, N-acetyltransferase (NAT) activity showed that magnetic field exposure significantly suppressed NAT during the mid-to late dark phase.

Radiofrequency frequency exposure and health: nonthermal, micro thermal and isothermal effects

The possibility of either nonthermal or micro thermal effects on human body is one of continuing concern. It needs to define the conditions of an experimental study when investigating the possibility of nonthermal effects, to be sure to take into account all the power components. It is thus important to be able to distinguish between thermal and nonthermal effects.

The exposure to nonthermal microwave EMF-generated by mobile phones affects the expression of many proteins. This effect on transcription and protein stability can be mediated by the mitogen activated protein kinase (MAPK) cascades, which serve as central signaling pathways and govern essentially all stimulated cellular processes. Indeed, long term exposure of cells to mobile phone irradiation results in the activation of p38 using a 915 MHz field, switching modulation frequencies from 55 to 65 Hz at coherence times of 10s or longer produced full enhancement. These microwave coherence effects are similar to those observed in ELF fields[176].

There is also controversy about the possibility of nonthermal or microthermal effects. Accepting the idea that RFs may cause nonthermal effects or microwave exposure implies that such an exposure could be of a low or very low level and this is not well accepted. On the other hand, it is also a misnomer to believe that all biological related effects are necessarily pathogenic. This underlies the whole question about how to establish guidelines for limiting electromagnetic field (EMF) exposure and more importantly to understand the mode of EMF biointeraction (e.g. with neurons and with bone cells) (Fig. 4). The question of thus accepting or rejecting nonthermal effects is a major unresolved question.

Investigating the possibility of isothermal effects does not preclude the attention to be paid to "nonthermal" effects, which should probably better be termed microthermal effects[177]. The question is: can extremely weak EM exposure have large biological effects and how is this possible? To answer this, one then has to consider the possibility of trigger action by microwaves.

Extensive research has undergone in investigating a variety of possible effects and includes epidemiologic, *in vivo*, and *in vitro* research. The overall epidemiologic evidence suggests that mobile phone use of less than 10 years does not pose any increased risk, of brain tumor or acoustic neuroma. For longer duration data are sparse. The safety standard assumes that EMF exposure cause biological damage only by heating, but several biological effect (including cell damage), have been reported which are caused by exposure below the safety limit. Cellular stress response where cells synthesize stress proteins in response to potentially harmful stimuli in the environment, including EMF. The stress response to both radiofrequency and microwaves shows the inadequacy of the thermal SAR standards (macromolecular effects).

It is possible that there are currently unrecognized health effects from the use of mobile phones. Children are more vulnerable, because of their developing nervous system; greater absorption of energy and a longer life time of exposure. As such unnecessary use of mobile phones by children should be avoided. Other users should use the device with the instructions as supplied by the manufacturers and as sparingly as possible. The hand free devices that move the handset away from the user's body tend to reduce exposure, though these may cause exposure to sperm and there is fear of infertility. The present day controversy regarding the mobile phone is probably because of non-thermal effects.

