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Interactions of zero-frequency and oscillating magnetic fields with biostructures and biosystems

Pietro Volpe

Department of Biology, University of Rome 'Tor Vergata', Rome, Italy.
E-mail: volpe@bio.uniroma2.it

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This review points to the investigations concerning the effects of zero-frequency (DC) and oscillating (AC) magnetic fields (MFs) on living matter, and especially those exerted by weak DC and low-frequency/low-intensity AC MFs. Starting from the analysis of observations on the action of natural magnetic storms (MSs) or periodic geomagnetic field (GMF) variations on bacteria, plants and animals, which led to an increasing interest in MFs in general, this survey pays particular attention to the background knowledge regarding the action of artificial MFs not only at the ionic, molecular or macromolecular levels, but also at the levels of subcellular regions, *in vitro* cycling cells, *in situ* functioning tissues or organs and total bodies or entire populations. The significance of some crucial findings concerning, for instance, the MF-dependence of the nuclear or cellular volumes, rate of cell proliferation *vs.* that of cell death, extent of necrosis *vs.* that of apoptosis and cell membrane fluidity, is judged by comparing the results obtained in a solenoid (SLD), where an MF can be added to a GMF, with those obtained in a magnetically shielded room (MSR), where the MFs can be partially attenuated or null. This comparative criterion is required because the differences detected in the behaviour of the experimental samples against that of the controls are rather small *per se* and also because the evaluation of the data often depends upon the peculiarity of the methodologies used. Therefore, only very small differences are observed in estimating the MF-dependence of the expression of a single gene or of the rates of total DNA replication, RNA transcription and protein translation. The review considers the MF-dependence of the interactions between host eukaryotic cells and infecting bacteria, while documentation of the harmful effects of the MFs on specific life processes is reported; cases of favourable action of the MFs on a number of biological functions are also evidenced. In the framework of studies on the origin and adaptation of life on Earth or in the Universe, theoretical insights paving the way to elucidate the mechanisms of the MF interactions with biostructures and biosystems are considered.

1 Introduction

Since life on Earth originated in natural MF, while a large part of the living matter became subjected to artificial magnetic, electric and electromagnetic fields only in the 20th Century, a question concerning the adaptation of organisms to these new unexpected fields emerged. Would an animal, for instance, maintain the normal ontogenesis in an artificial MF characterized by an amplitude much larger than that in which it evolved? In recent years, the number of reports posing this question increased. In particular, the epidemiological aspect was debated with emphasis, since the negative effects of extremely low frequency (ELF) MFs, generated by 50–60 Hz high voltage power transmission lines, video display terminals, electric blankets or other home appliances, was forcibly denounced as time went by.[1] The belief that, in the case of these sources, the field intensity is rationally fixed below a risk threshold functioned as an objection to the alarm. However, the available data were contradictory.[2] On the one hand, a benefit from the low-energy pulsed MFs in non-union bone fracture healing and in cell regeneration was reported.[3] On the other, the influence of MFs at 50–60 Hz exerted on nerves[1] induced preoccupation. In any case, the MFs showed a distinct influence on cell proliferation[4] and on the role of the calcium ions in the transduction of this influence.[5–10] In particular, it was reported that a 22 μT MF at 60 Hz modulated the calcium influx.[8] The MF-dependence of the state of the cell membrane was investigated through electron microscopy[11] and cytofluorimetry.[12] The influence of 1–10 μT MFs at 50 Hz on the membrane conductivity and permeability was taken into account.[11] A study was performed on the effects of very weak MFs (10^{-6} to 10^{-5} T) on chicken embryogenesis.[13] The results of this research were confirmed in some laboratory conditions[14] and contradicted in others.[15,16]

Pietro Volpe

Pietro Volpe. Full Professor of Biochemistry at the Department of Biology of the University of Rome 'Tor Vergata'. For many years he was Head of the Cellular Biochemistry and Biophysics Section at the International Institute of Genetics and Biophysics of the National Research Council in Naples. He was Fellow of the School of Molecular Biology and Biophysics of the European Molecular Biology Organization at the University of Oxford and Exchange Researcher at the Department of Biochemistry of the Albert Einstein College of Medicine in New York. His studies concerned the origin and evolution of the genetic code, gene structure, repair of radiodamaged gene sequences, DNA methylation, regulation of macromolecular biosynthesis during the cell cycle, cell-virus interactions, extraretinal pigmentation and colour discrimination, paramagnetic resonance in synchronized cancer cells, and influence of magnetic fields on living matter.

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The divergences encountered in the literature with respect to the MF-dependence of given biological structures and functions are due not only to the differences of equipment facilities or experimental accuracy, but rather to the intrinsic adequacy of proposed methodological approaches. In addition, there is still a largely recognized lack of theoretical analysis to explain the mechanisms which underlie the interactions between the MFs and the various cellular targets. Thus, the main aim of the present review is to draw the attention on the efforts that have been made up to now to define the basic physico-chemical laws describing the MF-biosensitivity.

2 Do magnetic-storm and geomagnetic-field forces influence life on Earth?

Bacteria, plants and animals have adapted to the Earth's physico-chemical environment and have learned to benefit from it. However, when they withdraw from the forces of the MS or those of the GMF, being inside an artificial MSR, they manifest a number of changes in their normal physiological functions.

2.1 The background magnetic mosaic on the Earth's surface essentially comprises the geomagnetic field and the magnetic storms

