MICROWAVE BIOEFFECTS. CURRENT STATUS AND CONCEPTS

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ABSTRACT. The information on microwave bioeffects /MWBE/ is derived from animal experimentation, model studies and epidemiological research on the health status of persons exposed occupationally to MW. The analysis of MWBE requires the consideration of a chain of events: biophysical mechanisms - the primary interaction, and physiological mechanisms - immediate local and generalized effects, and late effects. Animal experiments may be divided into acute high dose and chronic low dose exposures. High dose effects can be explained in terms of the field theory, non-uniform deep body heating and its physiological consequences. Such considerations are insufficient for the explanation of chronic exposure effects, particularly frequency and/or modulation dependent effects in the nervous and the hematopoietic systems. Quantum mechanical considerations constitute a promising approach. These statements are substantiated by the description of experimental systems and obtained results. Human epidemiological studies are far less informative because of their scarcity and insufficient quantitation of exposure conditions; the available data are reviewed. Practical implications for establishing permissible exposure levels and safety rules, as well as research needs are indicated.

INTRODUCTION. Lack of space does not allow a detailed review of the voluminous literature available. The interested reader is referred to the almost complete bibliography of the subject prepared by Glaser /1/, symposia proceedings /2-6/ and monographs /7-14/. The aim of this paper is to point out basic concepts and approaches, as well as to present well established facts and to indicate areas needing further research.

DEFINITION AND ANALYSIS OF MWBE. A functioning biological object /cell, organ, plant, animal/ is a highly complex self-regulating system, endowed with the ability to adapt to changes in the environment and to compensate for stresses imposed by it. The equilibrium of a living system is maintained within the normal-i.e. the physiological range by many inter-related feed-back mechanisms. Because of that a disturbance within the system usually triggers a set of reactions and the end result, detectable by biomedical methods, may be

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Conference Proceedings



pp. 348-357 - 5- Glarer

Monday: 1 to Thursday 4 September 1975

Congress Centrum, Hamburg, Germany

Supported by



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IEEE Group of Electron Devices

International Microwave Power Institute

German National Committee of URSI

In association with

MICROWAVE EXHIBITIONS AND PUBLISHERS LTD.

Published by Microwave Exhibitions and Publishers Ltd.

Temple House, 34-36 High Street, Sevenoaks, Kent TN13 1JG, England

Telephone: 0732-59533/4

Printed in Great Britain by Megoron Press Ltd., Bournemouth.

many steps removed from the initial event. This happens particularly in the case of bioeffects induced by radiant energy /16/. Therefore the understanding of MWBE requires an orderly, step-wise analysis. To facilitate this it is convenient to introduce a somewhat arbitrary distinction between the primary interaction of MW with the living system and the induced bioeffects. The mechanisms of radiant energy absorption and direct interference with biophysical, biochemical and bioelectrical mechanisms and phenomena in the living system, examined by biophysical methods and considered in terms of biophysics may be defined as the primary interaction.

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All changes in function and structure /above the molecular level i.e. starting at the level of subcellular structures/ resulting from the primary interaction detectable by biomedical methods and considered in terms of biology may be termed biological effects. Because of the feed-back mechanisms the early /immediate/ bioeffects arising at the site of the primary interaction and because of it may induce further changes i.e. early secondary /indirect/ effects. In some instances a considerable time may elapse between the primary interaction and the appearance of detectable MWBE. In such a case these may be termed delayed or late effects.

It should be also stressed that adaptative reactions induced by MW exposure may lead to measurable MWBE, which still remain within the range of normal i.e. physiological range of compensation. That means that an effect is not necessarily a hazard. On the contrary certain MWBE may improve the efficiency of certain physiological mechanism and are used for therapeutic purposes in medicine. Certain MWBE may be detrimental to the efficiency of living systems, and in this case may be termed MW health hazards.

It should be pointed out that frequent activation of adaptative mechanisms may lead to their exhaustion and to the classical sequence of events - stress, adaptation, fatigue. In view of that the effects of single and repeated exposures should be considered separately, even if each exposure takes place under exactly the same conditions. In consequence tolerance levels should be established also separately for single, short-term or acute /AE/, single prolonged or chronic /CE/ and repeated exposures /RE/. It should be noted that the current state of the biomedical knowledge does not allow to make reliable predictions, particularly in the case of CE and RE, therefore only empirically verified tolerance levels are acceptable.

