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Thermal Therapy, Part 1: An Introduction to Thermal Therapy

Riadh W. Y. Habash,[1*] Rajeev Bansal,[2] Daniel Krewski,[3] and Hafid T. Alhafid[4]

[1]McLaughlin Centre for Population Health Risk Assessment, Institute of Population Health/School of Information Technology and Engineering, University of Ottawa, Ottawa, Ontario, Canada; [2]Department of Electrical and Computer Engineering, University of Connecticut, Connecticut, USA; [3]McLaughlin Centre for Population Health Risk Assessment, Institute of Population Health, University of Ottawa, Ottawa, Ontario, Canada; [4]College of Engineering and Applied Sciences, Al Ghurair University, Dubai, UAE

Address all correspondence to Riadh W. Y. Habash, McLaughlin Centre for Population Health Risk Assessment, Institute of Population Health, University of Ottawa, One Stewart Street, Room 320, Ottawa, Ontario, Canada K1N 6N5; rhabash@site.uottawa.ca

ABSTRACT: Thermal therapy is widely known and electromagnetic (EM) energy, ultrasonic waves, and other thermal-conduction-based devices have been used as heating sources. In particular, advances in EM technology have paved the way for promising trends in thermotherapeutical applications such as oncology, physiotherapy, urology, cardiology, ophthalmology, and in other areas of medicine as well. This series of articles is generally written for oncologists, cancer researchers, medical students, biomedical researchers, clinicians, and others who have an interest in this topic. This article reviews key processes and developments in thermal therapy with emphasis on two techniques, namely, hyperthermia [including long-term low-temperature hyperthermia (40–41°C for 6–72 hr), moderate-temperature hyperthermia (42–45°C for 15–60 min), and thermal ablation, or high-temperature hyperthermia (> 50°C for > 4–6 min)]. The article will also provide an overview of a wide range of possible mechanisms and biological effects of heat. This information will be discussed in light of what is known about the degree of temperature rise that is expected from various sources of energy. The review concludes with an evaluation of human exposure risk to EM energy or the corresponding heat, trends in equipment development, and future research directions.

KEYWORDS: EM bioeffects, EM exposure guidelines, heat mechanisms, side effects of heat, EM risk assessment

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I. INTRODUCTION

Advances in electronics and electromagnetic (EM) theory have set the stage for an unprecedented drive toward the development of medical devices with various diagnostic and therapeutic applications. Radiofrequency (RF) (hundreds of kilohertz to a few megahertz) and microwaves (hundreds of megahertz to approximately ten gigahertz) are forms of nonionizing radiation unlike much higher frequencies (above visible light) in the EM spectrum, which are ionizing. Therapies using EM sources at RF and microwave frequencies have been called diathermy. These therapies have been applied in a number of frequency regions along the EM spectrum as shown in Figure 1. Included among these thermotherapies are hyperthermia and thermal ablation.

Thermal therapy, or thermotherapy, encompasses all therapeutic treatments based on the transfer of thermal energy into or out of the body. In clinical settings, the major objective of thermal therapy is to achieve an efficacious treatment outcome without damaging normal tissues. The extent of initial tissue necrosis is predominantly determined by the thermal power and energy applied to the tissue before charring.[1] The use of heat alone or in combination with radiotherapy or chemotherapy to increase direct ablation of tumors is the subject of this series of articles.

In recent years, a range of medical applications based on various sources of energy especially EM power have widely been investigated.[2–4] Due to the wide range of possible therapeutic effects, thermal therapy is practiced with large considerable variation in methodology based on geography as well as subdisciplines within the medical community.[5] Several books, handbooks, and review papers providing good background information on thermal therapy have been published over the years. Michaelson and Lin[6] reviewed biological effects and health implications of RF radiation. Thuery[7] described the industrial, scientific, and medical (ISM) applications of microwaves. Rosen and Rosen[8] discussed a number of topics related to microwave therapeutic medicine. Polk and Postow[9] reviewed biological effects of EM fields. Habash[10] discussed human bioeffects and safety consideration related to EM fields. Rosen et al.[3] highlighted medical applications of RF and microwaves with emphasis on newer emerging diagnostic and therapeutic applications such as microwave breast cancer detection and treatment with localized high power used in ablation of the heart and liver, benign prostate hypertrophy, angioplasty, and others. Habash et al.[11] reviewed and evaluated the literature on acute and long-term health risks associated with RF radiation. Dewhirst et al.[12] presented an overview on the carcinogenic effects of hyperthermia alone or combined with known carcinogens such as ultraviolet (UV), ionizing radiation, and chemical carcinogens. Stauffer and Goldberg[5] introduced thermal ablation therapy covering a range of ablation articles included in a special issue on the same subject published by the *International Journal of Hyperthermia*.

