

Low-intensity Millimeter Waves in Biology and Medicine

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1. Introduction

Electromagnetic millimeter (MM) waves ($\lambda = 1$ to 10 mm) correspond to the extremely-high-frequency (EHF) band: $f = 300$ to 30 GHz. In the electromagnetic spectrum, this band lies between the super-high-frequency (microwave) band and the optical (infrared) band.

The first wideband oscillator with an electric tuning of oscillation frequency was developed and brought into lot production in the U.S.S.R. under the leadership of Academician N. D. Devyatkov and Professor M. B. Golant in the mid 1960s. The oscillator was called an O-type backward-wave tube. It was employed both to improve radio navigation systems and to create new communications systems [1, 2].

In those days, scientists all over the world discussed possible application of electromagnetic waves in nontraditional fields—such as biology, medicine, and some others. Creators of the MM-wave oscillator suggested an idea of investigating biological effects of MM-wave radiation. These waves were of special interest for scientists because they were unlikely to take part in phylogenesis of terrestrial beings. The point is that MM-wave radiation is virtually absent in natural conditions. This is due to its strong absorption by the Earth's atmosphere: MM waves are absorbed eagerly by water vapor.

It was hypothesized that low-intensity (nonthermal) MM waves might have a nonspecific effect on biological structures and organisms. Foreground investigations, which have been performed in the U.S.S.R. and then in Russia for 30 years, made it possible to enunciate a hypothesis that vital functions in cells are governed by coherent electromagnetic EHF waves: the alternating electromagnetic field of these waves maintains interaction between adjacent cells to interrelate and control intercellular processes in the entire being. This hypothesis formed the basis for a new scientific lead that was originated at the turn of several branches of sciences: biophysics, radio electronics, medicine, and some others. This lead was thereafter named *millimeter electromagnetobiology*.

2. Fundamental Results of Experimental Investigations of the Effect of Low-intensity Millimeter Waves on Biological Objects

Early experimental studies were carried out at the All-Union Cancer Research Center of the U.S.S.R. Academy of Medical Sciences. This center is among leading medical establishments in Russia. Investigations made on microorganisms (bacteria *E. coli*) and laboratory animals (mice and rats) discovered an interesting experimental fact. It was found that different microorganisms exposed to MM-wave radiation exhibited a frequency-dependent biological effect [3]. The equivalent intrinsic Q -factor (calculated from the formula $Q = f_0/\Delta f_{0.5}$,

where f_0 is the resonance frequency and $\Delta f_{0.5}$ is the FWHM of the biological effect) amounted to hundreds and thousands of units. The mechanism of appearance of such great values is unexplained so far.

Another essential and accepted fact is that a biological effect plotted against the electromagnetic-wave power exhibits a “plateau.” Experiments made on microorganisms demonstrated that the plateau could extend for three orders of magnitude, or more [4, 5]. It was also found that a threshold intensity that gave rise to biological effects could be as small as units or tens of microwatts per square centimeter.

Hence, the very first experimental investigations established that MM waves can bring about biological effects at low radiation powers—at *low-intensity* or *nonthermal* powers. In this case, the integral heating of an exposed surface does not exceed a physiologically significant temperature increment, which amounts to approximately 0.1°C. The effect of MM waves on living beings was called *informational*. This was done from analogy with communication lines, which reveal the same behavior. A. S. Presman was the first to introduce the term *informational* to electromagnetobiology [6].

By now, scientists have amassed a great experimental and theoretical material about the effect of low-intensity MM-wave radiation on biological objects [7–9]. Below, we shall outline the most essential facts.

– *EHF radiation is strongly absorbed by water and aqueous solutions of organic and inorganic substances* [10]. When electromagnetic radiation is absorbed by water, its wave energy is converted into rotational, translational, and librational degrees of freedom. For example, a 1-mm thick water layer attenuates MM-wave radiation by 20 dB at $\lambda = 8$ mm and by 40 dB at $\lambda = 2$ mm [10]. This fact is of great importance for biology: suffice it to say that all biological organisms contain much water. For example, the human skin contains more than 65% water. Hence, almost all radiation is absorbed at a skin depth of 0.5 to 1 mm (the epidermis and the top dermis). When MM waves are incident on the skin, they are primarily targeted at its anatomical structures, such as receptors, capillaries, cells, liquid (aqueous) solutions of organic and inorganic substances [11].

– *MM-wave absorption violates the additivity law of a solvent (water) and solutes* [12]. For a particular solution, real absorption can be greater or smaller than the additive one. Absorption depends on the intermolecular interaction between a solvent and a solute. When an aqueous solution shows poor absorption, this may indicate, for example, that part of water molecules is in a bound state. As a result, absorption decreases because water molecules lose their rotational degrees of freedom [13].

An excess of real absorption over the additive one can arise from the “heating” of separate molecules or molecular groups due to the appearance of additional degrees of freedom (mainly, the rotational ones).

– *MM waves stimulate production of biologically active substances by immunocompetent cells*. This phenomenon is carefully discussed in [14] and was additionally proven in other studies. Indirectly, it is confirmed by the polytherapeutic effect of EHF therapy and by the enhanced nonspecific resistivity of an organism.

– *EHF radiation changes microbial metabolism*. This fact was observed in almost all experimental investigations on microbes. MM waves were reported to have a pronounced effect on the microbial vital activity. After MM-wave exposure, microorganisms began to produce biologically active substances. Now, this phenomenon is used in various biotechnological processes [15].

– *MM-wave radiation stimulates ATP (adenosine 5'-triphosphate) synthesis in green-leaf cells.* For the first time, the effect of radiation on ATP synthesis was observed in leaves of the indoor plant *Balsaminus* [16]. As is known, ATP is a universal chemical source of energy in living cells. The fact that MM waves stimulate ATP synthesis has an effect on microbial vital activity. This phenomenon was indirectly confirmed in medical practice (when a diseased being revealed normalization of vital processes) and in experimental studies (when an organism enhanced the synthesis of biologically active substances).

– *EHF radiation increases crop capacity (for example, after presowing seed treatment).* The first observations in this field were apparently made by the authors of [17]. Experiments were made on various indoor plants. It was reported [18] that MM waves have a stimulating effect both on the germination of popular garden seeds and on their crop capacity. A number of other investigations obtained similar results for seeds of other plants and trees.

– *MM waves change the rheological properties of blood capillaries.* Experimental studies revealed that dielectric capillaries (which simulate capillaries in tissues) exhibited resonance absorption of MM waves. The equivalent Q -factor of resonance peaks was found to be tremendously high—on the order of 10^3 to 10^4 . Note, it is rather hard to force metal cavities to yield such Q -factors in the microwave and MM-wave bands. The resonance absorption in water and in various aqueous solutions is accompanied by a considerable decrease in the adhesive force between the inner capillary wall and the flowing fluid [19]. However, the mechanism of this phenomenon is still unexplained. Nevertheless, the “capillary” effect can explain the efficiency of MM-wave-based treatment of obliterating endarteritis.

– *EHF radiation excites CNS (central nervous system) receptors and induces bioelectric responses in the cerebral cortex.* It is natural to question how information is transmitted from a thin skin layer to the internal organs. The fact that the human CNS is involved in the realization of MM-wave-induced effects is discussed in [20–22]. It was demonstrated that 80% of healthy people can reliably perceive low-intensity MM waves (sensory indication). However, such perception exhibits sensory asymmetry. Peripheral application of MM waves was shown to have an effect on the spatiotemporal organization of brain biopotentials. As a result, the cerebral cortex develops a nonspecific activation reaction (tonus enhancement). According to [20–22], pain receptors (nociceptors) and mechanoreceptors are the CNS receptors that perceive MM waves. MM-wave-induced effects are realized mainly by the nonspecific somatosensory system, which is linked to almost all regions of the brain.

– *Even a single MM-wave exposure is memorized (“water memory”).* The last several years have seen publications of new findings about the role of water and aqueous solutions in the realization of biological mechanisms of MM waves. For the first time, a hypothesis about an important role of water was advanced in 1979 in [23]. New properties of water exposed to MM waves are described in [24, 25]. The authors of [24] discussed the excitation of metastable states in the energy diagram of water structure. It was shown that the physical mechanism of “water memory” formation is associated with the network of hydrogen bonds. In a hydrogen bond between two water molecules, a hydrogen atom that is located between two oxygen atoms has two equiprobable positions. This atom (proton) can be regarded as a particle tunneling between two potential wells. The possible tunneling splits the proton energy level into two closely spaced levels with an energy difference of ΔE_p . In this case, the proton tunneling frequency is given by $\omega_p = \Delta E_p/h$, where h is Planck’s constant. The tunneling frequencies of clusters and clathrates $\{(H_2O)_n\}$, where $n = 50$ to 60 fall within the millimeter and submillimeter bands. As a result, these systems absorb MM waves in a resonant manner. Experimental investigations described in [25] showed that water (aqueous solutions) can store information (“memory”) about MM-wave irradiation for a long time—from a few minutes to

several tens of minutes). This information manifests itself in the retention of biological (biochemical) activity by water after irradiation termination.

– *Water and aqueous solution bleach as a result of the SPYo effect*[♦]. Sensational are the results of experimental and theoretical investigations that showed the feasible existence of “low-loss transmission windows” in water and water-containing objects (we mentioned about it earlier). These windows were observed at the intrinsic resonance frequencies of water clusters [26–28]. This phenomenon occurs in a narrow range of exposure power—on the order of fractions and units of microwatts.