THE PRIMARY INTERACTION. For many years the primary interaction of MW with living systems was considered almost exclusively in terms of the electromagnetic field theory /17, 18/ leading to the conclusion that at least in the MW range only conversion of the absorbed energy into kinetic energy of molecules i.e. microwave thermal effects are possible. This led in turn to an increasing discrepancy between the empirical biomedical observations and the theoretical explanations available /see 7, 8, 13/. Interesting concepts concerning direct interference with bioelectrical phenomena /11/ or the role of electromagnetics fields in transmission of biological information /14/ were advanced. These hypotheses need, however, further experimental verification. Only recently it was realized that quantum mechanical approaches /19, 20, 21/ offer possibilities of explanation of MW primary interaction with living systems, molecular and inter-molecular level complex subcellular structures such as membranes being possible physical substrates for unexplained functional MWBE /22/. Much further work remains still to be done and Illinger's statement /19/ that ". . . a complete predictive theory for the perturbation of biodynamical systems by microwave and millimeter wave EM radiation car not be said to exist . . . " may usefully be recalled at this place. It should be added also that MW and radiofrequency radiations can be used as a tool in the exploration of biophysics of living systems /23/ and many promising experimental models for the investigation of unexplained MWBE can be devised /24/.

iHERMAL MWBE. Therulal balance characteristics of animals exposed to MW were investigated early /25, 26/ and the results extrapolated to man to be used as a criterium for safe exposure limits in the USA /see 2/. The propagation and absorbtion of MW within the biocoject was approximated on the basis or planar, or at the best spherical, multilayred models and the blood circulation was considered as an efficient system for distribution of the generated heat uniformly throughout the body /17, 18/. In consequence thermal MW effects in animals were considered "volume heating", a point of view unacceptable at present. Guy and his associates /27, 28/ developed elegant thermographic models and demonstrated clearly that the absorption of MW energy and the resulting temperature increases lead to non uniform decp bodv heating. In physiological terms this means that direct, and even more secondary, MWBE depend on the internal distribution of the absorbed energy dose and local thermal stimulation of different organs. Local thermal stimulation of the brain and/or of the spinal cord /27, 30/ affects many body functions and may be responsible for behavioral changes. As it was shown that at several MW frequencies energy absorption may be "focussed" around the center of the head /28/ and thermal stimulation of the midbrain section and of the hypophysics is a practical possibility during whole body exposures at about 1 mW/cm² incident power density of rabbits, cats, monkeys and men. The secretory activity of the hypophysis, an endocrine gland, regulates the activity of the remaining ones, such as adrenals and the thyroid. These in turn regulate the metabolic activity of many organs and tissues. Starting from a local temperature increase in the hypophysis a sequential chain of events is initiated:

- elevation of temperature to $38-40^{\circ}$ C increases the metabolic activity of the **cells i.a.** rendering them more susceptible to hypoxia /local direct effects/, - compensatory thermoregulatory mechanisms lead to an increase in blood flow /cooling/, which in turn also affects cellular metabolism i.a. the rate of exchange of metabolites between rissue cells and circulating blood /local secondary effects/,

- cell secretions and metabolites liberated into the blood stream influence the function of other cells and organs, which in turn may influence still other parts of the body /generalized secondary effects/.

Time-honored physiological methods exist for the investigation step-by-step of such chains of events initiated by environmental factors or drugs. It is to be regretted that in spite of the many fascinating possibilities /24/ investigations of MWBE using such methods remain scarce. Biochemical and neuroendocrine effects particularly need reinvestigation and reassesement /32/. The authors feel that in certain instances electronic engineers, physicists, biophysicists even, do not realize fully how many intermediate steps exist between the

primary interaction and the observed biological end effect, and how many feed-back mechanisms contribute to it.

Thermal MWBE allow to demonstrate another particular property of living systems. Repeated exposures of dogs to 1285 MHz, 100 mW/cm² 5 days a week during 4 weeks led to diminishing rectal temperature increases on termination of the exposure each day within successive weeks /33/. After exposure on the first day of a successive week, i.e. after an interval of two days without irradiation, the temperature increase was higher than on the last day of the preceding week. The thermal reaction during the 4th week was, however, insignificant when compared with the reaction during the 1st week. Confirmatory evidence of adaptation to MW demonstrable by diminishing temperature increases after successive exposures is abundant /see 7 and 13/. Circulatory thermolegulatory reasons also change on successive exposures, particularly the reactions of skin blood v(sels /34/, A series of experimental investigations carried out by Subbota et al./see 13/ demonstrated that animals adapted to MWRE are less resistant to other environmental factors. On the other hand the status of animals adapted to other factors /eg. hot environment/ or recovering from X-ray injury rapidly deteriorates after a single low dose MW exposure. According to Subbota the interplay of adaptation and desadaptive stress may account for the diversity and changeability of reactions to MW exposures.