The Sun, with its electromagnetic and corpuscular irradiations, contributes to form an extremely complex MF on the Earth.[17] The so-called solar wind, rotating with the Sun's rotation around its axis, fills our celestial Space. The wind consists of four sectors: the first two, that show magnetic force-lines directed away from the Sun, are indicated as positive; the other two, that show opposing force-lines, are indicated as negative. The MSs are generated by the plasma flows from the regions of bursts of the solar activity. They arise ten or more times in a month, with an average frequency of about eleven years, corresponding to the oscillations in the same solar activity. The MSs reach the Earth two days after the Sun's bursts. With respect to the GMF, an MS can be subdivided into four general phases, defined as preliminary, initial, main and recovery. During the preliminary phase, small changes in the GMF are detected. During the initial phase, a drastic variation in the GMF occurs. During the main phase, *quasi*-periodical oscillations (low-frequency and ELFs) and a drop in the horizontal component of the GMF take place. During the recovery phase, all these variations fade. In turn, the flow of protons that rotates around the Earth, under the action of the GMF, forms a ring, defined as equatorial current, whose MF attenuates the GMF in the main phase of the MSs. Thus, the intensity of the GMF, varying from about 35 μT at the Equator (where it is almost parallel to the terrestrial surface) to about 70 μT at the Earth's magnetic Poles (where it is almost vertical), is significantly perturbated by the MS. An MS can produce alterations of the GMF lasting from several hours to several days all around the Earth, with a maximal magnitude of about 5 μT at the high latitudes and about 1 μT in the middle latitudes. In addition to the eleven year periods of magnetic fluctuations, due to the Sun's activity, there are other periods of variation in the GMF: one day cycle, due to the Earth's rotation; a 6–7 day cycle, corresponding to one sector of the solar wind; a 13–14 day cycle, corresponding to the passage of two solar wind sectors; a 27 day cycle, corresponding to the period of the Sun's rotation around its own axis. Other rhythms are also correlated with these cycles: a 29.5 day cycle, corresponding to the synodic period of the Moon; a 1 year cycle, corresponding to the period of the Earth's revolution; some cycles of the solar activity that are not so prominent when compared to the main eleven year cycle (2, 3, 8, 22 and 35 year cycles). Apart from the above listed GMF cycles of astronomic nature, one has to consider the continuous spectrum of quasi-periodic low-frequency processes which are caused by oscillations in the plasmasphere and magnetosphere of the solar wind and by the resonant oscillations (*Schumann's resonances*) of the ionosphere of the Earth.[17,18] This spectrum shows maximal values approximately at 0.001, 0.01, 0.1, 1, 3, 8, 21 and 100 Hz. Despite the obvious difficulty to distinguish the specific biological effects exerted by each one of these components of the MF mosaic that covers the Earth's surface, some information has been gathered by considering the GMF as a whole. Hence, pionieristic studies showed that the orientation of sea gulls or pigeons is strongly GMF-dependent,[19–22] while in the acoustico-lateral area of the skate's brain there are two groups of neurons, one excited by the MF with the South sense and another inhibited by the MF with the North sense.[23] It was also shown that the GMF plays a role in total plant branching, in orientation of the root branches, in metabolism and proliferation of the root meristem cells and in protein synthesis occurring in a number of vegetal cells.[24–27]

2.2 The attenuation of the geomagnetic field causes biological alterations

By attenuating the GMF in special MSRs (with shielding indexes of several tens up to 100), a decrease of the vital functions in bacteria occurs.[28] As for the plant kingdom, in meristem of seedling roots of pea, flax and lentil, electron microscopy reveals changes in the mitochondrial structure,[26] while a 68–75% reduction of cell proliferation is accompanied by a variation of the RNA and protein biosynthetic rates.[27] As for the animal kingdom, a change in timing of fibroblast division and an increase in sensitivity of *in vitro* cell cultures to poisons is described,[29] while a decrease in erythrocyte sedimentation is noted.[30] In rats, the hypogeomagnetic conditions cause a decrease of learning *vs*. an increase of hippocampus catecholamines.[31] When guinea pigs are subjected for 30 min to a GMF ten times weaker,[32] an increase of the epinephrine and histamine levels and a decrease of the serotonin level are observed in their blood.

2.3 The occurrence of the magnetic storms causes additional biological disfunctions

The influence of solar activity on the GMF and thus on the biosphere was noted as early as the beginning of the 20th Century, although experimental data were collected only recently. In fact, it is well known that the bacterial bioluminescent intensity varies according to the amplitude and duration of the MSs, since the synchronization of luminous radiation occurs as the frequency of the GMF perturbation increasingly approaches the intrinsic oscillation of the same bioluminescent system. On the other hand, medical studies correlated MSs with anxiety and irritability and with lower attention and accuracy on the job. These symptoms cause not only an increase of errors made by pilots, but also an increment of the probability of road accidents.[33] Under the MSs, glaucoma attacks rise,[34] while the number of ambulance calls increases because acute attacks of cardiovascular diseases become more frequent.[35] In addition, laboratory experiments showed that, during the days of GMF perturbation by MSs, changes occur in conditioning the activity of rats, pigeons and dogs, while reactions of single neurons are registered in the motor neocortex of cats.[36] During the strong double planetary MS of September 21–23, 1984, crucial physiological parameters of the cardiovascular system and ultrastructure of cardiomyocytes were investigated in rabbits:[37] at the initial and main phases of the MSs, the normal circadian structure in each cardiovascular parameter is lost; desynchronization increases with the MS, while an abrupt drop of cardiac activity is observed; the main phase of the MS is followed by a degradation of mitochondria in cardiomyocytes. Cell cultures of mouse, hamster, and trout were employed in other experiments to show that morphological and functional states are associated with the GMF variations, while the MS disturbance

of the GMF causes stepwise changes in the properties of the cell surface, in the appearance of heterokaryons and in the strengthening of cellular adhesion and aggregation.[38]

3 Do the experiments demonstrate a magnetic field-dependence of cell life?

3.1 Biological effects of zero-frequency magnetic fields

(a) Apoptosis is inhibited by relatively weak fields. DC MFs with intensities starting from 6 mT were found to decrease, in an intensity-dependent fashion reaching a plateau at 60 mT, the extent of cell death by apoptosis induced by several agents in different human cell systems.[39] This was not due to a change in the mode of cell death, *i.e.* to necrosis, or to a delay of the process itself, but, rather, to the presence of MFs which allowed the indefinite survival and replication of the cells hit by apoptogenic agents (Fig. 1). The protective effect was found to be mediated by the ability of the fields to enhance calcium uptake from the extracellular medium; accordingly, it was limited to those cell systems where calcium uptake was shown to have an anti-apoptotic effect. MFs might, therefore, interfere with human health by altering/restoring the equilibrium between cell death and proliferation; indeed, the rescue of damaged cells may be the mechanism explaining why MFs that are not mutagenic *per se* are often able to increase mutation and tumor frequencies.[2] The AC MF creates, in the biological target, a current able to cause a variation of calcium ion uptake,[40] whereas the DC MF does not although it may likely induce orientation effects as in the macroscopic case of the ordinate movement of the irradiated bull sperms.[41] This could explain the increased influx of calcium ions into DC MF-irradiated monocytes.[39] The question is discussed here below, in the framework of the various mechanisms of the MF interaction with living matter, which still needs to be elucidated.[42–45]

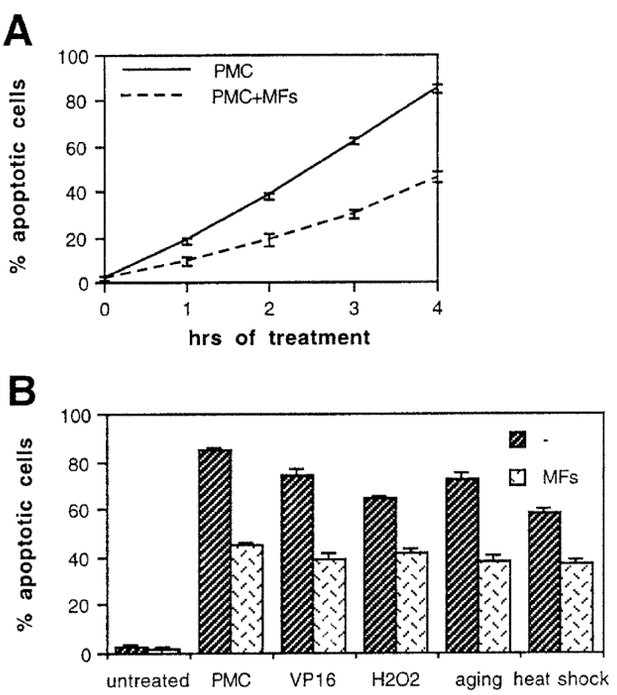

Fig. 1 *Zero-frequency magnetic fields reduce apoptosis induced by different agents tested on U937 cells.* (A) 6 mT magnetic fields (MFs) reduce puromycin (PMC)-induced apoptosis at all time points (average values ±SEM; n = 19). (B) MFs affect apoptosis induced by PMC, etoposide (VP16), H_2O_2, aging and heat shock. Values are the average of at least five experiments for each treatment ± SEM. Apoptosis was measured at 4 h of continuous treatment (PMC and VP16); at 6 h of recovery (H_2O_2); and at 4 days of aging; heat shock was performed at 43 °C for 1 h, followed by recovery in fresh medium. Reprinted from ref. 39 with permission from FASEB Publications. © 1999.