– *MM waves induce convective motion in the bulk and thin layers of fluid*. MM waves may give rise to compound convective motion in the intracellular and intercellular fluid. This lifts restrictions from diffusive motion of fluid near cells. As a result, the transmembrane mass transfer and charge transport become more active. Model experiments confirmed this statement. Convection is readily observed at a power density of 0.5 to 1 mW cm⁻². The results of such experiments are described in [29, 30]. Note, convection may occur not only in the bulk of fluid but also in thin layers whose depth is less than 1 mm. This phenomenon can be observed at threshold powers of incident radiation—on the order of several microwatts [30].

– *EHF radiation increases the hydration of protein molecules*. It is known that dehydration of protein molecules affects them. As a result, proteins go from a functionally active to functionally passive state [12]. It was demonstrated by experiment that MM waves can restore the hydration number. Experiments unfinished by Yu. I. Khurgin were a cause for such a statement. They were made using chymotrypsin. It served as a catalyst for a biochemical reaction. Chymotrypsin catalytic reactivity was varied by changing its hydration number: when the hydration number decreased, the reaction yield also decreased. It was observed that MM-wave irradiation increased the reaction yield. This could result solely from an increase in chymotrypsin hydration, which enhanced protein activity. The hydration number increased because of electromagnetic energy conversion into the rotational-translational energy of water molecules. This changed the “protein-water” complex from a functionally passive to functionally active state.

– *MM waves give a microthermal massage*. It was demonstrated by experiment that MM waves produce a nonuniform distribution on the skin surface. Experiments were carried out using the “Yav’-1” device having a rectangular horn. When exposed to MM-wave radiation, the skin surface exhibited several thermal extrema, which were visualized by a thermal imager. Although the average temperature rise was insignificant, two or three maxima were overheated by several degrees of centigrade. In a thermal image, the extrema looked like points—“thermal spikes.” When the EHF carrier was modulated in frequency or amplitude, the spikes were found to migrate across the skin surface. The author of [31] suggested that this effect could give a thermal massage to the skin receptors (by analogy with conventional thermal acupuncture).

– *EHF radiation excites acousto-electric oscillations (the Frohlich oscillations) in plasma membranes*. A theoretical study [32] showed that plasma membranes may generate coherent oscillations, which are sustained by metabolism. These oscillations occur either in the entire plasma membrane or in its separate parts. In the electromagnetic spectrum, these oscillations fall within the EHF band. The authors of [33] believe that such oscillations are nothing else but acousto-electric oscillations. The purpose of these oscillations is to stimulate the transport of water and other substances across the membrane, sustaining it in the active

[♦] *SPYo effect* stands for Sinitsyn, Petrosyan, and Yolkin (these scientists were the first to observe and describe this effect)

state. Later on, some authors who tackled the problem of EHF therapy expressed another interesting view. An illness deranges the intrinsic oscillations of the membrane, whereas an EHF therapy device simulates the dying oscillations of the membrane. As a result, EHF radiation restores the oscillations, normalizes membrane functioning, and cures the sick person.

3. Experimental Clinical Investigations

L. A. Sevast'yanova was among the first scientists who launched investigations into the biological effects of low-intensity MM waves on mammals (1969–1971) [34–36]. She demonstrated that preliminary MM-wave irradiation may counteract X-ray-induced effects in the bone marrow [37–41]. She also estimated MM-wave penetration into the skin of animals. L. A. Sevast'yanova determined the distribution pattern of MM-wave power for some animals and human beings. The estimated penetration depth showed that MM waves produce a mediate protective effect.

Investigations that lasted for more than 20 years were performed on more than 12,000 laboratory animals (mice and rats). The response of the hematogenous system was evaluated by the count and state of marrow cells (karyocytes) present in the right and left femoral arteries as well as in the spleen. The results obtained are given below.

– *The biological effect depends on the power flux density.* The biological effect has one feature observed *in vivo* and *in vitro*. This is a threshold dependence of the biological effect on the power flux density. It was found that an excess of the power flux density above the threshold value produces no changes in the biological effect.

– *The biological effect depends on the wavelength.* Experiments were made on laboratory animals which were sequentially exposed to MM waves and X rays. When MM-wave irradiation was performed at wavelengths of 7.07 mm, 7.10 mm, 7.12 mm, 7.15 mm, 7.17 mm, 7.20 mm, 7.22 mm, 7.25 mm, and 7.27 mm, karyocytes constituted 85% to 90% of the control values. However, when MM-wave irradiation was performed at wavelengths of 7.08 mm, 7.09 mm, 7.11 mm, 7.13 mm, 7.14 mm, 7.16 mm, 7.18 mm, 7.19 mm, 7.21 mm, 7.23 mm, 7.24 mm, and 7.26 mm, karyocytes made up 50% to 60% of the control values. This karyocyte count corresponded to that obtained for X-ray exposure alone.

– *The biological effect depends on the MM-wave exposure site location.* The damage degree of karyocytes decreased when the occiput and the hip were exposed to MM waves at wavelengths of 7.10 mm and 7.12 mm. However, this degree remained unchanged when irradiation was performed at wavelengths of 7.11 mm and 7.13 mm. Similar results—but at different wavelengths—were obtained for other bodily regions of animals, such as the flank, head, abdomen, and brachium. For example, the damage degree of karyocytes decreased at wavelengths of 7.11 mm and 7.13 mm, whereas it remained unchanged at wavelengths of 7.10 mm and 7.12 mm. Hence, some particular wavelength produces a biological effect in each bodily region.

– *The biological effect depends on the MM-wave exposure area.* The combination of X rays with overall and local MM-wave irradiation produced similar biological effects. The latter consisted of decreasing the X-ray-induced damage degree of karyocytes. It was found that MM waves took effect even if the exposure area was as small as 10 mm². However, when MM waves were not modulated in frequency, the effect was unstable. Conversely, when they were modulated in frequency, the effect was stable.

As far back as the 1970s, W. R. Adey advanced a hypothesis that the electromagnetic spectrum should contain “amplitude-frequency windows” in which biological effects are more

pronounced [42]. The above-described results served as the first experimental verification of this hypothesis. It was inferred that biological effects of electromagnetic radiation, and particularly of MM-wave radiation, are determined by its biotropic parameters, such as the intensity, frequency, signal waveform, location, exposure, etc.

It is known that cells exposed to X rays reveal different types of lesions that depend on the X-ray dose. These lesions manifest themselves in the form of chromosome aberrations, decreased mitotic activity, and inhibited reproductive ability. In turn, this leads to reduced karyocyte and blood-cell counts.

Most radioprotectors do not exhibit sufficient selectivity. As the radiation dose increases, they themselves may produce toxic effects. Results obtained by L. A. Sevast'yanova were evidence that MM waves have a protective effect and that they influence karyocytes selectively.

When MM-wave irradiation was followed by X-ray exposure, *intact* animals (without grafts) revealed a smaller damage degree of karyocytes as compared to those exposed to X rays alone: by the fifth day, the karyocyte deficiency was 15% only, whereas it amounted to 38% in animals exposed sequentially to X rays and MM waves.

Like radiation, antineoplastic compounds isolate the DNA-membrane complex and retard the DNA and RNA synthesis. At the cellular level, the effect of X-ray exposure has much in common with the effect of chemotherapy compounds: a sluggish cellular cycle, delayed mitosis, chromosome aberrations, as well as reproductive and interphase death.

Investigations were made of the combined influence of MM waves and antineoplastic compounds. They demonstrated that MM-wave radiation with some particular parameters can counteract the detrimental effect of antineoplastic compounds on the hematogenous system. Furthermore, MM waves were found to stimulate the functional activity of stem cells.

Speaking about hematogenous system responses, the combined influence always yielded more karyocytes than X rays or antineoplastic compounds alone. This held true for all combinations used in the experiments. Being combined with antineoplastic compounds, both single and multiple MM-wave exposures produced a decrease in the damage degree of karyocytes. MM-wave irradiation alone produced no changes in the hematogenous system of animals.

A big scientific problem is to govern the sensitivity of tumor cells to radiation and chemotherapy. Almost all known compounds and their combinations cause lesions of healthy tissues. Quite often, toxic effects become noticeable before the antineoplastic effect. They may be so severe that the patient has to be withdrawn from the cure.

Experimental results demonstrate that MM waves do not affect healthy cells and tissues. At the same time, they favor a more rapid recovery of vital functions in affected tissues. When combined with X rays or antineoplastic compounds, MM waves act as a protector. This arises from an increased proliferative activity of stem cells of the hematogenous system. As a result, mitotic activity of karyocytes increases.

The effect of MM-wave radiation on the hematogenous system was studied in animals with malignant tumors. The experiments were made on 1,500 animals receiving X rays in combination with an antineoplastic compound—cyclophosphane. It was found that MM-wave radiation prolonged the life expectancy of the animals by 10 to 15 days, as compared to the control group.

Investigations of the combined influence of MM waves and X rays were performed on primary tumors grafted into the CBA mice. It was found that, when X-ray exposure was

followed by MM-wave irradiation, the tumor growth was retarded significantly. By the thirtieth day, the tumor growth retardation reached 80% to 90%. However, when X rays were applied alone or when MM-wave irradiation preceded X-ray exposure, the tumor growth retardation—determined by the thirtieth day—was 60% to 65%. In this case, the karyocyte count exhibited virtually no decrease: by the seventh day, it was at the level of the physiological norm.