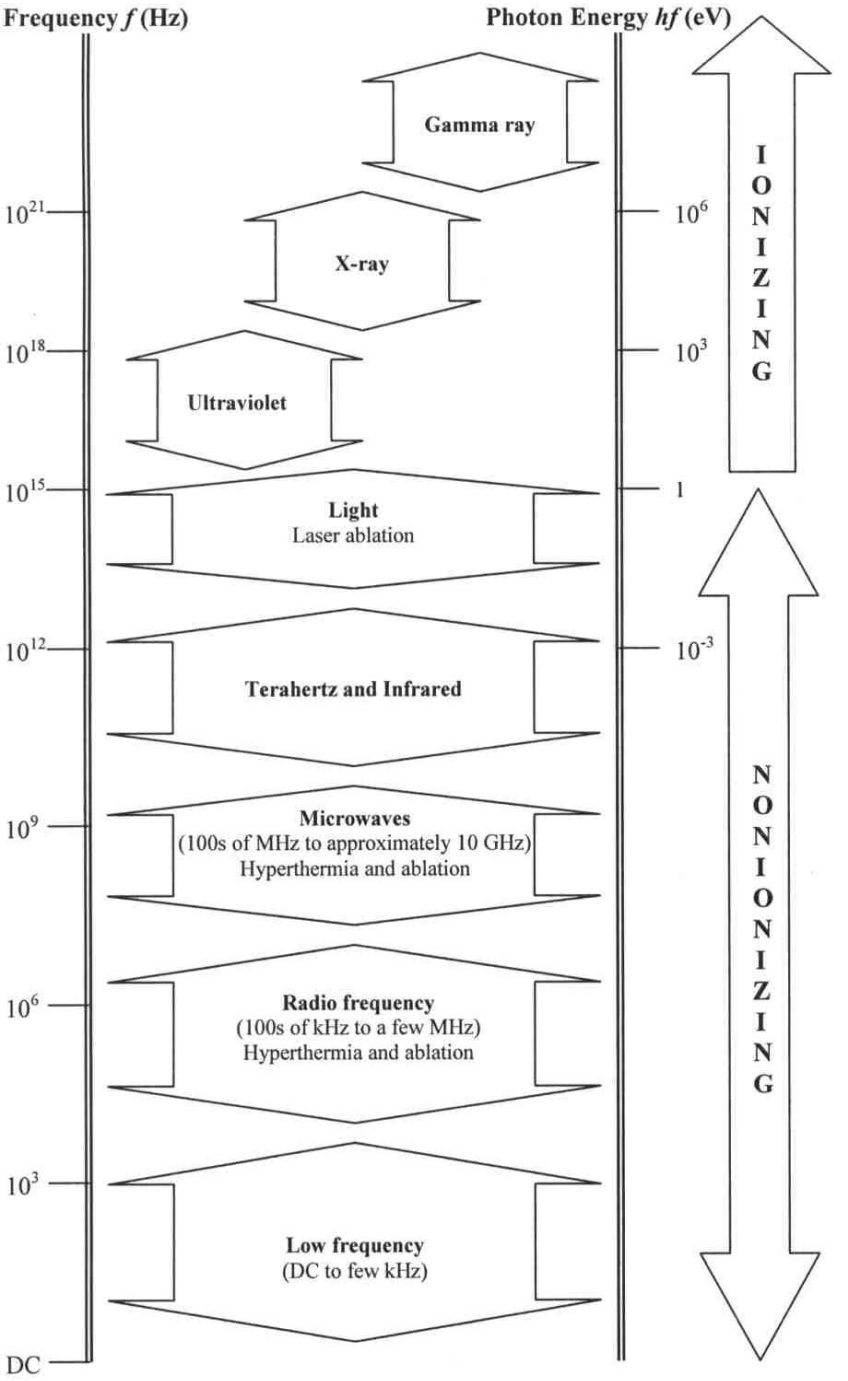

FIGURE 1. Thermal therapy applications along the EM spectrum.