(b) Macrophage defence against mycobacterial infection is depressed by relatively strong fields. Investigations[46] revealed that DC MFs, from very low intensities up to 670 mT, exert a continuous effect on the expression of the human monocyte-derived macrophage (MDM) CD14 and CD64 membranal protein markers, on MDM viability, necrosis and apoptosis, on MDM–*Mycobacterium tuberculosis* (MTB) interactions,[47] and on division of the same MTB inside the MDM cytosol.

(i) In uninfected MDMs, there appeared a biphasic MF-dependence of the CD14 and CD64 proteins: their expression was significantly inhibited at 0–232 mT and partially or completely recovered at 232–670 mT. In MTB-infected MDMs, the biphasic pattern of the CD14 protein did not actually change, although it showed decreased values; however, the biphasic pattern of the CD64 protein dramatically changed since in its initial part the inhibition, exerted by the fields, was likely masked by the one caused by the infection itself. The following re-increase of the CD14 and CD64 expression, both in uninfected and infected MDMs, could not be interpreted in terms of adaptation to fields of higher intensities (as it was wrongly thought at first), because they did continue to exert a harmful action.

(ii) In uninfected MDMs, in fact, viability dramatically went down at 0–232 mT and remained at the lowest level, at 232–670 mT. This progressive decline of viability was confirmed, as in a specular reflection, by the development of the MDM necrosis which reached the maximal level at 232 mT and remained at a plateau as high as 670 mT. As for apoptosis, at the lower intensities of the fields (0–232 mT), a distinct inhibition of the process occurred, in agreement with a previous observation made in human monocytes.[39] This inhibition could appear as a countertendency with respect to the decreasing MDM viability and to the increasing MDM necrosis; but, a further increase of the MF intensity, at 232–670 mT, led to a resumption of apoptosis. Hence, at the highest MF intensities, the MDMs died not only through necrosis, but also through apoptosis. This definitely excluded any hypothesis based on a possible MDM adaptation to the increased intensity of the DC MF, and the situation became rather intriguing, when the MDMs were infected with MTBs. Although still reciprocally specular, both patterns of MDM viability and necrosis became flattened. Despite the progressive increase of field intensity, the MDMs did not die. This could be explained by the fact that the MTB caused a hyperactivation of the host,[47] *i.e.* the MTB-infection would re-inforce the MDM resistance to the fields. The pattern of apoptosis of the infected MDMs was qualitatively similar to that of the uninfected MDMs. So, the higher field intensities also caused a re-increase of apoptosis in infected MDMs. The flattening of the patterns of viability and necrosis in MTB-infected MDMs needs, therefore, a different explanation.

(iii) A starting hypothesis was that at particular intensities the MFs might facilitate or prevent the penetration of MTBs into MDMs or, independently from the number of MTBs entering an MDM, facilitate or prevent direct MDM digestion. Indeed, transmission electron mycroscopy showed that the MF-dependence of the interactions between the MDMs and the MTBs reflects an extremely complex picture. Without applying artificial fields, one MTB per MDM was observed; in this case, the MDM was able to entrap the MTB into a very large phagolysosome (Fig. 2, upper panel). At 91 mT, about 10 MTBs per MDM were observed; in this case, the phagolysosomes showed a reduced size but were still able to entrap the MTBs to be digested (Fig. 2, lower panel). The reason why MTBs became free to divide was because the MDMs were unable to construct phagolysosomes at 670 mT. In this respect, the DC MFs induced the following changes in the MDM–MTB interactions: without application of the fields, there were 40% of infected MDMs, while on average one MTB per MDM was found; under 91 mT, there were 63% of infected