When X rays were applied alone, karyocytes exhibited a sluggish recovery. Even by the seventh day, the karyocyte count failed to reach the control level. When X-ray exposure was followed by MM-wave irradiation, the karyocyte count—made by the seventh day—reached the physiological norm.

Peripheral blood examination was also made during the experiments. It revealed that animals subjected to MM-wave irradiation followed by X-ray exposure exhibited greater erythrocyte and leukocyte counts as compared to animals subjected either to X rays alone or to X rays followed by MM waves.

A group subjected to the combined influence revealed a reduced karyocyte count on the first day only, with the karyocyte deficiency being 20%. By the fifth day, the karyocyte count reached the physiological norm. After X-ray exposure, the karyocyte count was recovered by the twenty-first day.

The sequential application of X rays and MM waves brought about a significant tumor growth retardation. It was more pronounced than that caused either by X-ray exposure alone or by MM-wave irradiation followed by X-ray exposure. After a seven-day irradiation, the tumor growth retardation reached 90% to 95%. However, the karyocyte count remained decreased for 5 days. The cell deficiency amounted to 30% within the first days. After that, the karyocyte count exhibited gradual normalization. When the double combination was applied, the tumor growth retardation amounted to 90% by the thirtieth to thirty-fifth day.

Thus, the double combination not only counteracted the hematogenous system damage, but it also retarded the tumor growth, with both effects being stronger as compared to X rays alone.

Combined X rays and MM waves potentiated the effect of cyclophosphane on the tumor within 13 days. The effect was greater by a factor of 3 to 4 as compared to that without MM waves. The peak of effect was observed by the twenty-fifth day.

The hematogenous system response was studied on a group of animals subjected to the combined influence of cyclophosphane and MM waves. By the third day, the karyocyte count of animals reached the control level and retained it over the entire observation time (for 14 days). When the compound was employed alone, the karyocyte count—made by the fourteenth day—did not reach the control level.

The encouraging results of the first course of treatment suggested that the treatment should continue. After the second course of treatment, the antineoplastic effect became noticeable within 24 days. By the thirtieth day, the whole group of animals receiving cyclophosphane was found dead, whereas all the animals receiving the combined treatment were alive. The percent of tumor resolutions reached 90% to 100%. These animals were followed up for 18 months, with no relapses being observed. The time history of erythrocytes was recorded for animals that received two courses of treatment. It was found that the combined influence ensured the protection of erythrocytes during the entire cure. In animals receiving combined treatment, the erythrocyte count—made for 51 days—proved to be normal.

Hence, the combined application of MM waves and cyclophosphane in animals with sarcoma-180, on the one hand, decreases the compound toxicity and, on the other hand, potentiates its effect on the tumor.

In vitro experiments were made to study the effect of low-intensity MM-waves on hemopoietic cells of the bone marrow [43]. With this end in view, L. P. Ignasheva and E. I. Soboleva investigated the problem of survival of mice that had received a lethal radiation dose. In their investigation, they transplanted a cryogenically preserved bone marrow. After defrosting, they exposed the bone marrow to MM waves.

Success for myelotransplantation depends on the preservation quality of hemopoietic stem cells. Usually, bone marrow sanguification recovers later in animals which underwent transplantation using a defrosted bone marrow: it is delayed by 7 to 8 days as compared to animals which underwent transplantation using an *extempore*-produced bone marrow. It is believed that quality of karyocytes is sufficient when animals that had received a lethal radiation dose stay alive for more than 30 days.

Hybrid mice were used as donors and recipients. Cryogenically preserved karyocytes were subjected to MM-wave irradiation at a wavelength of 7.1 mm. Irradiation was carried out according to an optimum program mode. Animals of the control group were not performed transplantation. By the fifteenth day, they all died of acute radiation sickness. The disease revealed typical clinical manifestations: weight loss, adynamic motion, and receding hair.

When a defrosted bone marrow was transplanted without MM-wave irradiation, only 45% of animals survived by the thirtieth day. When the defrosted bone marrow was subjected to MM-wave irradiation before transplantation, 53% of recipients remained alive within the observation time. The animals of both groups exhibited a slight hypodynamia and an insignificant weight loss that showed tendency towards recovery by the end of the observation time.

Hence, nonthermal low-intensity MM-wave irradiation produced a beneficial effect on the stem cells of cryogenically preserved bone marrow and increased the survival rate of post-myelotransplantation recipients that had received a lethal radiation dose. The above-described technique can be used to enhance the repopulation ability of cryogenically preserved bone marrow.

Unorthodox experimental studies were made at the Institute for Radio Engineering and Electronics of the Russian Academy of Sciences in collaboration with the P. A. Gertsen Moscow Cancer Research Institute. Launched in 1989 and 1990, these investigations dealt with the interaction between malignant tumors and low-energy nanosecond MM-wave and microwave pulses having a giant peak power—tens and hundreds of millions of watts [44, 45]. Despite a giant radiation power, the heating of an object was virtually absent because of a short pulse duration—on the order of 10 ns. At the same time, such short-pulse radiation was not ionizing, i. e., it did not cause bond scissions due to a very small quantum energy in this spectral range. A distinguishing feature of such pulsed radiation was a high intensity of the external alternating electric field—from 10^4 to 10^5 V cm⁻¹. This intensity is comparable with the natural quasistatic intensity of an electric field in cell membranes.

Investigations were performed on the Walker carcinosarcoma grafted intramuscularly into the Wistar rats.

Multiple experiments were made using MM-wave and microwave radiation with the above-mentioned parameters. They revealed that exposed animals revealed a number of features, as compared to the control ones. These features were as follows:

- life expectancy was prolonged after the application of such waves;
- the growth rate of grafted tumors decreased and stabilized (it was halted for several days);
- the tumor growth was halted, and the life expectancy was much longer when MM waves or microwaves were combined with chemotherapeutic compounds; and
- the metastasis degree profoundly decreased both when MM waves and microwaves were used alone as well as when they were combined with chemotherapeutic compounds.

In vitro experiments revealed that the tumor-cell count at different destruction stages (up to their death) was greater in exposed suspensions than in the nonexposed ones. A follow-up study that lasted for 12 to 18 months revealed no noticeable changes in the behavioral reactions and general state of exposed healthy animals. A postmortem examination of exposed animals revealed no pathologic changes in their liver, kidneys, adrenal glands, and immunocompetent organs (such as the thymus, spleen, and lymphatic nodes) as compared to the control animals of a corresponding age. These investigations thus showed that pulsed radiation has both direct and indirect—through the immune system’s activation—effects on tumor cells.

A research team headed by V. I. Govallo at the Central Research Institute for Traumatology and Orthopedy in collaboration with the “Istok” Research and Production Association conducted investigations into the effect of MM waves on human lymphocytes and fibroblasts [46]. It was demonstrated *in vitro* that human lymphocytes and fibroblasts produce a *factor-phytokine* under MM waves. It enhances the growth and functional activity of similar cells. In high concentrations, *phytokine* is contained in destroyed irradiated cells (lysates), and it is released in a cultural medium. MM-wave irradiation itself does not stimulate cell growth, does not change the expression of superficial lymphocyte receptors, and does not have an effect on their sensitivity to mitogens or exogenous immunomodulators. However, when added to a culture, *phytokine* vigorously stimulates the proliferative potential of lymphocytes and fibroblasts.

This factor-phytokine is produced in cytoplasm. It is bound up with the activation of dehydrogenases: the concentration of lactate dehydrogenase increases by a factor of 3 to 5 in irradiated cells. This activation factor is attributed to a class of cell regulators—cytokines. It does not belong to a group of interleukins or interferons. However, it may be attributed to lymphokines or monokines. This is a low-molecular glycosylation factor, secreted locally or distantly. It acts in a paracrine or autocrine way, but not in the endocrine one.

It is apparent that the described mechanism may underlie the immunomodifying effect of MM-wave radiation. This effect was observed while treating inpatients with suppurative diseases and complications at the Central Research Institute for Traumatology and Orthopedy. Difficulty in treatment of such diseases is associated with a high severity of injuries, complicated and long-term operations, insufficient immunologic reactivity of patients, as well as with changes in the properties and behavior of suppurative infections, which appear to be resistant to many antibacterial agents.

MM waves were applied to treat severe missile and shotgun injuries of the locomotor system. The injuries were complicated by suppurative and wound infections. The results obtained are as follows [47]:

- the duration of separate phases of the wound process, including bad infected wounds, decreased by a factor of 1.5 to 2 as compared to the control group;

- MM waves produced a pronounced stimulating effect on wound tissue regeneration (the daily fractional decrease in the wound surface area virtually corresponded to that for uncomplicated wounds);
- grafts revealed a 100% retention;
- the osteomyelitic process was eliminated: MM waves relieved pain and subsided inflammation in the injured region of a limb; they also stimulated total and local closing of fistulae as well as epithelization of injured soft tissues;
- 92.3% of the patients showed satisfactory outcomes shortly after operations;
- postoperative relapses decreased by 20%; and
- microbial semination of wounds was reduced after opening and excision of festerous-necrotic foci.

Microbiological examinations were conducted *in vitro* to study the effect of MM waves on microbes. It was found that MM waves produce no direct effect on microbial susceptibility to antibiotics as well as on their biochemical and cultural properties.

Investigations carried out demonstrated that MM waves normalize immune-system parameters, which is of value for MM-wave therapy efficiency. Patients who underwent serious reconstructive operations suffer from secondary immunodeficiency, which complicates their recovery. MM waves brought about pronounced shifts in the patients' immunograms. As a result, the patients showed a fractional and absolute increase in T-lymphocyte and T-helper counts (by 30 to 50% and 30 to 80%, respectively). The patients also revealed an increased natural-killer count (by 40 to 60%).