Haveman et al.[13] overviewed the current knowledge about effects of hyperthermia at temperatures used in clinical oncology on the peripheral nervous system. Stauffer[14] reviewed the technology used for thermal therapy of cancer, with emphasis on the evolution of equipment from basic single-element devices of the early 1980s to adjustable multielement heating devices in use or in final stages of development. Vander Vorst et al.[4] addressed the needs of today's engineering community with an interest in the use of RF and microwave energy in public health and in medicine. These authors devoted one chapter of their book to thermal therapy and another chapter to delivery systems for therapeutic applications. Ayrapetyan and Markov[15] edited a book covering a very broad range of frequencies and amplitudes in 24 articles arranged in four chapters on the mechanisms of EM interactions with biological systems, EM therapy, EM dosimetry, and epidemiology and policy.

In general, thermal therapy is categorized into the following three different modalities according to the temperature level and time duration:

1. **Diathermia.** Heating up to 41°C, with applications in physiotherapy for the treatment of rheumatic diseases.
2. **Hyperthermia.** The temperature of a part of the body or of the whole body can be raised to a higher-than-normal level (41–45°C), which may allow other types of cancer treatments (radiation therapy or chemotherapy) to work better. This type of hyperthermia has applications in oncology for cancer treatment and will be investigated in our second article (Part II).
3. **Thermal ablation.** Very high temperatures (above 45°C) can be used to destroy cells within a localized section of a tumor. This is commonly used in oncology for cancer treatment, in urology for benign prostatic hyperplasia (BPH) treatment, and in cardiology for heart stimulations, and also in other areas. Thermal ablation will be discussed in the third article (Part III).

This article reviews key aspects of thermal therapy applications emphasizing two techniques, namely, hyperthermia and thermal ablation, with particular emphasis on EM energy sources. The article will also provide an overview of the heating mechanisms and health effects of heat. This information will be discussed in light of what is known about the degree of temperature rise that is expected from EM exposures. The review concludes with an evaluation of human exposure risk to EM energy or the corresponding heat, and trends in equipment development. Future research directions are also suggested.

II. BIOLOGICAL EFFECTS OF EM ENERGY

The interaction of EM fields with living systems can be considered at the molecular, subcellular, cellular, organ, and/or system levels, as well as within the entire body. The word "interaction" is important here since it signals that the end

results do not only depend on the action of the field but are also influenced by the reaction of the living system to exposure to EM fields. Living systems have a great capacity to compensate the effects induced by external influences, including exposure to EM fields.[16] Biological effects due to exposure to EM radiation are differentiated into three levels, namely, (1) high-level (thermal) effects, (2) intermediate-level (athermal) effects, and (3) low-level (nonthermal) effects.

A. Thermal Effects

Thermal effects have been known since investigations into therapeutic applications of electricity were carried out based on studies in electromagnetics by Faraday, Ampere, Gauss, and Maxwell, and the development of alternating current (AC) sources by d'Arsonval and Tesla. Heating is the primary interaction of EM radiation at high frequencies, especially those above about 1 MHz. Below about 1 MHz, the induction of currents in the body is the dominant action of EM fields. A possible effect of EM fields at low frequencies on living systems has been theorized to involve the ability, through magnetic induction, to stimulate eddy currents at cell membranes and in tissue fluids, which circulate in a closed loop that lies in a plane normal to the direction of the magnetic field. However, secondary magnetic fields produced by such currents may be neglected. The above currents can be calculated using only Faraday's law and Laplace's equations, without simultaneously solving Maxwell's equations. Hence, both current and electric fields are induced inside living systems by external magnetic fields.

When EM radiation interacts with matter, it can be absorbed, transferring the energy to the medium. The absorption process is divided into certain categories that correspond to modes of molecular energy storage. These categories include thermal, vibrational, rotational, and electronic modes. The thermal mode of energy storage consists of translational movement modes in which atoms move horizontally and vertically about their lattice points in a medium. This is commonly referred to as heat. The amount of energy that a material will absorb from radiation depends on the operating frequency, intensity of the beam, and duration of exposure. The most important of these parameters is the operating frequency. EM radiation can excite translational and vibrational modes and generate heat. The intensity of the beam is also a factor in determining how much energy is absorbed. The larger the intensity of the beam, the more energy is available to be transferred. Also, the longer the duration of exposure, the greater the amount of energy that will be absorbed. The rate of change of the energy transferred to the material is called the absorbed power. This power is also called power transferred, but from the bioelectromagnetics point of view, the term specific absorption rate (SAR) is the preferred one. SAR is a quantity properly averaged in time and space and expressed in watts per kilogram (W/kg). SAR values are of key importance when validating possible health hazards and setting safety standards (see Part IV for details).