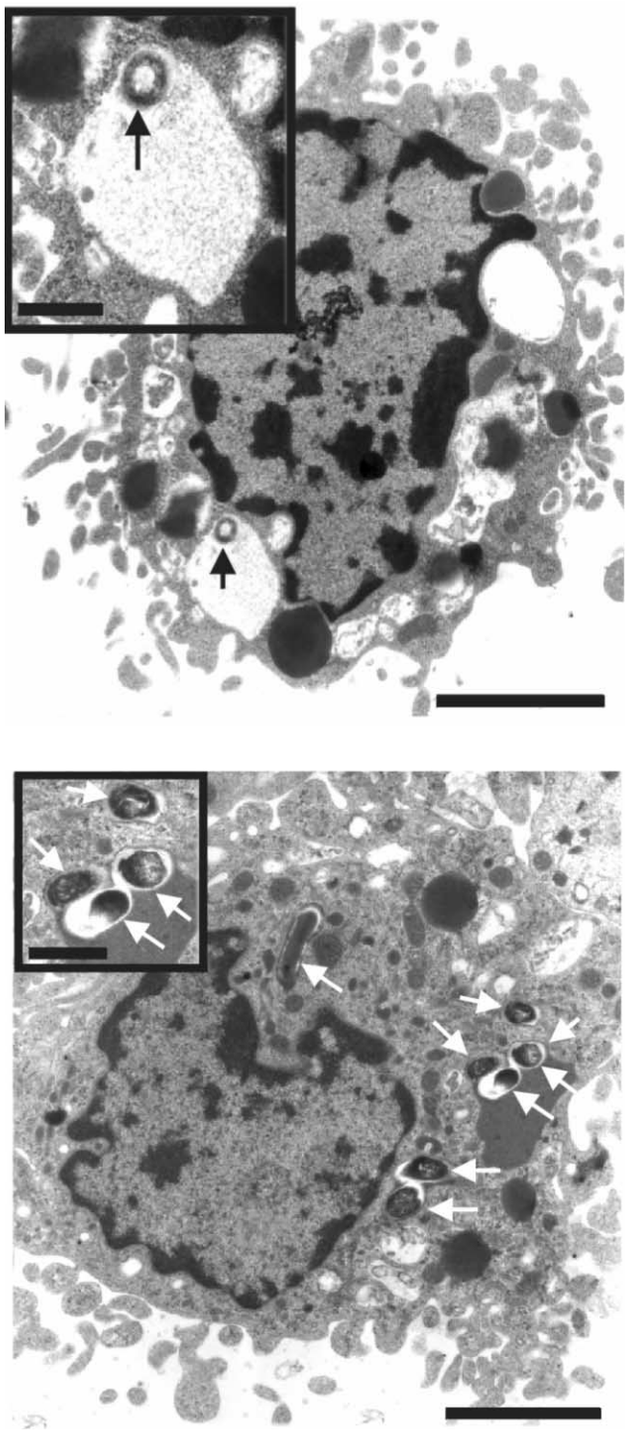

Fig. 2 *Microstructural changes induced by zero-frequency magnetic fields of relatively lower intensity in human macrophages (MDMs) infected with Mycobacterium tuberculosis (MTB)*. In the control unexposed MDMs (upper panel), an MTB (dark arrow) was located inside a cytoplasmic vacuole (the large bar measures 2.5 μm; in the insert, the small bar measures 500 nm). In the MTB-infected MDMs, exposed to 91 mT (lower panel), several MTBs (white arrows) were located inside cytoplasmic vacuoles which, in some cases, were fused with each other, as shown in detail in the upper left corner: the large bar measures 2.5 μm; in the insert, the small bar measures 500 nm. Reprinted from ref. 46 with permission from Demokritos Publishers. © 2002.

MDMs, while on average 7.5 MTBs per MDM were found; under 670 mT, there were 81% of infected MDMs, while on average 3 MTBs per MDM were found (Table 1). Likely, in this case, the high MDM necrosis and apoptosis allowed an escape of the newly-born MTBs. Alternatively, in order to explain the presence or absence of the phagolysosomic vacuoles at the corresponding lower or higher MF intensities, two possibilities may also be considered: at 91 mT the MDMs would still be strong enough to entrap a high number of entering MTBs into their phagolysosomes while at 670 mT the MDMs would be unable to construct a sufficient number of phagolysosomes to destroy the high number of entering MTBs. In the latter case, there would be an equilibrium between the MTBs entered and those digested. With regard to MTB division, its free occurrence in the cytosol—at 670 mT but not at 91 mT—should deserve further attention, since it is unclear whether the same higher MF intensity was determinant for such a free division or whether this took place because the number of entering MTBs was too high. But why did this not occur at 91 mT, when the number of MTBs per MDM was even higher? The question assumes particular interest, considering that, at the moment of their division, the two newly-born MTBs do not look alike: one is small, while the condensed DNA occupies only half of its internal space; the other is large, containing dispersed DNA (Fig. 3). The MFs of high intensity might have increased such an unequal distribution, with consequences in the development of the bulk MTB population in the host. In addition, the membrane of one newly-born MTB assumed, in comparison with the membrane of the other, a surprisingly regular polygonal shape which still needs to be understood.

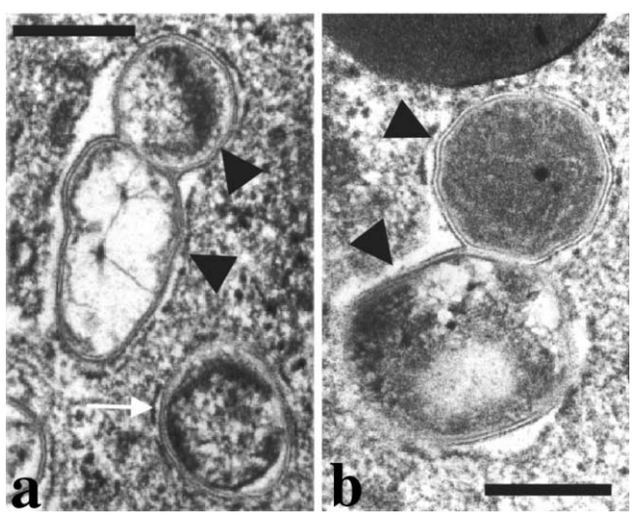

Fig. 3 *Mycobacterial division induced in human macrophages by static magnetic fields of relatively higher intensity*. Under 670 mT, the free mycobacteria (MTBs) undergoing division yielded newly-born MTBs (dark arrowheads) showing different shapes and DNA condensation. (a) Different forms of the newly-born MTBs. (b) Uniqual distribution of DNA and diversification of the membrane microstructure. The bar measures 300 nm. Reprinted from ref. 46 with permission from Demokritos Publishers. © 2002.

In sum, the idea of an adaptation phenomenon to relatively intensive DC MFs was rejected by the fact that the uninfected MDMs at the lower intensities essentially died because of necrosis, while at the higher intensities they died not only because of necrosis but also because of apoptosis.[46] The MDMs infected with the MTBs, although showing flattened patterns of viability and necrosis, at the higher intensities, died because of apoptosis.[46] Apparently, infection prevented necrosis.[46] This observation assumed particular interest when evaluated in the framework of the debate concerning the question of whether or not certain artificial MFs of given intensities are harmful to living matter.[2,48] The interest depends not only upon the question concerning the weak DC MFs influencing the origin of life on Earth or in the Universe,[49,50] but also upon the efficiency of given biological functions under DC MFs of relatively high intensities.[51] Let us consider, for instance, the possible risks of patients undergoing 1.0–1.5 T exposure during magnetic resonance or of workers routinely exposed to a series

Table 1 Changes of the percentage of macrophages infected with *Mycobacterium tuberculosis* and variations of the number of mycobacterial cells per macrophage under the influence of static magnetic fields

Sample	Percentage of MTB-infected MDMs[a]	MTBs per MDM[b]
Unexposed	40.0	1.25
Exposed to 91 mT DC	63.6	7.50
Exposed to 670 mT DC	81.8	3.20

[a] The data represent the percentages of the MTB-infected MDMs calculated by observing at least 40 cells per sample through TEM. [b] The data represent the mean of the number of MTBs per infected MDM calculated by observing at least 40 cells per sample (ref. 46).

of MFs.[52] In harmony with the knowledge suggesting the influence of AC MFs on the transport of calcium across the membranes,[40,53] a previous work demonstrated the inhibition of apoptosis by DC MFs *via* a calcium influx.[39] In that case, the MF intensities were varied from 0 to 66 mT, almost 1000 times the MF intensity of the GMF which was around 45 μT.[4] In the present case, when compared with the GMF, the MF intensities used, at 0–670 mT, increased about 10 000 times. The choice of the MDMs as targets for these MFs was triggered by the knowledge that any stress signal was heavily interfering with the immune defence system.[6,54]

(c) Cytokine gene expression in normal and mycobacterium-infected macrophages is perturbated. This study,[47,55] exploiting the reverse transcriptase-polymerization chain reaction, showed that the exposure of human MDMs to two DC MFs of different intensities (91 and 670 mT)—out of the eight cytokine genes examined (IL-1β, IL-6, IL-10, IL-12, 1L-16, TNF-α, IFN-γ and TGF-β)—causes well visible Southern blotting variations in the transcription of three of them (IL-1β, IL-10 and INF-γ). In particular, the MF of 91 mT induced a stronger production of mRNAs for IL-10 and IFN-γ, when compared with the MF of 670 mT. On the contrary, the MF of 670 mT induced a higher production of mRNA for IL-1β. TNF-α and IL-16 mRNA transcription was influenced to a lesser extent by the exposure to MFs, with no difference between the two intensities. TGF-β mRNA transcription did not show any difference between the unexposed and exposed samples. In the presence of a concomitant infection of MDMs with MTB, the MF effect was rather flattened probably because the infection with a pathogen provides a stronger stimulus for an MDM response. In our case, IL-6 and IL-10 mRNA transcription was higher in MDMs exposed to the MF of 670 mT, when compared to that occurring either in MDMs exposed to the MF of 91 mT or in unexposed MDMs.