Hence, instead of a direct antimicrobial effect on pathogenic microflora, MM waves produce an indirect effect on it. They enhance an organism's general reactivity and increase wound-tissue viability.

The immunostimulating effect of MM waves was clearly demonstrated by a research team from Leningrad [48]. These researchers investigated how MM-wave radiation protects against and prevents from influenzal infections. To this end, animals received a lethal dose of the influenza A virus. MM waves were applied to healthy animals (preliminary irradiation) and to infected animals (subsequent irradiation). It was found that they produced a protective effect in both cases. The results obtained were as follows:

- MM waves produced favorable therapeutic and preventive effects on the survival rate and average life expectancy in all experimental groups;
- the protection efficacy depends on the irradiation procedure: the best protective effect (the death rate was zero) was observed for a long-term *preventive* irradiation of healthy animals before they were infected;
- the protective preventive effect was potentiated when exposure time was extended to 7 to 17 days; and
- MM-wave irradiation proved to be a sufficiently effective therapeutic means.

Besides experimental investigations, the researchers retrospectively analyzed the epidemiological situation of influenzal and acute respiratory viral infections in a group of patients who underwent MM-wave therapy with respect to gastric ulcer. The MM-wave course coincided with the epidemiological period of influenza epidemy caused by the influenzavirus A. The group of patients receiving MM-wave therapy was compared to the control group (comparable by the age, health state, and conditions of work). It was found that

influenzal and acute-respiratory-disease rates in the group of patients receiving MM-wave therapy were smaller by a factor of 1.75 during the *epidemy* as compared to the control group.

Inasmuch as many diseases cause *secondary immunodeficiency*, many scientists pay special attention to the immunomodifying effect of MM waves.

Gastric and duodenal ulcers, as well as many other diseases, are caused by an imbalance between an organism's aggression and its protective factors. Immunity ranks first among protective factors. In order to compare the efficiency of MM-wave therapy and conventional treatment of ulcer, nonspecific immunity (phagocytosis and lysozyme) and specific immunity (T lymphocytes, B lymphocytes, IgA, IgM, and IgG) were examined [49]. Although the ulcer healed over, the conventional pharmacotherapy did not enhance protective factors. When MM waves were applied, the ulcer healed over *without a keloid scar*. Furthermore, protective factors exhibited a pronounced normalizing effect. In particular, this concerned nonspecific and specific immunity. A dynamic observation of the patients revealed that their protective factors were at a maximum 3 months after the cure termination. Since MM waves produced a normalizing effect on an organism's protective factors, *preventive* MM-wave therapy was put forward.

When *atopic dermatitis* was treated using MM-wave therapy [50, 51], the patients' immune state was monitored using a number of laboratory techniques. They were as follows: an active T-lymphocyte count; total T-lymphocyte count; B-lymphocyte count; agar-gel radial immunodiffusion for the IgA, IgM, and IgG counts of blood serum; circulating-immune-complex (CIC) count of blood serum; as well as immunoenzymic analysis of the total IgE and allergen-specific IgE counts. Note, the allergen-specific IgE includes antibodies against indoor, pollen, and food allergens. The treatment performed favored the positive dynamics and stable improvement of immunologic indices. This concerned both the cellular immunity (such as rosette-forming cells) and the humoral immunity (such as CIC, IgM, IgG, and IgE). Patients receiving conventional therapy exhibited virtually no changes in cellular and humoral immunity indices.

A research team [52] investigated the effect of MM waves on the immune state of patients with *sarcoidosis of lungs*. Investigations were made at the Central Research Institute for Tuberculosis of the Russian Academy of Medical Sciences. The researchers counted T lymphocytes and determined their functional and phagocytic activity. They also counted B lymphocytes, immunoglobulins, as well as CICs in blood serum (both before and after the treatment). The application of MM waves gave rise to a *universal* stimulation of functional activity of immunocompetent cells. They stimulated the phagocytic activity of macrophages in the granulomatosis-stricken region, in various lung regions, and in blood. Macrophage activation facilitated the elimination of CICs from the body. They were devoured by macrophages, and their content decreased in 87% to 91% of the patients after MM-wave therapy. This restored the blood flow in lungs. As is known, when the CIC count of blood decreases, it prevents microvessels of many organs from being damaged.

The last several years have seen a wide spread of *herpesviruses*. This is associated with the absence of reliable prevention and drug therapy insufficiency. Furthermore, the number of immunodeficiency states is growing, which is caused by wide application of antibacterial and hormonal compounds. The immune state was examined when conventional treatment was combined with MM-wave therapy. The examination involved counting T lymphocytes, B lymphocytes, CICs, IgA, IgM, IgG, as well as studying the immune-response-modifier tolerance. It was found that MM waves produced an immunostimulating effect, which manifested itself in stimulated phagocytosis and T-lymphocyte activity. This is of great

importance for prevention and treatment of diseases complicated by secondary immunodeficiency [53].

At present, *urogenital inflammatory diseases* are also widespread in men and women. Most often, these diseases are caused by chlamydias, mycoplasmas, and ureaplasmas. A distinguishing feature of these microbes is their ability to cause stable immunodeficiency. When antibiotic therapy is combined with immunomodification, the recovery rate increases up to 70% (as compared to 30% to 50% after conventional therapy) [54].

It is known that immunosuppression exacerbates *acne*. Investigations were made of the effect of MM-wave therapy on the cutaneous microbiocenosis in vulgaris-acne patients. All the patients were recorded an immunogram showing cellular and humoral immunity indices before and after the treatment. It was found that conditionally pathogenic microbes did not grow on the skin of patients whose immunologic indices were normalized by MM-wave therapy. In these patients, clinical results were regarded as a recovery or significant improvement. In general, the immunologic indices of most patients exhibited positive dynamics, which was accompanied by an improved state of skin microbiocenosis [55].

The experimental clinical investigations performed thus provided evidence that low-intensity MM-wave radiation has a pronounced immunomodifying effect.

The central nervous system (CNS) is the main regulatory system. It governs almost all processes occurring in a living being. Classical investigations into electromagnetic biology revealed that the CNS is the most sensitive system for electromagnetic fields [6, 56, 57]. Studies of the CNS role in the realization of biological effects of low-intensity MM waves began at the earliest stage of MM-wave therapy formation.

Professor Yu. A. Kholodov and Professor N. N. Lebedeva have been heading experimental investigations at the Institute for Higher Nerve Activity and Neurophysiology of the then-U.S.S.R. and now-Russian Academy of Sciences since 1989. These investigations deal with the sensory and subsensory (EEG) responses of healthy human beings to peripheral stimuli of low-intensity MM-wave radiation. Investigations of *sensory responses*, i. e., *electromagnetic sensitivity of human beings* [21, 58–62] yielded a number of interesting results. They are as follows:

- A human being reliably discerns MM-wave signals from sham signals.
- Human sensitivity to MM waves depends both on his or her individual features and on the biotropic parameters of the field.
- Perception modality (such as pressure, touch, pricking, and burning) is evidence that MM-wave perception involves skin analyzers.
- The latent time of a MM-wave response is tens of seconds.
- MM-wave perception exhibits sensory asymmetry: it is different for left and right hands.

An analysis of subjective feelings in human beings demonstrated that a MM-wave stimulus “actuates” mechanoreceptors, nociceptors, and free nerve endings—unmyelinated efferent fibers without corpuscular structures at their ends. Evidently, we may ignore fast-adapting mechanoreceptors because they discharge within 50 to 100 ms after sending an adequate stimulus. Nonspecific and weak stimuli, such as low-intensity electromagnetic fields, can be perceived by receptors that are slowly adapting or that have a background activity (or

when receptors combine these features). Of mechanoreceptors, such features are inherent in Ruffinier's endings, tactile disks, and Merkel disks.

The nociceptors (pain receptors) of the skin are free nerve endings with thin myelinated or unmyelinated nerve fibers. It was hypothesized that nociceptors can perceive electromagnetic signals. This hypothesis was based on a number of prerequisites. First, they were found to exhibit polyspecificity to MM-wave stimuli. Second, they revealed perception modality: pricking and burning, which are regarded by experts as "prepain". Third, electromagnetic sensitivity disappeared in people whose exposure site was treated with chloroethane that inactivated pain receptors [61]. Fourth, clinical practitioners observed that, when electromagnetic radiation was incident on a particular dermatome, it induced a sensory response in the corresponding diseased organ. This may arise from convergence of nociceptive efferent fibers from dermatomes of internal organs to the same neurons of pain pathways. This gives rise to skin hypersensitivity because visceral impulses raise the excitation of intercalary neurons, which leads to facilitation (relief).

An investigation was made of EEG responses of healthy subjects to a long-term (30- to 60-min) peripheral MM-wave irradiation. It was found that such irradiation produced changes in the spatiotemporal organization of cerebral biopotentials. The alpha rhythm exhibited a significant increase in its power in occipital cortical regions. Furthermore, the theta rhythm revealed an average increase in its coherence in central and frontal regions. Note, this increase was more pronounced in the right brain, independent of exposure site location [21].

The effect of EHF radiation on the CNS can also be evaluated by studying *behavioral reactions*. For example, S. V. Khromova in her Ph.D. thesis [64] demonstrated that EHF radiation can modify the behavior-reflex activity of rats. This phenomenon manifested itself both in the accelerated alteration of a developed conditioned food reflex and in the delayed impairment of a conditioned defense reflex.