Thermal effects of EM radiation depend on the SAR spatial distribution. For example, 1 W/kg yields an increase of 1°C in the human body, taking thermal regulation into consideration. SARs above 15 W/kg can produce temperature increases of more than 5°C.[16] Thermal effects imposed on the body by a given SAR level are strongly affected by ambient temperature, relative humidity, and airflow. The human body attempts to regulate a temperature increase due to thermal effect through perspiration and heat exchange via blood circulation. Certain areas with limited blood circulatory ability, such as the lens of the eye and the testes, are at particularly high risk of being damaged by the induction of cataracts and burns. Finally, it is worth mentioning that most adverse health effects due to EM radiation between 1 MHz and 10 GHz are consistent with responses to induced heating, resulting in raising tissue temperatures higher than 1°C.

B. Nonthermal and Athermal Effects

Controversy surrounds two issues regarding the biological effects of intermediate- and low-level EM radiation. The sources of controversy are both scientific and extrascientific. First, there has been scientific debate about whether the radiation at such low levels can cause harmful biological changes in the absence of demonstrable thermal effects. Second, there has been discussion about whether effects can occur from EM radiation when thermoregulation maintains the body temperature at the normal level despite the EM energy deposition, or when thermoregulation is not challenged and there is no significant temperature change. In response to the first issue, investigations on the extremely low-level EM radiation have been conducted, but the results to date remain inconclusive. Regarding the second issue, there can be two interpretations of the term "effect." It may mean an effect when there is no evident change in temperature or when the exposure level is low enough not to trigger thermoregulation in the biological body under irradiation, suggesting that physiological mechanisms maintain the exposed body at a constant temperature. Such cases are related to a nonthermal effect where the effect occurs through mechanisms other than those due to macroscopic heating. The second interpretation is that EM fields cause biological effects without the involvement of heat. This is sometimes referred to as an "athermal effect." In this case, the thermoregulatory system maintains the irradiated body at its normal temperature. Meanwhile, the macroscopic behavior of the body emerges out of quantum dynamics producing the physics of living matter to a point where biochemistry has to be considered.[10]

A review of the literature on the effects of intermediate- and low-level EM radiation shows that exposure at a relatively low SAR (less than 2 W/kg) under certain conditions could affect the nervous system.[17–20] This includes effects on the blood-brain barrier (BBB), morphology, electrophysiology, neurotransmitter activity, and metabolism. Also, EM radiation at such levels might affect the immune system, gene and chromosomal morphology, enzyme activity, neurological

function, cell morphology, membrane ion permeability, intracellular ion concentration, mutation rates, tumor promotion, endocrine secretion rates, etc. A few of the above effects are contradicted by other research findings, leaving our understanding unclear. In most cases the mechanisms of the effects are not understood.

C. Exposure Guidelines for EM Radiation

Scientists, engineers, technicians, and physicians have been concerned about the potential hazards of EM radiation since WW II. There have been repeated calls for measures that reduce EM exposure. During the past few decades, people have been especially concerned about the safety of radar equipment and microwave ovens. Currently, there is considerable concern about EM exposure from mobile phones and other EM equipment including those used for medical treatment and diagnosis. Exposure to EM fields can occur in residential, occupational, and medical settings. Common human-made sources of EM fields include monitors and video display units (3–30 kHz), AM radio (535–1705 kHz), industrial induction heaters (300 kHz–3 MHz), RF heat sealers, FM radio (88–108 MHz), television broadcast (54–88/174–220; 470–806 MHz), cellular phones (453–1880 MHz), microwave ovens (2450 MHz), radar, satellite links, and microwave communications (3–30 GHz).[11,21] Medical exposures can come from thermal therapy equipment to treat cancerous tumors, electrosurgical devices for cutting and welding tissues, and from diagnostic equipment such as medical resonance imaging (MRI).[22]

Expert scientific groups have conducted critical assessments of the reported biological effects of EM fields. The evaluations form the basis for EM exposure guidelines. Extrapolating from biological effects to possible adverse human health consequences is not straightforward and is subject to uncertainty. Biological effects can be defined as any measurable changes in a biological system in response to exposure to, for example, EM fields, although not all biological effects will necessary be harmful. The exposure levels considered likely to be harmful to human health are determined based on careful evaluation of the available scientific data. Guidelines for human exposure to EM fields are generally called maximum permissible exposure (MPE) values, or reference levels. Guidelines recommending limitations in RF exposure have been continually evolving for over a decade.