(d) Transposition of bacterial elements of insertion does not seem to be influenced. This study[56] considered the effect of two MFs (91 and 670 mT DC) on transposition of the IS-6110 and IS-MYC elements specific for MTB. Transposition was analyzed under various conditions: using different media for MTB cultivation; comparing the laboratory MTB strain H37Rv with the clinical MTB isolate CMT97; estimating differences between MTBs grown inside unexposed and exposed MDMs. It emerged that transposition of the IS-6110 element, although varying in the different MTBs, was not influenced by the media. In fact, there was no difference in the fingerprinting pattern of the bacillus grown *in vitro* and the one grown *in vivo*. The DC MFs did not change transposition, since they did not cause variation in the number or position of the electrophoretic bands. The fingerprinting pattern of the IS-MYC element revealed, however, some differences when one compared the laboratory MTB strain H37Rv, the clinical MTB isolate CMT97 and the MTB strain H37Rv.P (used for sequencing the full MTB genome). Going from a replication *in vitro* to a replication *in vivo*, the number of electrophoretic bands, characterizing the laboratory strain, tended to decrease, although this decrease was not influenced by the MFs. Probably, this was due to the intracellular replication of the bacillus.

3.2 Bioeffects of low-frequency/low-intensity magnetic fields

(a) Cell cycle kinetics is accelerated. This work[4,57] was undertaken to compare the behaviour of Friend erythroleukemia (FL) cells in a solenoid (SLD), where the MF was 70 μT at 50 Hz (plus 45 μT DC of the Earth), with that of the same cells in a MSR, where the MF was attenuated to 20 nT DC and 2.5 pT AC. The control laboratory MF corresponded to 45 μT DC and a stray 50 Hz field below 0.2 μT. The culture growth cycle (CGC) of cells maintained inside the SLD was slightly accelerated when compared with that of cells maintained outside the SLD. This stimulation probably depended on the sensitivity of the cell cycle to a MF, because, inside the SLD, the percentage of G_1 cells slightly increased during CGC, whereas that of S cells slightly decreased. Acceleration of growth was detected soon after exposure of the cultures to the SLD field. The fact that no further growth occurred, even when the action of the field was protracted, accounts for adaptation whereas the experiments with DC MFs, reported above, seemed to exclude adaptation altogether. The SLD field also caused a small increase of cell survival without influencing cell volume. By contrast, the CGC of cells maintained inside the MSR was slightly decelerated when compared with that of cells maintained outside the room (Fig. 4). The absence of any field inside the MSR caused a small increase of cell volume, whereas, during the CGC, the percentage of G_1 cells decreased, and that of S cells increased. The majority of these events did not change in cells induced to differentiate hemoglobin (Hb) through dimethylsulfoxide (DMSO).

(b) Membrane fluidity, cell survival and programmed cell death are influenced. The generalized polarization (GP) function of the fluorescent probe 2-dimethylamino-6-lauroylnaphthalene (LAURDAN) has been used to evaluate the lipid dynamics in FL cell membranes.[12,58] The values of this function varied during CGC, showing decreased lipid dynamics 24–48 h from cell seeding. When the cycle occurred in a SLD producing a MF of 70 μT at 50 Hz in addition to the 45 μT DC of the Earth (short-term 4-day exposure), the membrane lipid dynamics during the same time-period decreased by about 10%. After long-term (184 days) or extremely long-term (395 days) exposure of the cells to the MF, little additional variation in the membrane lipid dynamics was observed (Fig. 5), again accounting for adaptation. A variation of membrane lipid dynamics was also observed due to *in vitro* cell differentiation. Nevertheless, the exposure of both undifferentiating and DMSO-differentiating cells to a highly attenuated MF in a MSR (20 nT DC plus 2.5 pT AC) did not induce any modification of membrane lipid dynamics. Another important observation showed that both non-static (70 μT AC in addition to 45 μT DC of Earth) and static (0.15–66 mT) MFs, through a small decrease of the rate of spontaneous cell death, slightly increased cell survival: particularly with static MFs, this appeared to be due to an inhibition of apoptosis.[39]

(c) An evolutionary adaptation of the membranal state occurs. During the CGC of FL cells, proliferation, survival and percentage of cells traversing the G_1 and S phases followed divergent patterns in the presence or absence of the MFs

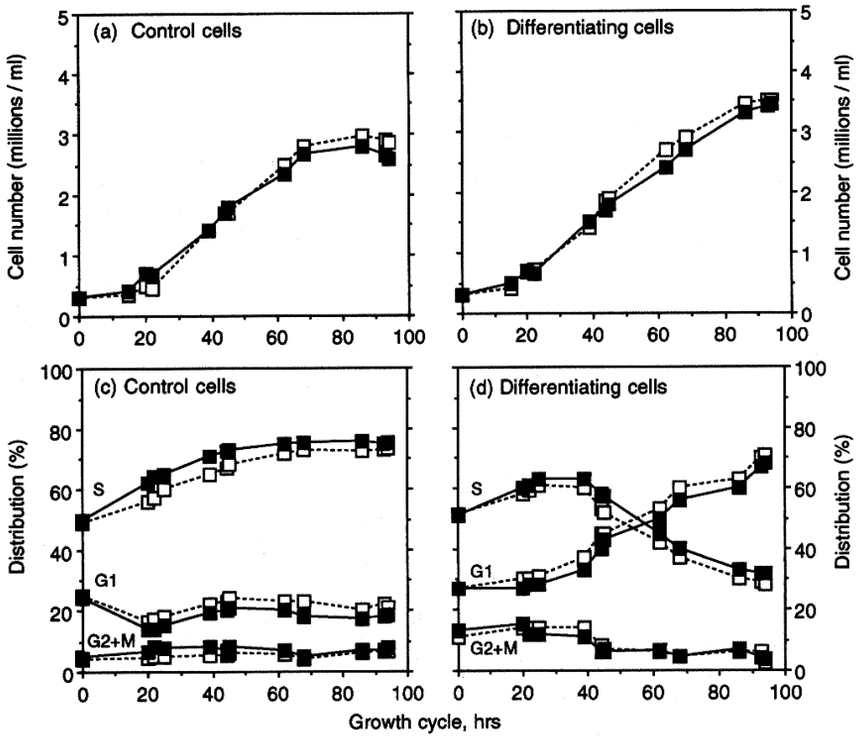

Fig. 4 *Influence of magnetic-field deprivation on the Friend erythroleukemia (FL) culture growth cycle (CGC) and cell-cycle kinetics.* (a, b) Comparison of the CGCs of undifferentiating and differentiating cultures that were followed for 4 days. (c, d) Comparison of the corresponding percentage of cells traversing the phases G_1, S and G_2 + M. The open squares show the FL cultures maintained outside the magnetically shielded room (MSR), *i.e.* under 45 μT DC of Earth and a stray 50 Hz field below 0.2 μT; the closed squares show the FL cultures maintained inside the MSR, *i.e.* under 20 nT DC of Earth and 2.5 pT AC. The values represent the mean of three experiments. From 50 to 100 h, the Student's paired *t* tests showed *P* values of 0.02. Reprinted from ref. 4 with permission from John Wiley. © 1997.