Investigations of a *stress-protective effect* of MM waves were made on animals at the State Research Center for Narcology, the Russian Federation Ministry of Health. Such investigations were carried out by Yu. L. Arzumanov with co-workers [65, 66]. The effect of MM-wave radiation on the CNS was evaluated by special tests. They were based on studying the inborn behavior that reflected various fields of motivation-emotion activities. In the case of a conflict-defense situation with stress, MM-wave radiation modified the behavior of an experimental group of animals in such a way that it was identical with the behavior of a passive control group.

A research team headed by Prof. N. A. Temur'yants achieved a pronounced antistress effect of MM waves [67, 68]. In their experiments, they studied the effect of MM-wave radiation on the development of hypokinetic stress in rats. As distinct from control animals, the experimental ones showed no decrease in the protective functions of blood after a 9-day hypokinesia. Furthermore, they revealed an increase in the examined indices (such as the cytochemical state of neutrophils and lymphocytes in peripheral blood) as compared to the control animals. However, the efficiency of antistress effect of MM waves depended on the individual features of the higher nerve activity of rats. It was at a maximum in rats with a low and medium moving activity.

It was also demonstrated that MM waves produce a modifying effect on the functional CNS state in human beings under simulated stress conditions [69]. This was proven by means of EEG spectrum-correlation analysis, psychological test findings, as well as cardiac-rhythm and exertion indices dynamics.

An investigation of the psychophysiological state of patients [70] and development of new methods for inpatient *psychoemotional rehabilitation* [71] revealed that MM-wave therapy relieves situational and personal anxiety, improves memory, raises attention, accelerates sensorimotor responses, as well as restores and stabilizes the psychoemotional state of human beings.

It was also found that MM waves have an *energizing* effect. MM-wave therapy was administered in combination with light therapy to patients having a depressive symptomatology. These patients suffered from maniac-depressive psychosis, cyclothymia, schizophrenia, as well as vascular and involuntal psychosis. It was found that the combined treatment produced a favorable clinical effect in 97% of the patients. A distinguishing feature of patients who revealed a virtual recovery was a different degree of the anxiety component in the depression structure, irrespective of its nosological attribute. Furthermore, the vegetative nervous system revealed hypersympathicotonic phenomena. An improvement was observed when the vegetative nervous system had a mixed type and when apathy predominated in the syndrome structure [72].

4. Fundamental Biophysical and Physiological Mechanisms of Biological Effects of Low-intensity MM-wave Radiation

The results of tentative experimental and theoretical investigations of biological effects of MM waves were summarized at a special session of the General Physics and Astronomy Division of the U.S.S.R. Academy of Sciences in 1973. This session was initiated by Academician N. D. Devyatkov, and it was held in order to familiarize the scientific community with unorthodox MM-wave-induced biological effects.

The first attempt to explain the resonance pattern of the MM-wave influence was made by V. I. Gaiduk and L. G. Koreneva in 1970 [73]. By way of example, they considered hemoglobin. They investigated the effect of MM-wave radiation on distal histidine E7. It was shown theoretically that distal histidine E7—in engineering mechanics, an analog for histidine is “a beam fixed at one end”—has an intrinsic resonance frequency, which falls within the EHF band. Although this work had no continuation, the idea of a direct resonance interaction between radiation and biological systems was developed in other studies.

As far as 10 years ago, our concepts of biophysical mechanisms of the interaction between low-intensity MM waves and biological systems were reduced to basic ideas ensuing from the analysis of biological effects enumerated in Section 2. In brief, they can be described as follows. The primary reception of MM waves occurs in a thin layer of an exposed surface. This is because all biological objects contain water, which is the strongest MM-wave absorber. The absorption mechanism is very simple. Water molecules possess a great dipole moment—approximately 1.9 D, whereas their rotational frequencies cover a wide range, the EHF band included. Hence, there are ideal conditions for absorption of MM-wave radiation by water molecules. The wave energy is converted into the kinetic energy of water molecules: it is transformed mainly into the translational degree of freedom. In addition, the wave energy is converted into the rotational and librational degrees of freedom. By virtue of molecule collisions, the acquired energy is rapidly thermalized. The thermalization time is on the order of 10^{-13} s. Apparently, it is this energy thermalization that causes the convective motion of liquid and gives rise to the capillary effect. Apart from that, water molecules “heated” by EHF radiation produce an effect on hydration of protein molecules. As a result, they change from a functionally passive to functionally active state. After that, a trigger mechanism may come into action. It initiates biochemical reactions that are governed by protein molecules. Note, it is this

mechanism that may govern the synthesis of biologically active substances (including the immunocompetent ones), produce an effect on cell metabolism, stimulate the ATP synthesis, etc. It can be hypothesized that MM waves are “embedded” in basic vital processes according to this pattern.

Now, let us consider a key idea that was suggested by EHF-therapy founders. The matter concerns the excitation of acoustoelectric oscillations in plasma membranes. As was mentioned in Section 2, coherent Frohlich oscillations and acoustoelectric membrane oscillations evidently represent the same physical phenomenon. However, it is infeasible to check this statement at present: modern measuring equipment falls short of approximately five to seven orders of sensitivity. Nevertheless, the idea of plasma membrane oscillations is very fruitful by itself. Let us note that it has been confirmed by other independent theoretical estimates. They were obtained when the problem of electric stability of a native plasma membrane was attacked. The membrane functions normally under giant electric intensities—on the order of 10^5 V cm^{-1} (!). This issue is carefully considered in [33]. Note, pushing off this fundamental idea, one can explain almost all known experimental phenomena.

Completing our narration about the early formation of biophysical mechanisms of the interaction of MM waves with biological systems, we shall consider the problem of MM-wave perception by the entire being. The matter concerns the role of the skin receptor system, spinal cord, and CNS in the mechanisms of low-intensity MM-wave identification in the presence of intrinsic noise. It is also necessary to assess the significance of information carried by the waves.

When such signals are perceived, a living being encounters two problems. First, a mammal being (the human being included) has no special-purpose system to perceive electromagnetic stimuli. Second, low-intensity MM-wave radiation can be attributed to weak and extremely weak influences. There are a few physical mechanisms that enable biological systems to “receive” weak signals. Let us dwell on some of them with due account of MM waves.

The key idea that biological objects can sense weak electromagnetic fields is consistent with a hypothesis that MM waves are “native” to biological objects and that biological objects use these waves to govern their vital functions. As was mentioned, this concept was proposed theoretically by a team of Russian scientists headed by N. D. Devyatkov in the mid 1960s. Thereafter, this hypothesis received an indirect theoretical corroboration in an independent study made by a prominent German physicist—H. Frohlich.

Electric dipoles of a plasma membrane generate narrow-band electromagnetic waves whose power is about 10^{-23} W . Hence, living cells should be sensitive to such a small power. Furthermore, according to the reciprocity principle, cells should be sensitive to *external* radiation that has such a power. The effect of amplification of weak external electromagnetic fields may take place immediately in the skin [74]. A volt-ampere dependence of slit contacts has a domain with negative differential conductivity. The existence of this domain is a sufficient and necessary condition for realization of input signal amplification. Especially large gain factors—on the order of 30 to 60 dB by power—can be achieved by means of regenerative and superregenerative amplification.

The authors of [76] discussed a new physical mechanism of high sensitivity of water-containing biological objects to weak electromagnetic fields (on the order of units of microwatts). This mechanism is based on the generation of intrinsic resonance frequencies by water clusters. These frequencies were discovered by Saratov physicists. They fall within a frequency range from about 50 to 70 GHz. When biological objects are exposed to weak

electromagnetic waves at these frequencies, their water-molecule oscillators lock on to the external signal frequency and amplify the signal by means of synchronized oscillation or regenerative amplification. Waves at these frequencies pass through aqueous media almost without loss—like the Davydov soliton waves [77]. As a result, they penetrate deeply into an exposed object and involve deep structures in the interaction process.

Another approach was also taken to explain the sensitivity of biological objects to weak electromagnetic fields. It is based on the “water memory” phenomenon [78]. The essence of this phenomenon is as follows. It is known that liquid water is structured and that it consists mainly of clusters, with water molecules being bound to each other by hydrogen bonds. It was found that a hydrogen atom that is located between the two nearest oxygen atoms can take up one of two positions: near either of the oxygen atoms. One of the positions is stable, whereas the other is not. The energy of hydrogen-atom transition from the stable to unstable state corresponds to that of an EHF quantum. As a result, hydrogen atoms may change to unstable states under EHF radiation. They may thereafter return to their stable states with inevitable reemission of EHF quanta (“water memory”). Hence, water acts as a low-intensity molecular oscillator of electromagnetic waves in the EHF band. As was shown in [79], water molecules may stay in the unstable state for a long time—on the order of several weeks.

A physical phenomenon that was discovered 20 years ago, or thereabouts, provided new and unexpected explanations of the mechanism of the effect of weak signals on biological systems. This physical phenomenon was called *stochastic resonance*, or stochastic filtration in radio engineering. The most complete information about the *stochastic resonance* and about its possible applications, including biology and medicine, is presented in an unorthodox review [80]. In the early 1980s, researchers discovered that the presence of noise sources in nonlinear dynamic systems can provide such operation modes of the systems that are new in principle. These operation modes cannot be realized in the absence of noise. Noise was demonstrated to play a “favorable” role in nonlinear systems by means of enhancing the motion order strength in the systems. Furthermore, it was shown to improve system performance, for example, “to form more regular structures, to increase the coherence degree, to raise the gain factor, and to increase the signal-to-noise ratio” [80]. Let us remember that according to the generally accepted, classical, point of view, specialists always regarded the presence of noise as a negative factor. Noise always had to impair the behavior of dynamic systems, and it always had to be “controlled.” “*Stochastic resonance* specifies a group of phenomena such that a nonlinear system’s response to a weak external signal increases considerably with an increase in noise intensity. Furthermore, the effect shows a maximum at some optimum noise level” [80].