Many countries have developed guidelines by either adopting or adapting the recommendations of major organizations such as the Institute of Electrical and Electronics Engineers (IEEE),[23–26] the National Radiological Protection Board (NRPB) of the United Kingdom,[27–30] the Federal Communications Commission (FCC) of the United States,[31] the International Commission on Non–Ionizing Radiation Protection (ICNIRP),[32–34] Health Canada,[35] and the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA).[36] In 1999, the Council of the European Communities issued recommendations concerning exposure of

the general public to EM fields, adopting the ICNIRP guidelines.[37]

As with exposure limits for many potentially hazardous substances, exposure safety standards in most countries have two tiers, which vary in definition but correspond approximately to limits for occupational groups (controlled environments) and the general public (uncontrolled environments). In the controlled environment, the exposure is limited to individuals who are aware of the possibility of exposure. Uncontrolled environments are accessible to individuals who may not have this awareness, including the general public, which may limit their ability to respond appropriately if they enter areas with excessive exposure. For the above reasons, exposure limits for many agents are higher for occupational groups as compared to those of the general public.

The SAR value of 4 kW/kg was set up by the IEEE for the whole-body-averaged SAR. This value is reduced by a factor of 10 to establish exposure guidelines in controlled environments, and then by another factor of 5 for a total factor of $5 \times 10 = 50$ for exposure in uncontrolled environments. These uncertainty factors of 10 and 50 are introduced in order to allow for unfavorable thermal, environmental, and possible long-term effects. Therefore, the resulting basic restrictions on whole-body SAR are 0.4 W/kg for controlled environments, and 0.08 W/kg for uncontrolled environments. The same restriction is adopted by the ICNIRP and other organizations. There are two local SAR safety limits, namely, 1.6 W/kg averaged over 1 g (SAR_{1g}) in North America, and 2 W/kg averaged over 10 g (SAR_{10g}), developed by the ICNIRP and accepted for use in Europe, Australia, Japan, and other parts of the world. Whether 1.6 W/kg or 2 W/kg is the correct limit for EM exposure remains controversial.

Many forms of EM fields find applications in medical practice, often at exposure levels that are much greater than MPE levels. Thermal and EM exposures of patients lie outside the scope of MPE limits for workers and members of the public, since the risk/benefit considerations are very different in these circumstances.[22]

III. THERMAL THERAPY

A. History

The use of thermal energy for therapeutic purposes dates back thousands of years. In the splendor of the Roman Empire, thermal baths constituted a habit, often with complete facilities for the treatment of diseases involving the use of humid and dry heat in local or general applications. Probably the oldest report related to thermal therapy was found in the Egyptian Edwin Smith surgical papyrus, dated around 3000 BC. Researchers like to cite Hippocrates (460–370 BC) in particular, although the method he describes in one of his aphorisms, i.e., hot irons, involves higher temperatures, such as those used in cauterization. In the nineteenth and

twentieth centuries, fever therapy has been used as a method to increase temperature, while other investigators started to apply RF techniques in medicine.[38]

The modern discipline of thermal therapy emerged from a number of radiation-biology-oriented laboratories in the mid- to late 1970s.[39] Studies on cell cultures and on experimentally induced tumors in vivo provided convincing justification for the clinical application of heat. The rationale is based on a direct cell-killing effect at temperatures above 41–42°C.[40] At higher temperatures, equivalent levels of killing can be achieved with shorter exposure times.

Two key papers, published in the mid-1980s attracted attention to the opportunity to assess the efficacy of cell killing with heat.[41,42] These papers established the first concepts for thermal dosimetry and indicated that significant cell killing could occur if cells or tissues were heated to higher than 42°C for 1 hr or more. The application of heat has continued to increase in sophistication. Initially, treatments were limited to very cold (ice) or very hot (cautery) temperatures that could not be controlled but were maintained for a sufficient time to obtain visually obvious effects on surface tissues. Over time, there has been renewed interest in therapeutic applications of hot and cold temperatures, primarily due to limitations of conventional therapeutic modalities (surgery, chemotherapy, and radiotherapy) and improvements in devices and techniques used to deliver and monitor the effect of energy.[5,43,44]

Overall, enthusiasm for thermal therapy waned significantly in the mid- to late 1990s, partly as a result of the perceived difficulties in achieving adequate treatment as defined by the need to kill cells directly by heating.[45] The problem that was faced by the thermal-therapy community at that juncture was unrealistic thermal goals because of lack of adequate equipment for delivering thermal treatment and an inability to measure the treatment delivered. A combination of the above difficulties is still a challenge to the design and implementation of successful clinical trials.[46]