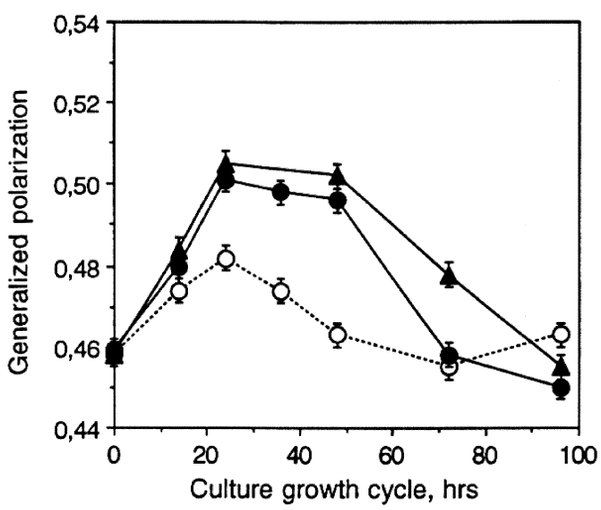

Fig. 5 *Variation of the membrane molecular lipid dynamics revealed by the LAURDAN GP values in Friend erythroleukemia (FL) cells as a function of the short- and long-term exposure to the magnetic field (MF) of a solenoid (SLD).* Three groups of cells were followed in parallel in the course of 184 days: the first group, the control group, was maintained for 184 days always outside the SLD (open circles); the second, serving for short-term exposure to 70 μT at 50 Hz (plus 45 μT DC of Earth), was maintained for 180 days outside the SLD and then for 4 days inside it (closed triangles); the third, serving for long-term exposure to 70 μT at 50 Hz (plus 45 μT DC of Earth), was maintained for 184 days inside the SLD (closed circles). At the indicated times through the culture growth cycle, during the last 4 of the 184 days of cultivation, FL cells were collected for fluorescence measurement. The values represent the mean of four experiments. For control *vs.* MF-irradiated FL cells, the Student's paired *t* test showed $P = 0.04$. Reprinted from ref. 12 with permission from John Wiley. © 1998.

compared with the Earth's normal field. Cell proliferation, as already mentioned (Fig. 4), was slightly accelerated in the SLD and slightly decelerated in the MSR.[4] In the case of cell membrane fluidity, this kind of "symmetry" did not appear.[12,58] The values of the GP function, used to evaluate the lipid dynamics in the FL cell membrane, varied during the CGC, showing decreased lipid dynamics 24–48 h from cell seeding. When the cycle occurred in a SLD producing a MF of 70 μT at 50 Hz in addition to the 45 μT DC of the Earth (short-term 4-day exposure), the membrane lipid dynamics during the same time-period decreased by about 10%. After long-term (184 days) or extremely long-term (396 days) exposure of the cells to the MF, little additional variation in the membrane lipid molecular dynamics was observed (Fig. 5). This fact was in favour of the occurrence of an adaptation phenomenon. Then, is there a lack of adaptation to relatively higher DC MFs *vs.* the presence of adaptation to lower AC MFs?

(d) DNA stability and gene expression are moderately altered. Although with contradictory observations, the literature suggested some influence of MF on gene expression. However, studies[59,60] shed some light, on the one hand, on the MF-dependence of the DNA, RNA and protein biosynthetic rates and, on the other, on the MF-dependent efficiency of expression of the genes for α and β chains of Hb in FL cells induced to differentiate this protein through DMSO. During a whole CGC, lasting 4 days, the cells were either irradiated with 70 μT AC at 50 Hz plus 45 μT DC in a SLD or kept in the absence of any MF in a MSR. It emerged that not only the bulk duplication and repair of the genome, the bulk transcription of pre-mRNA, rRNA and tRNA and the bulk translation remained constant in irradiated or MF-deprived cells,[59] but also that the expression of a single quaternary protein like Hb did not change as a function of MF variation.[60] In turn, the differentiating state induced by DMSO did not add any sensitivity to replication, transcription and translation to the MFs.[59] Thus, while the machinery responsible for cell cycle kinetics and cell proliferation was slightly sensitive to MF variation, as shown

earlier, both the double helix and gene expression were rather stable with respect to such variation.

(e) Metamorphosis results accelerated. Earlier studies concerned the biological effect of a continuous exposure of embryos and young chickens to AC MFs emitted by VDUs or other sources.[61] Following these studies, in the conditions of SLD irradiation,[57] a further work showed the influence of a 2 mT MF at 50 Hz on *Xenopus laevis* tadpoles.[62] The analysis regarded the development of metamorphosis in the course of 65 days, *i.e.* from the moment of egg fertilization up to the stage when the tadpole tail is readsorbed. Such a development was successful for 85% of individuals in the unirradiated tadpole population and for 45% of individuals in the irradiated tadpole population. During exposure, there was a notable reduction of the rate of metamorphosis of the tadpoles, causing a striking 6-day delay with respect to the rate of metamorphosis occurring in the unirradiated tadpole population (Fig. 6). Thus, the *Xenopus laevis* population proved to function as a very sensitive biological indicator of the effect of weak AC MFs. Its interest emerged not only from the belief that the MF's action should be necessarily associated with death, but also from the fact that it induced a change in a crucial ontogenetic function.

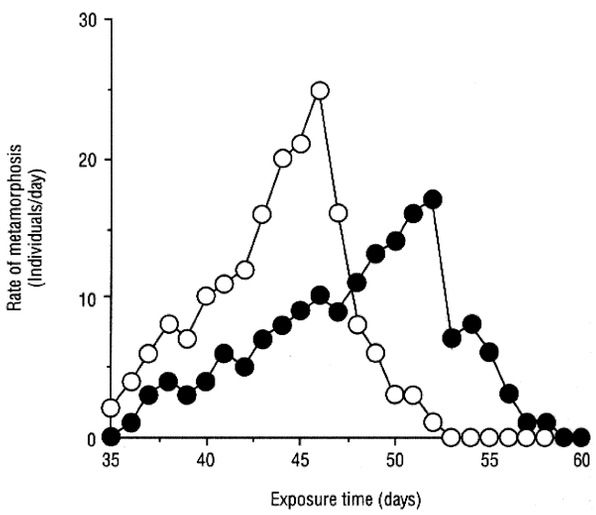

Fig. 6 *Magnetic-field dependence of the rate of the daily tadpole metamorphosis.* As daily rate of metamorphosis, a number of individuals undergoing metamorphosis in 24 h was taken. The open circles show the control population with unirradiated individuals maintained outside the solenoid (SLD); the closed circles show the experimental population with individuals maintained inside the SLD. The points represent the mean of three determinations. Reprinted from ref. 62 with permission from *Int. J. Radiat. Med.* © 2000.