Numerous experimental studies were afterward performed on various physical objects. The results obtained made it possible to draw a principal conclusion: *stochastic resonance is a fundamental physical phenomenon that was unknown earlier; it is observable in nonlinear dynamic systems and makes it possible to control their main parameters*. Note, *stochastic resonance* can also take place in nondynamic or threshold systems. It can be realized in the presence of external noise or in the presence of internal noise of an investigated system. This is of special interest for biological systems, which meet the requirements for *stochastic resonance*.

A more sophisticated problem is to investigate and comprehend the *physiological mechanisms* of biological and therapeutic effects of low-intensity MM-waves at the level of an entire organism. This is owing to the fact that the investigated object—the human being—is a very complex biological system. It possesses myriad positive and negative feedback loops and regulation levels [81]. To begin with, one needs to analyze the primary *physiological* targets present in the MM-wave exposure site. As is known, MM waves penetrate into the human skin

at a depth of 300 to 500 μm . In other words, they are absorbed almost completely in the epidermis and the top dermis. Hence, MM waves directly influence CNS receptors (such as mechanoreceptors, nociceptors, and free nerve endings), APUD cells (such as the diffuse neuroendocrine cells, mastocytes, and Merkel cells), and immune cells (such as the T-lymphocyte skin pool). In addition, these waves produce a direct effect on the microcapillary bed and biologically active points.

It is apparent that these five primary physiological targets are the five “entry” gates. They determine the involvement of corresponding systems in realization of biological and therapeutic effects of MM-wave radiation. The latter acts on every basic regulation systems of an organism as a peculiar triggering factor. This has been confirmed by many clinical investigations. The direct and simultaneous “triggering” of the aforementioned systems initiates a complex mediate influence on other organs and systems (such as the hematogenous, humoral, vegetative nervous systems). As a result, a MM-wave-induced reaction involves the entire being. The features of this reaction depend both on the *biotropic* parameters of the MM-wave stimulus and on the functional state of the human being. MM-wave radiation produces both nonspecific and specific effects. The latter include wound healing, injury sanitation, tissue regeneration, pain relief, itch mitigation, hyperemia elimination, etc.

At present, a nonspecific effect is regarded as a reaction of enhanced nonspecific resistivity of an organism. In turn, this initiates adapting and antistress reactions of higher reactivity levels [82].

A promising approach was also developed in [83]. The authors of that work made an attempt to create a unified concept. To this end, the entire being’s response to low-intensity MM waves was bound up with some principal elements of pattern-recognition theory. The authors did it with respect to the problem of neurocomputing. The key notions of this concept are autodiagnosics (when MM waves begin to interact with an organism) and autotherapy (when an organism uses autodiagnostic findings to begin the production of medicinal agents). These functions are realized with the aid of lamellar formations of the spinal cord (the Rexed lamellae). They preprocess and identify information about the external stimulus (MM waves). Hence, these formations act as a peculiar neurocomputer that prepares specific information to actuate systems that govern and maintain bodily homeostasis.

5. Application of Low-intensity MM-wave Radiation in Medicine

In the early 1970s, Academician N. D. Devyatkov initiated a program of clinical evaluation of MM waves in respect of treating various diseases. This program was approved by the U.S.S.R. and R.S.F.S.R. Ministries of Health and was executed in a number of medical establishments. The MM-wave technique was tested in more than 60 clinics, including large medical centers, such as the All-Union Cancer Research Center of the Russian Academy of Medical Sciences, the Central Research Institute for Traumatology and Orthopedy of the Russian Federation Ministry of Health, the P. A. Hertsen Moscow Cancer Research Institute, as well as clinics affiliated with the State Medical University, Moscow Medical Academy, and Moscow State Institute for Dentistry. The results obtained provided evidence for high efficiency of MM-wave therapy for the following diseases: cardiovascular (stable and unstable stenocardia, hypertonia, and myocardial infarction), neurological (pain syndromes, neuritis, radiculitis, and osteochondrosis), urological (pyelonephritis, impotence, and prostatitis), gynecological (adnexitis, endometritis, and uterine neck erosions), dermatological (neurodermite, including psoriasis, streptoderma, and acne), gastroenterological (gastric ulcer, duodenal ulcer, hepatitis, and cholecystopancreatitis), stomatological (periodontosis,

periodontitis, some types of stomatitis, and periostitis), as well as oncological (to protect the hematogenous system and to remove side effects of chemotherapy).

The experience of applying MM waves in clinical practice revealed no ultimate side effects. MM-wave therapy went well with other therapeutic techniques (such as pharmacotherapy, physiotherapy, etc.). Furthermore, it exhibited no absolute contraindications. As distinct from drug therapy, MM-wave therapy had no side effects.

MM-wave therapy reveals some features such as noninvasiveness, polytherapeutic effect, monotherapeutic effect, antistress effect, immunomodifying effect, and painkilling effect. Currently, low-intensity MM-wave radiation (MM-wave therapy) finds wide application in medicine. It is employed both to treat and prevent a wide gamut of maladies.

Cardiovascular diseases are among the most urgent problems of present-day medicine. The ischemic disease of the heart is among the most widespread cardiovascular pathologies. The death rate of this illness ranks high worldwide.

The first report on the application of electromagnetic MM waves in treatment of cardiovascular diseases came to light as far back as 1980. Over the years passed by, researchers have acquired broad experience in using MM waves to treat heart ischemia and hypertonia [84–88]. It was demonstrated that MM-wave therapy produced a clinical effect, which was verified by laboratory and instrumental findings. Apart from that, researchers developed techniques for individual selection of MM-wave treatment. It was shown that MM-wave therapy can substantially reduce the dose of antianginal compounds. Moreover, a nitrate therapy was stopped completely in patients having exertion stenocardia of the first and second functional classes. In such patients, MM-wave therapy proved to be most effective in treating both painful and painless myocardial ischemia.

The most severe patients had exertion stenocardia of the third and fourth functional classes and rest stenocardia complicated by one or several stenotic coronary arteries. Although these patients received great doses of nitrates, beta adrenoblockers, calcium antagonists, and disaggregants, the treatment appeared ineffective. By the end of a MM-wave therapy course, 80% of the patients revealed a positive clinical effect. The application of MM waves reduced the number of episodes of painful and painless myocardial ischemia. Hence, MM-wave therapy produced both painkilling and antianginal effects.

Unstable stenocardia is classified among acute ischemic diseases of the heart. It is especially dangerous in the case of an abrupt onset (within a few days) or intensifying anginal attacks. Unstable stenocardia may take a bad course, resulting in myocardial infarction, sudden death, or chronic stenocardia. The clinical application of MM-wave therapy was found to be effective in 60% of the cases. The treatment was successful even when MM waves were used as a monotherapy. Being combined with pharmacotherapy, MM-wave therapy increased the rate of positive clinical effects. The conducted therapy produced favorable effects in every patient of the examined group. According to literature findings, myocardial infarction develops in 12% to 20% of patients having unstable stenocardia. However, after MM-wave therapy, myocardial infarction developed in none of the patients with unstable stenocardia. Thus, the involvement of MM-wave therapy in the combined treatment of unstable stenocardia decreased the risk of myocardial infarction.

Myocardial infarction is the most severe ischemic disease of the heart. At the acute stage, it is most dangerous for the patient to develop such complications as a cardiac-rhythm disorder or acute left ventricular failure. Serious postinfarction complications include the development of chronic circulatory deficiency and early postinfarction stenocardia. When MM-wave therapy was administered within the first hours of myocardial infarction and its complications, it

decreased the number of episodes of acute left ventricular failure. It also decreased the rate of postinfarction stenocardia and chronic circulatory deficiency. Furthermore, MM-wave therapy substantially increased the Garkavi-Kvakina-Ukolova index [82]. It is known that myocardial infarction shocks a person. Shock reactions worsen the disease course. This forms a vicious pathogenic circle. It was shown that patients with an acute stress reaction revealed a greater leukocyte count and a longer pain syndrome. Such patients exhibit the greatest death rate. Before treatment, stress reactions were observed in 55.6% of patients, whereas calm activation reactions were found in 21.0% of patients. After a course of treatment, stress reactions decreased down to 11.1%. Calm activation reactions and training reactions were observed in 50.4% and 34.2%, respectively. Patients retaining stress reactions develop postinfarction stenocardia more often (as compared to those with reactions of other types). It was also found that patients who received MM-wave therapy revealed a raised degree of antioxidant protection. They exhibited a decrease in the malonic dialdehyde content. This substance is among the products of peroxide oxidation of lipids. It was also established that drug treatment caused no decrease in this index (Table 1).