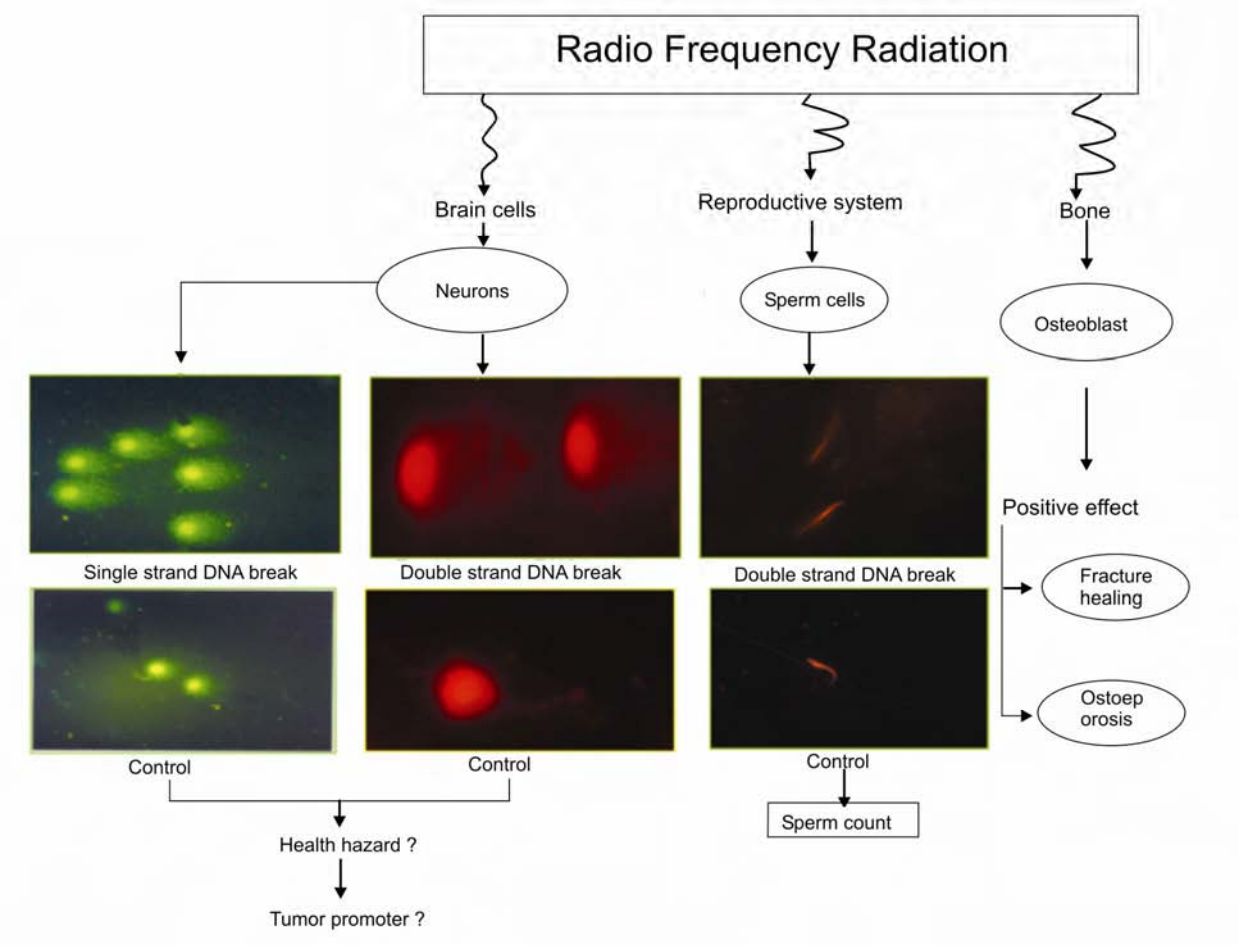

Fig. 4—Dual behavior of radiofrequency radiation on neuronal and osteoblastic cells

It may be concluded that somewhat correlation exits between sperm motility and sperm chromatin structure, which are brought about by distorted epididymal protamination[178]. ROS causes DNA fragmentation in somatic cells reducing protamination[179].

Discussion

Exposure to human population is from two sources: hand set and base station. There are important differences between the two. The typically very low exposure to microwaves from base stations, rarely exceeding 1 mW/cm^2, is unlikely to produce any adverse effect. Assuming energy equivalence of effects a 24 h exposure at 1 mW/cm^2 from a base station would be roughly equivalent to 30 min exposure to a mobile phone operating at a power of 20 mW (average output power in areas of good coverage). Because we do not know whether time dose reciprocity holds for RF-EMF and whether there is a threshold for biological effects, and there is an argument that such low exposures in vicinity of homes near base stations could affect health.

The most important difference between mobile phone use and exposure from base station signals is one of duration of exposure. While mobile phones are used intermittently with normal exposure duration around 1-2 h per day, exposure to base stations is continuous (up to 24 h a day). It may be mentioned that the exposure of mobile phone users is in the near field and localized at the head (or waist) region, while base stations exposure to the whole body is essentially in the far field. Strictly speaking exposure from mobile phones and their base stations have almost nothing in common except for the almost equal carrier frequency that is likely of lesser importance for determining biological effects. However both the exposure is non thermal in nature.

Concerning reconstruction of exposure to base station signals there is no greater difficulty than for retrospective assessment of exposure to mobile phones. It is not always necessary to determine

exposure precisely. For epidemiological investigations it often suffices to have a certain gradient of exposures. As long as any two persons can be differentiated along such a gradient epidemiological investigations can be relevant.

There are several field studies of well being and exposure to base stations signals available to date. Two were in occupational groups working in a building below[180] or below as well as opposite a building with a roof mounted base station antenna[181]. The other five were in neighbors of base stations: Santini *et al.*[182,183], Navarro *et al.*[184], Hutter *et al.*[185], Blettner *et al.*[186] and Thomas *et al.*[187]. Studies had different methodologies with the least potential for bias in the studies of Hutter *et al.*[185] and Blettner *et al*[186]. All other studies could be biased due to self selection of study participants. One study explored personal dosimetry during 24 h but results were inconclusive due to insufficient power and omission of nighttime measurements[187]. The study of Blettner *et al.*[186] had an interesting design with a first phase in a large population based representative sample and a second phase with individual measurements in the bedrooms of participants that were a subgroup of the larger sample. Unfortunately this second sample did not contain a sufficiently large fraction of individuals with relevant exposure (99% had bedside measurements below 0.3mW/m^2).

Despite some methodological limitations of the different studies there are still strong indications that long term exposure near base stations affects well being. Symptoms most often associated with exposure were headaches, concentration difficulties, restlessness and tremor. Sleeping problems were also related to distance from base station or power density, but it is possible that these results are confounded by concerns about adverse effects of the base station, or more generally, by specific personality traits. While the data are insufficient to delineate a threshold for adverse effects the lack of observed effects at fractions of an mW/m^2 suggests that exposure around 0.5-1 mW/m^2 must be exceeded in order to observe an effect.

Conclusion

While a lot of data have accumulated on the biological effects of extremely low and mobile phone frequency exposure, many are contradictory and need to be explored further, particularly in relation to human being. There is a need for more independent replications of above findings.

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