4 Is the question of the mechanisms of magnetic-field bioeffects still open?

Following the well known important contributions of several laboratories, which attracted the attention of the scientific community on the possible involvement in MF bioeffects of resonance at the cyclotron frequency under the combined influence of DC and AC MFs,[63–66] Blanchard and Blackman[67] tried to enrich the magnetobiology with a theory based on an ion parametric resonance model. However, despite the list of MF bioeffects, reported above, the research is still unable to provide a proper explaination, from a unifying physico-chemical point of view. For this reason, it is convenient to reconsider, in detail, other contributions which could help to make the efforts more circumstanciated in allowing a comprehensive theory of the MF bioeffects.

It is known that many years ago it was suggested that the rise of a ponderomotive force, caused in a biostructure by non-uniform static MFs, could be the basis of the magnetotropism of plants, where "paramagnetic cells", which represent a minor biomass, would be forced towards a point of maximal field, while "diamagnetic cells", which represent a major biomass, would be forced towards the opposite direction. Studying the interaction of the neuromembrane ionic channels with the spreading action potential, Volobuev *et al.*[68] proposed that "external" MFs interact with hypothetical "internal" MFs created by the ionic channels and nodes of Ranvier. This, in their opinion, could explain the decrease observed in the speed of propagation of the action potentials in static MFs. Agulova *et al.*,[69] in a study concerning the behaviour of non-equilibrium systems in low-frequency/low-intensity MFs, distinguished the direct perception of the MF by biomolecular structures from the signaling role of the MF through the central nervous system. Also, they noted an influence of the GMF variations on the precipitation and agglutination reactions in acqueous solutions and on the Piccardi test.[70] Kislovsky,[71] in an attempt to explain the biovariations caused by GMF perturbations, suggested the occurrence of dissipative clathrate structures in the aqueous medium and on its borders in non-equilibrium conditions. The length of conservation of such structures was considered as an example of near-critical phenomena that are close to the temperature of phase transitions of the second kind: liquid–liquid. In this case, the phase transitions would be at the lower critical temperatures of stratification of the aqueous solutions, when the elements of short-range order inherent in clathrate structures are abolished. Zhvirblis,[72] being interested in the influence of solar activity on the biosphere, paid attention to the correlation of some medico-biological tests with the index of GMF perturbation, in which sector boundaries of the interplanetary MF, associated with the solar wind, were taken as zero. This study revealed that the direction of moving along the phase trajectory contour changed when the Earth crossed the sector boundary. Vladimirsky and Temurjants,[17,73] on the basis of the fact that the Piccardi test was sensitive to the polarity of a radial component of the interplanetary MF, supposed that this sensitivity could be due to the geomagnetic micropulsations in the range from 0.007 to 0.1 Hz. Then, they presented a list of crucial principles concerning the influence of weak ("non-thermal") and ultraweak ("natural") AC MFs on inorganic and biological systems. In contrast with the opinion of Binhi,[74] who considered the nuclear magnetic resonance as impossible in biological magnetoreception, this list re-encouraged the idea of a possible role of nuclear magnetic resonance in the GMF variations. Hence, Lednev *et al.*[75] suggested that the calcium-binding proteins constitute the location of primary action of combined MFs. In their opinion, these cause a splitting of energetic levels of Ca^{2+} oscillation in the protein (Zeeman effect), while the width of the splitting is equivalent to the cyclotron frequency of calcium and the applied DC MF. On this basis, parametric resonance was proposed as a mechanism for increasing ionic energy. Further, the same authors proposed that DC, AC and combined DC + AC MFs can change the polarization degree, while the biological effects of the MFs can be induced by the same polarization degree of the Ca^{2+} oscillation. Binhi *et al.*[44,76,77] studied the mechanism of the magnetosensitive ion binding by proteins, under the influence of external AC MFs, in the framework of an idealized quantum model. From this analysis, it emerged that the dissociation probability of an ion–protein complex depends on frequency and amplitude. This was shown to be a consequence of the interference of angular modes of the ion wave function. In addition, some attention was drawn on the problem of the dielectric response of some biological tissues[78] together with the orientation of ions, molecules and cells in a DC MF.[41] In any case, Zhadin[79] investigated the thermal oscillations of Ca^{2+} in a calcium-binding protein, under the influence of combined DC + AC MFs. From their study it emerged that the DC MF causes the Larmor precession of ion oscillations. Since the cyclotron frequency is twice as large as the

Larmor frequency, this led to the suggestion that the phenomenon could serve as a basis for increasing the kinetic energy of Ca^{2+} due to parametric resonance. In the framework of this suggestion, an AC electric field perpendicular to a DC MF (or an AC MF parallel to a DC MF) was expected to increase the ionic energy, while a maximal effect was expected at the cyclotron frequency of an AC MF. Zhadin[79] tried to solve equations of motion of the ion in a macromolecule under the influence of the MFs, considering the damping effects and the influence of particles surrounding this ion. So, in contrast to Lednev *et al.*[75] and Blanchard and Blackman,[67] he showed that the possibility of parametric resonance is not credible for the AC MF frequencies, being many orders of magnitude lower than the natural frequency of an ion in a macromolecule. Indeed, resonance-like phenomena were found to be induced by the influence of a DC MF alone and by a combined DC and AC (ELF or modulated high frequency) MFs without any parametric resonance. Zhadin[79] estimated that the MFs may cause changes in energy of the ionic thermal motion which, in turn, would be sufficient to trigger variations in the conformational state of a macromolecule.

Therefore, the state of the art suggests that the mechanism or the mechanisms which are at the basis of the interactions of the MFs with the biostructures and biosystems represent up to now an open question.[80] In this respect, it was suggested that the approach towards the non-equilibrium thermodynamics of the systems under EM waves was of primary importance.[81] It still remains to be explained why pulsed electromagnetic fields can be more active biologically than continuous ones.[82] This assumes interest in connection with the fact that an alternative basic mechanism of MF bioeffects could be the forced-vibration of all the free ions in proximity of a cell plasma membrane, caused by an external AC field. The model, proposed by Del Moral *et al.*,[45] which explains the bioelectric activity of single unit neurons under DC and ELF MFs, based on the strong anisotropy of diamagnetic susceptibility of membrane phospholipids acting cooperatively (superdiamagnetism), would also seem to deserve particular attention.