Table 1. Malonic dialdehyde content in the blood plasma of patients with unstable stenocardia, nmol ml⁻¹

Group of patients	MM-wave therapy alone	Combined therapy (MM waves + drugs)	Placebo	Drug therapy
Before treatment	18.52±0.85	18.61±1.07	18.94±1.44	18.14±1.08
After treatment	14.61±1.03	13.76±0.97	17.97±1.17	17.90±1.24

The superoxide-dismutase (SOD) enzyme is an important component of antioxidant protection. According to present-day views, when the SOD activity decreases below 50% of the norm, the concentration of superoxide anion radicals shows an uncontrolled increase. This may cause irreversible changes in cells and tissues. MM-wave therapy enhances the activity of this enzyme, which increases the degree of cell protection. These changes take place in blood plasma and thrombocytes (Table 2).

Table 2. Superoxide dismutase activity in patients with unstable stenocardia

Group of patients	MM-wave therapy alone	Combined therapy (MM waves + drugs)	Placebo	Drug therapy
Before treatment				
– in plasma (a.u./ml)	1.87±0.08	1.82±0.12	1.85±0.12	1.91±0.14
– in thrombocytes (a.u./protein mg)	6.95±0.28	6.78±0.24	6.92±0.45	6.81±0.63
After treatment				
– in plasma (a.u./ml)	4.52±0.50	4.23±0.29	2.96±0.38	2.94±0.46
– in thrombocytes (a.u./protein mg)	8.75±0.61	8.81±0.32	6.64±0.72	6.93±0.49

The deposition of immune complexes on the arterial wall may cause atherosclerosis. The liberation of vasoactive amines under the action of immune complexes increases the vascular wall permeation. This promotes the penetration of immune complexes into tissues, the arterial

wall included. The interaction between immune complexes and thrombocytes enhances the activation and adhesion of thrombocytes, which may cause thrombus formation.

MM-wave therapy was found to significantly decrease the CIC count of blood plasma in patients with cardiac ischemia. This phenomenon was not observed in the control group. This means that conventional drug therapy has no effect on the pathogenic aspect of cardiac ischemia. The complimentary activity of serum was found to decrease. This can be associated with a sluggish stimulation of the compliment by immune complexes. Hence, MM-wave therapy makes it possible to correct for immunologic disorders in patients with cardiac ischemia. This can be of value not only for treating this nosology, but also for treating the atherogenic process on the whole.

Microcirculatory disorders are a serious element of cardiovascular pathologies. Tissue perfusion can be impaired not only in the case of atherosclerosis of main vessels but also in the case of microcirculatory blocking. The latter is caused by microscopic thrombi and inelastic erythrocytes.

Investigations were made of microcirculation in the bulbar conjunctiva of patients with cardiac ischemia who received MM-wave therapy. It was found that the MM-wave therapy produced a significant decrease in the total conjunctival index as well as in the index of vascular and intravascular changes. It also enlarged the arteriole caliber, increased the number of functioning limbic ansae, and decreased the content of erythrocyte aggregants in venules. The cerebral blood circulation was estimated in hypertonic patients administered to MM-wave therapy. This was done with the aid of dynamic scintigraphy of cerebral circulation using ^{99m}Technetium labeled compounds. The results obtained revealed blood flow improvement in affected arteries and improved blood circulation in ischemia-stricken regions.

According to the World Health Organization, the death rate of cancer ranks second to the cardiovascular one.

Clinical evaluation of low-intensity MM-wave radiation and development of therapeutic techniques for cancer treatment have been carried out since 1980. These investigations were pursued at the P. A. Gertsen Moscow Cancer Research Institute [44]. They were made in patients with mammary cancer. First, this disease is widespread, and, second, this pathology is often treated using radiotherapy and antineoplastic pharmaceuticals. Such treatment causes changes in human vital functions. The studies were made in patients having mammary cancer of the II-b and III-b stages who received chemotherapy and radiotherapy. The structural and functional state of blood cells was examined before treatment, after three MM-wave irradiation sessions, in the middle of the cure, and after its termination. The human general state was assessed by subjective data, symptomatology, and adapting reactions. The type of such reactions was determined from lymphocyte percentage, leukocyte formula, and the ratio of leukocytes to segmented neutrophils.

Chemotherapeutic compounds were introduced before surgical excision according to the following scheme: 3 g of fluoruracil, 2.8 g of cyclophosphane, and 60 mg of methotrexate.

Before antineoplastic pharmacotherapy, patients were subjected to a 3-day MM-wave irradiation: 60-min daily sessions. During chemotherapy, irradiation was performed 1 h before the introduction of antineoplastic compounds. When a chemotherapy course was finished, MM-wave irradiation was administered for the next 3 days. Usually, a course of MM-wave therapy consisted of 14 to 15 sessions. This cure was administered to 343 patients. A control group embraced 339 patients who received chemotherapy according to the above-described scheme. When the combined treatment was finished completely, 95.1% of the patients exhibited a satisfactory general state (without blood-circulation stimulants). When the chemotherapy

course (without MM-wave irradiation) was finished, 74.2% of patients revealed an unsatisfactory general state as well as a reduced leukocyte count of blood. This occurred in spite of the fact that the patients received blood transfusion and blood-circulation stimulants. This regularity persisted during subsequent (adjuvant) chemotherapy courses. In the first year of treatment, adjuvant chemotherapy was administered every three months (not more than three courses). In the second year of treatment, it was administered twice at an interval of 5 months.

The ability of MM waves to normalize the leukocyte count was investigated in patients with leukopenia. The investigation was made in 900 patients whose initial leukocyte count of blood was less than 3,000 (from 2,300 to 2,700). A course of treatment lasted for 12 days. The sessions were administered daily. After the cure, the leukocyte count of blood was normalized in 80% of the patients. This allowed the patients to undergo a complete course of chemotherapy.

The bone marrow was examined in patients taking antineoplastic compounds and receiving MM-wave therapy. The results obtained demonstrated that MM-wave therapy initially ejected reserved blood from blood pools. It increased the total volume of circulating blood, which improved oxygen exchange. This might result in a better tolerance to antineoplastic compounds and reduced side toxic effects. The proliferative activity of the bone marrow was found to grow 4 to 5 days after the MM-wave therapy commencement.

Hence, the clinical findings show that MM waves allow cancer patients to undergo a complete course of chemotherapy without a significant decrease in their blood indices and without blood-circulation stimulants.

Melanoma is a highly malignant tumor of the skin. It spreads to other parts of the body via the bloodstream or the lymphatic channels. The rate of this disease has increased over the last several owing to environmental pollution. Surgical excision is common for treating melanomas. When melanoma has metastases, it is regarded incurable: a five-year survival remains very rare. According to Russian and foreign scientists, the survival rate constitutes 75% at the first clinical stage, 32% at the second one, and 0% at the third one. Skin melanoma metastases occur in 20% to 25% of primarily treated patients within 6 to 18 months. When the process has spread, chemotherapy is used. However, melanoma remains resistant to antineoplastic compounds. Adjuvant chemotherapy courses following surgical excision postpone neither metastasis development nor tumor relapses. MM-wave radiation was employed to prevent relapses and metastases in patients with primary melanoma of the skin after surgical treatment. The clinical experience gained demonstrated a beneficial effect of MM waves. The first course of treatment consisted of 10 daily sessions lasting for 60 min. The MM-wave irradiation sessions were performed immediately after surgical intervention. The second course was administered 1 month after the first one terminated. The third course was performed 3 months after the second, whereas the fourth course was conducted 6 months after the third. Dynamic observation lasted for 9 to 18 months. None of the patients revealed relapses or metastases. Apparently, MM-wave irradiation stimulated the immune system and thus enhanced the individual's natural antineoplastic protection.

Apart from that, scientists of the P. A. Gertsen Moscow Cancer Research Institute studied the effect of MM-wave radiation on the course of wound processes. The investigations were performed in 1,302 patients having both sutured and open wounds (after laser tumor excision). The experimental and control group consisted of 651 patients. The wound process was evaluated by the degree of inflammation, necrosis, and granulation, as well as by the terms of granulation, epithelization, and healing. A course of treatment comprised 15 daily sessions lasting for 60 min. In the case of open superficial wounds, the device's horn was positioned on the skin at a distance of 2 to 2.5 cm from the wound. When operations were performed on the

abdominal cavity and thorax, the horn was positioned on the sternum. The results obtained revealed that MM-wave radiation produced a favorable effect on wound healing. The patients noted pain and discomfort alleviation in the wound. At the first stage of wound process (when tissue alteration is most pronounced), MM-wave irradiation suppressed necrosis and perifocal inflammation. When vascular reactions (such as edema and hyperemia) predominated, MM-wave irradiation eliminated them 3 to 5 days after the treatment commencement. In the control, these reactions persisted for not less than 8 days. An antiphlogistic effect of MM-wave radiation was most pronounced in patients with sutured wounds. None of the patients subjected to MM-wave irradiation revealed the opening of sutures, whereas 9% of patients of the control group did not hold their sutures. Presumably, MM waves recovered microcirculation and effective receptors, which normalized wound healing autoregulation. It is significant that MM-wave-based wound healing did not result in ugly scars or keloids. This is of special importance for facial treatment.

When MM-wave radiation was used to heal open wounds, the following results were obtained. Granules revealed an early maturation—on the third to fifth day. Wounds revealed overall mature granulation (as distinct from nonlaser wounds that exhibit insular granulation). Overall mature granulation expedited wound closure by 5 to 7 days. Granulation overgrowth was not observed. MM-wave radiation facilitated wound epithelization. It started uniformly at wound edges. This resulted in the concentric contraction of wound edges and skin regeneration. A daily growth of epithelium reached 2 to 3 mm. So, MM-wave radiation gave rise to optimum wound healing, which curtailed the healing by 3 to 5 days.