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In short lethal levels of thermal effects during AE and CE /whole body/ are fairly well established for many animal species /7, 8, 13, 14/. These data may be extrapolated to safe levels for single exposures taking into account the internal distribution of the absorbed energy dose and possible physiologic consequences. The effects of RE depend on many factors: spacing in time, probably also time of the day, duration, adaptation and desadaptation /stress-fatigue/ phenomena etc. Delayed secondary effects are difficult to predict. Further research is needed, the present empirical data may serve only as rough guidelines.

Microwave hyperthermia finds more and more biomedical applications. One of the more promising research problems is the use in cancer therapy /35/. Local elevation of temperature to about 43 °C renders the cells susceptible to many factors i.a. X-rays and possibly cytotoxic drugs /36/. MW hyperthermia combined with therapeutic methods already in use may offer new possibilities for combating cancer. This problem was discussed in detail at a recent symposium organized by the National Cancer Institute, the proceedings will be published shortly as a supplement to Radiology.

EFFECTS ON THE EYE. The cataractogenic effects of AE at 100-150 mW/cm incident power density are well established in experimental animals. Because of lack of blood vessels the cristalline lens of the eye is easily overheated, the capsular epithelial cells damaged and the proteins of the lens undergo denaturation /37/. The lens becomes nontransparent with subsequent . development of a subcapsular cataract and loss of vision. MW cataracts are characterized by a variable latency period of a few days up to two weeks between the termination of exposure and the appearance of changes in the lens /38/. Most authors are inclined to relate MW cataracts to secondary effects of local temperature increase /see 7, 13/. Time - power tresholds for the induction of experimental MW cataracts, particularly in the case of

RE, are controversial /39/. Difficulties in relating incident to absorbed energy in various exposure conditions contribute much to the controversy. About 50 cases of MW occupational cataracts were described /40/ but the causal relationship between MW exposure and the subsequent cataract is questioned /39/. No less controversial is the problem of lenticular opacities among microwave workers and the causal relationship between MW exposure and incidence of opacities. More recent publications seem to indicate that workers observing safe exposure limits recommended in the USA /see 5/ and the more conservative Polish or USSR rules /see 7, 13, 15/ are not subject to eye hazards. Retinal lesions were also described in microwave workers /41/ the possible mechanisms are obscure.

EFFECTS ON THE NERVOUS SYSTEM. In experimental animals CE, RE lead to disturbances in conditioned reflexes and to behavioral changes at incident power densities of 0.1 - 1 mW/cm². RE of a few hours duration continued for several mode induce metabolic changes and disturbances in the bioelectric activity. These facts are well documented and reproducible papers concerning these effects number several hundreds /see 3, 6, 7, 8, 9, 13, 14/. The mechanisms responsible are still unclear, part of the nervous system MWBE may be the secondary effects of temperature increase. A large part, particularly RE effects, can not be explained that easily. The functional consequences for the efficiency of the irradiated animal are not always clear, the hazard inherent in behavioral changes is a matter of arbitrary evaluation.

Still less clear is the mechanism of changed susceptibility after RE to drugs acting on the nervous system /42/, particularly convulsant drugs /42, 43/. This phenomenon has practical implications in the cases, where medication of MW workers is needed. On the other hand as the action of many drugs is understood in detail, the phenomenon may serve for the clarification of MWBE mechanisms in Ithe nervous system /24/. It should be also stressed that simultaneous use of alternating electric currents and drugs found an application in electro-anesthesia and electrosleep. These phenomena are obtainable at frequencies well below the MW range, but indicate strongly a frequency dependence of nervous system effects. This dependence was clearly demonstrated by experiments of Adey and his associates /see 44, 45, 46/. These authors obtained disturbances in bioelectric function of the brain by exposure to 147 MHz radiation, amplitude modulated at 9 - 16 Hz, accompanied by calcium efflux from the brain. These effects can not be obtained if the frequency of amplitude modulation is changed to below 9 Hz or to 20 - 35 Hz. Further research is needed, but it seems highly probable that these effects depend from a direct interaction of electro-magnetic fields with the cellular membrane. This hypothesis, pertaining specifically to nervous cell membranes, may be of a more general impact. Cells in tissue culture, in which ionic transport through the membrane was impaired by digitonin or the cell membrane structure was damaged by bacterial toxins /sphingomyelinase or phospholipase C/ are more susceptible to MW hyperthermia, than to equal hyperthermia obtained by placing in a hot chamber /47/.