5 Concluding remarks

In recent years, the findings concerning the MF-dependence of the FL cell and nuclear volumes[4,83] were supported by those regarding the MF-dependence of the electrokinetic properties of nuclei in human buccal epithelial cells.[84] Other studies of general character were devoted to the analysis of the so-called "electromagnetic man" *vs.* the magnetic resonance tomography[85] and of the effect of MFs on synchronization of mammalian cell permeabilization *vs.* the MF-dependence of gene delivery.[86] From a methodological point of view, attempts were made to employ programmmed chronopotentiometry as a tool to study electroporation and resealing of pores in bilayer lipid membranes,[87] while an EU-wide initiative to characterize the biological effects of EMF on human and mouse cell lines by gene expression profiling was taken.[88]

There exist a consensus about the effect of MFs on cell cycle kinetics. In fact, the changes of FL cell cycle kinetics, following the addition or deprivation of MFs,[4] were consistent with the alteration of the onset of the S-phase observed after a 50 Hz magnetic field exposure of normal human fibroblasts[89] and with variation of cell cycle kinetics and colony forming ability after exposure of budding yeast to 50 Hz magnetic radiation.[90] This was shown to influence, in turn, the change in growth and differentiation of PC6 cells exposed to pulsed EMFs.[91]

Although the question about the influence of MFs on the development of programmed cell death remains in many respects open, especially in terms of the correlation of ion homeostasis and apoptosis,[92] investigations strikingly suggested that the MF causes an inhibition of apoptosis.[39] In fact, while Annexin V was shown to counteract apoptosis by inducing Ca^{2+} influx in human lymphocytic T cells,[93] it was demonstrated that by using the patch clamp technique there is an effect of MF exposure on the calcium channel currents.[94] It was suggested that membrane dielectric changes may indicate induced apoptosis in HL-60 cells more sensitively than surface phosphatidylserine expression or DNA fragmentation.[95] In any case, there was no question about the influence of the MFs on apoptosis: a transient suppression of X-ray-induced apoptosis by exposure to power frequency MFs in MCF-7 cells was evidenced,[96] a change in the rate of DNA repair due to apoptosis mediated by MF exposure was detected,[97] and an exposure to 50 Hz magnetic fields of a neuroblastoma cell line definitely caused changes in the apoptotic rate.[98]

Initially, the alarm of possible harmful effects by MFs on human health encountered scepticism not only in the telecommunications industry, but also in the scientific community.[52] On the one hand, it was observed that given AC MFs proved to be completely harmless. For instance, it was described that 50 Hz MFs do not exert an influence on the progression of acute myeloid leukaemia in rats,[99] that sinusoidal 50 Hz magnetic fields do not affect the structural morphology and proliferation of human cells *in vitro*,[100] and that elliptically polarized MFs do not alter immediate early response gene expression levels in human glioblastoma cells.[101] On the other hand, MFs proved to exert even a positive influence on certain functions, as in the case showing that calcium protects differentiating neuroblastoma cells during 50 Hz EM radiation[102] or in the case suggesting that magnets could be effective in pain control.[103] However, during the last two years, the amount of information that has accumulated suggests that in the majority of the cases investigated, both DC and AC MFs are harmful.

Let us first look at the harmful DC bioeffects, considering that they were essentially manifested at the tissutal and cellular levels. An *in vitro* human blood aging was observed,[104] while the cell proliferation–cell death balance in renal cell cultures after exposure to a DC MF was shown.[105] A melanophore aggregation was described,[106] while there was an increased antibiotic resistance of *E. Coli* exposed to DC MFs.[107] Strong constant MFs affected the muscle tension development in bull frog neuromuscular preparations.[108] There was an induction of primary root curvature in radish seedlings.[109] Zero-frequency uniform MFs interfered with amoebe life.[110] There was an effect of 0.25 T DC MFs on microcirculation in rabbits.[111] The convergence of artificial DC MFs and GMF produced a harmful impact on cardiovascular regulation,[112] while there was an effect of non-uniform DC MFs on the rate of myosin phosphorylation.[113]

Here is a list of the harmful AC bioeffects, since they have been studied at various levels. At the morphological level, developmental changes in *Drosophila melanogaster* following exposure to alternating EMFs were observed,[114] while effects of permanent MF on wing size parameters of the same insect were found.[115] At the cellular level, there were some effects of extremely low frequency EMFs on mammalian follicle development.[116] ELF EMFs as well as heat shock proved to increase microvesicle motility in astrocytes.[117] There was an osmolality MF-dependence of erythrocyte sedimentation and aggregation.[118] At the macromolecular level, electric relaxation processes were observed in lipid-bilayers after exposure to weak magnetic pulses.[119] In the framework of studies on genotoxicity of radiofrequency signals, the occurrence of DNA damage in cultured human blood cells was seen,[120] while there were clear cytogenetic effects of 900 MHz (GSM) microwaves on human lymphocytes.[121] Also, there was an increase in X-ray-induced gene mutations by exposure to AC MFs in NF-kappa B-inhibited cells and an increase in hypoxanthine–guanine phosphoribosyl transferase gene mutations by exposure to an electric field.[122,123] ELF-pulsed MFs modulated opioid peptide gene expression in myocardial cells,[124] while an effect of ultra-

violet B radiation and 100 Hz EMFs on DNA synthesis of Jurkat cells was detected.[125]

As for protein macromolecules, there were effects of high ELF magnetic fields on DNA and RNA polymerases *in vitro* and on a cell-free mismatch repair.[126] At the molecular level, effects of exposure to weak radiofrequency fields on acethylcholine release in hippocampus of freely moving rats were revealed.[127] Effects of 60 Hz MF on the immune system in Wistar rats was described.[128] Moreover, at the level of the ionic events, factors confounding cytosolic calcium measurements in Jurkat cells during exposure to ELF MFs were revealed,[129] while there was a calcium spiking in ROS 17/2.8 cells exposed to ELF EMF.[130]

The hypothesis suggesting that the rescue of damaged cells may be the mechanism explaining why MFs, which are not mutagenic *per se*, are often able to increase mutation and tumor frequencies,[39] is being considered in a number of laboratories. As a matter of fact, it appears that there is a general consensus on MFs which may be indeed correlated with cancer.[131] Effects of a 50 Hz MF exposure were also observed on tumor experimental models.[132] The correlation of the MF action with cancer must also be added to the general concern about the harmful effect of MFs on human health.

Abbreviations

MF, magnetic field; GMF, geomagnetic field; EMF, electromagnetic field; MS, magnetic storm; ELF, extremely low frequency; DC, direct current; AC, alternating current; SLD, solenoid; MSR, magnetically shielded room; GP, generalized polarization; MDM, monocyte-derived macrophages; PBM, peripheral blood mononuclear; FL, Friend erythroleukemia; CGC, culture growth cycle; MTB, *Mycobacterium tuberculosis*; Hb, hemoglobin; DMSO, dimethyl sulfoxide

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