The clinical studies of MM waves applied in traumatology and orthopedy were launched at the N. N. Priorov Central Research Institute for Traumatology and Orthopedy. Since 1987, this technique has been used there in thousands of patients with various bone-muscular pathologies. The latter include serious shotgun wounds of limbs, which are often encountered in the Russian Federation. Between 1987 and 1990, this technique was used to treat severe war pathologies of the locomotor system under extreme conditions. MM-wave therapy was approved by the Central Military Hospital of the Defense Ministry of the Afghanistan Republic (the N. N. Priorov Central Institute for Traumatology and Orthopedy had direct scientific contacts with this hospital during that time). MM-wave therapy was also applied to the victims of the Armenian earthquake, various natural disasters, and diverse catastrophes. They were also treated at the N. N. Priorov Central Institute for Traumatology and Orthopedy [89–92]. Cytological examinations were conducted to demonstrate that the therapeutic effect of MM waves may result from the enhanced proliferative potential of exposed cells. The action of MM waves stimulates the synthesis of cytotoxins in cytoplasm. Cytotoxins produce an effect that is similar to the growth factor. Although cytotoxins are accumulated in cytoplasm, they can be secreted out. As a result, they can produce both contact and distant effects. It seems that the stimulating effect of MM waves on cell growth is not restricted to cutaneous fibroblasts and blood lymphocytes. Evidently, this effect has a universal character and involves cells of various tissue architectures.

When treating orthopedic and traumatic patients, MM waves should produce an effect on cellular growth regulation and cytodifferentiation. This is essential to stimulate reparation processes in the affected region. MM-wave therapy acts as a biological component of the complex therapy. The latter is targeted at the recovery of functional capabilities of tissue structures that are either affected by or involved in the bone-muscular pathology.

Over the last decade, EHF therapy has been firmly established as one of the most effective methods of conservative treatment of orthopedic, traumatic, and surgical patients. The application of EHF therapy at the N. N. Priorov Central Institute for Traumatology and Orthopedy yielded broad experience of using MM waves in the complex treatment of patients with trophic and tissue-viability disorders (typical of shotgun wounds). It can be stated that

MM waves provide a new quality of treatment, which overcomes the previous problems of medical rehabilitation of such patients. This is confirmed by an analysis of the results of using EHF therapy for different bone-muscular pathologies complicated by impaired tissue trophics and inhibited repair processes in the affected region.

An investigation was made of applying EHF therapy to patients with neurodystrophic changes in tissue trophics. These changes were caused by shotgun wounds of limbs. Clinically, these patients revealed persistently aggravating suppurative-necrotic processes in their amputation stumps. The results of MM-wave treatment are listed in Tables 3 and 4.

Table 3. Results of using EHF therapy to prepare ample festering wounds of amputation stumps for skin plasty

Preparation technique	Number of patients	Wound stage duration	
		Exudation	Regeneration
With EHF therapy	15	10±0.4	7±0.2
Without EHF therapy	10	14±0.6	10±0.7

Table 4. Wound planimetry of amputation stumps under EHF therapy

Groups of patients	Number of patients	Initial wound area (mm ²)	In-a-week wound area (mm ²)	Daily wound-area decrease (mm ²)
With MM-wave therapy	22	741.6±180.7	539.1±134.4	3.9±0.2
Without MM-wave therapy	26	985.1±250.3	981.0±240.4	0.1±0.04

The normalizing effect of MM-wave therapy on wound healing was also confirmed by the time history of adapting reactions. Before MM-wave treatment, an absolute majority of patients (91.8%) revealed a stress reaction that was prognostically unfavorable. Under the action of MM-wave therapy, they changed their type of adapting reactions. This resulted from a sharp decrease in the number of patients with stress reactions (13.5%) as well as from a simultaneous increase in the number of patients with raised (59.5%) and calm (24.3%) activation. These findings were evidence that MM waves can produce a beneficial effect on neurodystrophic processes. This improves tissue trophics and viability in the affected region.

MM-wave therapy was also found to be highly effective in treating chronic (shotgun and traumatic) osteomyelitis and pressure sores. It was also demonstrated both to decrease the microbial semination of wounds and to facilitate the jointing of bone fractures.

MM-wave therapy efficiency was investigated at the Central Research Institute for Tuberculosis. To this end, patients with various forms of pulmonary tuberculosis received a basic course of chemotherapy using 3 or 4 tuberculostatic compounds (such as isoniazid, rifampin, pyrazinamide, and kanamycin). At different stages, basic chemotherapy was combined with a course of MM-wave therapy. Experimental and clinical studies revealed that low-intensity MM waves produced a normalizing effect on many clinical parameters, such as the formed elements of blood and blood plasma proteins. In addition, MM waves stimulated lymphocyte proliferation in immunogenic organs. As a result, macrophages present in the bone marrow actively invaded tuberculosis-stricken organs (mainly, the lungs) to normalized external respiration and regional circulation in them. Additionally, macrophages favored the homeostasis recovery during chronic infections, such as tuberculosis [52].

MM-wave therapy was also employed in the complex treatment of sarcoidosis of lungs and intrathoracic lymph nodes. After a course of treatment (20 sessions), the patients were

subjected to X-ray examination. It revealed a noticeable resolution of parenchymal-interstitial infiltration, disappearance of granuloma shadows, as well as reduction of alveolitis symptoms, interstitial edema, and pleural reactions. The size of intrathoracic lymph nodes decreased by half. The phagocyte function of macrophages was substantially activated in granuloma-stricken regions, separate lung regions, and blood. In other words, the functional activity of immunocompetent cells was universal. It is significant that MM-wave therapy reduced the dose of corticosteroid compounds: they were taken at a dose of 10 to 15 mg every other day. Moreover, corticosteroid compounds were completely cancelled in half of patients with firstly-diagnosed caroidosis.

Gastric and duodenal ulcers are among widespread digestive diseases. Ulcer strikes 7% to 10% of adult population in developed countries. The last several years have shown tendency to increase the number of primarily diagnosed ulcers, especially in young people.

At present, ulcer is widely treated using complex pharmacotherapy. The latter is targeted at different pathogenic mechanisms of the disease. However, pharmacotherapy is not very effective: chronic ulcers heal over for a long time, therapeutic results are unstable, and 30 to 40% of the patients are resistant to the treatment. When patients simultaneously take up to 3 drugs, 18% of them may exhibit side effects. A simultaneous intake of 5 to 6 drugs may cause side effects in 81% of the patients. This is because many drug compounds suffer from various toxic side effects and may cause allergies.

MM-wave therapy efficiency was assessed in more than 3,000 patients with ulcer (experimental group). The results obtained were compared to those obtained for drug-treated patients (control group). These patients received a traditional complex of drug compounds (such as antacids, spasmolytics, secretion inhibitors, and reparants).

Ulcers healed over in 98.6% of patients of the experimental group and in 82% of patients of the control group. The healing lasted for 21.1 ± 1.4 days in the experimental group and for 37.5 ± 1.9 days in the control group. Note, duodenal ulcers healed over faster than gastric ulcers in both groups. For example, the healing of duodenal ulcer lasted for 17.6 ± 1.2 days in the experimental group and for 35.8 ± 2.0 days in the control group, whereas the healing of gastric ulcer lasted for 28.1 ± 2.1 days in the experimental group and for 45.1 ± 5.3 days in the control one.

Patients who underwent MM-wave therapy were subjected to a follow-up study. To this end, a dynamic endoscopic examination was made 3 to 4 months after the treatment. Relapses were revealed in 51% of patients of the experimental group and in 82% of patients of the control group. MM-wave therapy increased the level of antioxidant activity and normalized the rheological properties of blood. For example, it decreased blood viscosity, packed cell volume, and erythrocyte deformability index. It is also significant that patients with erythrocyte aggregation exhibited a decreased aggregation rate, and conversely, patients without erythrocyte aggregation revealed a raised aggregation rate. In addition, MM-wave therapy normalized phagocytosis [49].

Unfortunately, the limited space of this publication disallows us to tell the reader about all MM-wave therapy capabilities. Clinical studies have reliably verified the high efficiency of this technique with respect to more than 120 nosologic forms (and this number is becoming larger). Evidently, MM-wave therapy is a method about which ancient physicians used to dream: it “treats a person, not a disease.”

Conclusions

Summarizing the results of the 30-year study of biological effects of low-intensity MM waves, we may ascertain the following. As it often happens, applied research and commercialization have outdistanced fundamental investigations. The wide application of MM waves in medicine, biotechnology, animal husbandry, and plant cultivation has taken a giant step forward. By this time, Russia has manufactured more than 10,000 MM-wave therapy devices, organized more than 2,500 MM-wave therapy rooms, and treated over 2,500,000 patients. Since 1992, twenty-seven volumes of the Journal on *Millimeter Waves in Biology and Medicine* (*Millimetrovye Volny v Biologii i Meditsine*) have been published as well as 12 symposia on *Millimeter Waves in Biology and Medicine* and 11 workshops have been held. During this time, we have issued 13 volumes of symposium and workshop proceedings, 4 monographs, 3 popular scientific brochures, and more than 2,600 articles. Furthermore, our scientific attainments have been protected by 22 Russian Federation patents. In the year 2000, we were awarded the Russian Federation State Prize in Science and Technology for our research in this field of science.

However, scientists—biophysicists, physiologists, and physicians—carry on their further scientific investigations into the mechanism of biological effects. By now, they have approached a more complete understanding of the role of low-intensity MM-wave radiation in the vital processes of biological systems at different organization levels.

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