The central nervous system seems to be a convenient model for the study of frequency and/or modulation dependent effects. Information on these effects

is urgently meeded for the determination of safe exposure levels and rules. The possibility that particularly hazardous frequencies and/or modulations exist can not be dismissed lightly. More over any effects in a system of such prime importance in the functio al efficiency as the nervous system should be carefully investigated.

EFFECTS ON THE HEMATOPOIETIC SYSTEM. The importance of the observations reported in the literature lies in that, that similary as nervous system MWBE, effects obtained in the hematopoietic system are dependent on modulation.

Continuous or pulse modulated MW exposures at the same wavelength and mean power density affect differently iron metabolism hemoglobin synthecis and red cell production /48/. Whole body exposure leads to stimulation of lymphocyte production in the number of mitoses in lymph nodes. Continuous or pelsed MW of the same power density /mean/ and the same wavelength having different effects /49/. Lymphocytes undergo stimulation and what is called blastoid transformation both in vitro /50/ and in vivo /51/ following MW irradiation. The latter phenomenon may be possibly used in biological MW dosimetry /51/. RE change the immulogical reactivity of animals. It follows that easily demonstrable and easily quantified effects on the lymhocyte and the lymphocytic system exist. This may be used for developing convenient models for further studies on MWBE at the cellular level.

MW exposure at different times of the day change the circadian rhythm of bone marrow cell mitoses /52/. It should be stressed that cells belonging to various hermatopoietic cell lines react differently. This may serve to stress the importance of taking into account the physiologic properties of cells, tissues and organs, when investigating MWBE.

GENETIC EFFECTS AND EFFECTS ON DEVELOPMENT. Chromosome aberrations induced by MW exposures in cells in tissue culture /53/ and in bone marrow cells in vivo, as well as mitotic aberrations were described by several authors /see 2, 6, 7/. Genetic effects in Drosophila /53/ were also reported. Changes in the development of chick embroys and mammalian foetuses were also obtained by MW exposure /see 2, 3, 7/. Several observations may be interpreted as secondary effect of MW induced temperature increases. Because of the extreme practical importance the problem of possible genetic effects and effects on development should be thoroughly investigated, present data being insufficient

HEALTH STATUS OF PERSONS OCCUPATIONALLY EXPOSED TO MW. Epidemiological research on e. cupational MW health hazards offers numerous difficulties. Perhaps the main of these is the complexity of the working environment. Noise, temperature and humidity variations, disturbances in the normal rhythm of sleep and waking periods, causel by working shifts, stresses caused by the Leed to concentrate end simila: factors the health status of this group of workers. Another obstacle is the lack of reliable methods of individual microwave dosimetry. Incident power density measured in air in absence of the worker gives only an approximation of the real configuration of the field after a moving object i.e. the worker is introduced into it. In the case of moving human group and moving beams and/or antennas the evaluation of the real exposure becomes doubtful.

in view of the specific conditions of work the selection of adequate control groups is also very difficult. On the other hand analyses of the health status must allow for the age factor, which increases with duration of occupational exposure.

In view of these difficulties it is impossible to present a review of the data published in various countries. Most of the papers are not comparable. A detailed review of USSR data can be found in references /8, 9, 10, 13/, the safety rules and exposure limits are presented in detail in references /10, 11, 12/. Polish data were recently published in English /54, 55, 56/ additional information is contained in /7/. The very scare USA studies are discussed in /5/.

All available data agree in one respect. If safe exposure limits and safety rules existing in the USSR and Poland are observed, no detrimental health effects are expected during occupational exposure of healthy adults. The lack of well documented epidemiological studies leaves the question open in respect to the much higher safe exposure limits recommended in the USA.

CONCLUDING REMARKS. During the last few years the gap between empirical biological observations and the biophysical theoretical explanations dimishes steadily. Interdisciplinary cooperation of biologist, physicists, biophysicists, electronic engineers and medical research workers is necessary to close this gap completely. It should be pointed out that such cooperation contributes to the advancement of the fields in question - more insight is gained into the biophysics of living systems, new applications of microwave technics developed in biology, medicine and in future possibly in agriculture. At the same time it should be remembered that the electromagnetic pollution of the atmosphere increases steadily, the natural background of microwave and radio-frequency radiation is insignificant in comparison with the emission of man-made sources. As electromagnetic fields have demonstrable biological effects, biological colerance limits should exist. This limit must be determined before it is too late, not only in the interest of the health of the general human population, but also because of the need to protect the natural environment. Further research is urgently needed.

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