B. Cell Killing and Thermal Injury

The most apparent property of cells that is modified by temperature is growth rate, which increases with increasing temperature to some maximum temperature above which growth is sharply inhibited. In the hyperthermic region above the maximum growth temperature, there are three significant cellular responses for thermal therapy, namely, cytotoxicity, radiosensitization, and thermotolerance. These changes at the cellular level must be due to temperature-induced alterations in molecular pathways.[47]

The precise mechanism by which heat kills cells is still not known despite decades of scientific, medical, and commercial interest.[48] However, there is a widespread view that this killing is caused by thermal denaturation of critical targets in the cell.[49] Cell killing in the temperature range below 8°C increases sharply with decreasing temperature, and this process is called hypothermic kill-

TABLE 1
Effect of Temperature on Biological Tissues

Temperature Range (°C)	Time Requirements	Physical Effects	Biological Effects
< –50	> 10 min	Freezing	Complete cellular destruction
0–25		Decreased permeability	Decreased blood perfusion, decreased cellular metabolism, hypothermic killing
30–39	No time limit	No change	Growth
40–46	30–60 min	Changes in the optical properties of tissue	Increased perfusion, thermotolerance induction, hyperthermic killing
47–50	> 10 min	Necrosis, coagulation	Protein denaturation, not subtle effects
> 50	After ~ 2 min	Necrosis, coagulation	Cell death
60–140	Seconds	Coagulation, ablation	Protein denaturation, membrane rupture, cell shrinkage
100–300	Seconds	Vaporization	Cell shrinkage and extracellular steam vacuole
> 300	Fraction of a second	Carbonization, smoke generation	Carbonization

ing.[47] Classical hyperthermia relies on a temperature of 42°C to 45°C for periods of 30 to 60 min to cause irreversible cellular damage.[50] As the tissue temperature rises to 50°C, the time required to achieve irreversible cellular damage decreases exponentially. Protein denaturation occurs and leads to immediate cell death. Vaporization of tissue water is superimposed on this process between 100°C and 300°C. In addition, carbonization, charring, and smoke generation occurs at 300°C to 1000°C.[14,47,51,52] Table 1 summarizes the effects of temperature on biological tissues.

Tissue injury caused by heat occurs in two distinct phases. The initial phase is direct heat injury that is predominantly determined by the total energy applied to the tumor, tumor biology, and tumor microenvironment.[53] The mechanisms of direct thermal injury and thermosensitivity involve complex interactions within tumor tissue at cellular and subcellular levels. The cell membrane appears to be the cellular component most vulnerable to heat injury. The significance of Joule heating as a mode of injury can be estimated by first determining the tissue temperature as a function of time. Tropea and Lee[54] simulated Joule heating dynamics using a numerical method to solve the bioheat equation.[55] Joule heating density is the product of the electrical conductivity and the time-averaged square of the electric field. In vitro[56] and in vivo[57] studies demonstrate that tumor cells are destroyed at lower temperatures than normal cells.

The second phase is indirect injury after focal hyperthermia application, which produces a progression in tissue damage. This progressive injury may involve a balance of several factors including microvascular damage, ischemia-reperfusion injury, induction of apoptosis, Kupffer cell activation, altered cyto-

kine expression, and modulation of the immune response. The effects of heat depend on tissue temperatures attained, determined by the total thermal energy applied, rate of removal of heat, and the specific thermal sensitivity of the tissue.[1]

The underlying physical principles and engineering aspects of heating mechanisms have been described in a number of excellent review articles[12,52,58–65] and books.[4,38,66–69] In a comprehensive review of the literature, Dewhirst et al.[64] summarized the basic principles that govern the relationships between thermal exposure (temperature and time of exposure) and thermal damage, with an emphasis on normal tissue effects. Methods for converting one time-temperature combination to a time at a standardized temperature are provided as well as a detailed discussion about the underlying assumptions that go into these calculations. This review makes it clear that much more work needs to be done to clarify what the thresholds for thermal damage are in humans.

C. Thermal Therapy Treatment Protocols

Thermal therapy is currently implemented as a minimally invasive alternative to traditional surgery in the treatment of benign disease and cancer, as well as repair of sport injuries and tissue reshaping or modification.[39] Thermal ablation, thermal coagulation, hyperthermia, and thermotherapy are terms often used to describe the use of heat to directly modify or destroy tissues.[14] Figure 2 shows a schematic range for thermal therapies.

Throughout these four articles, we will use the following protocols that describe thermal therapy:

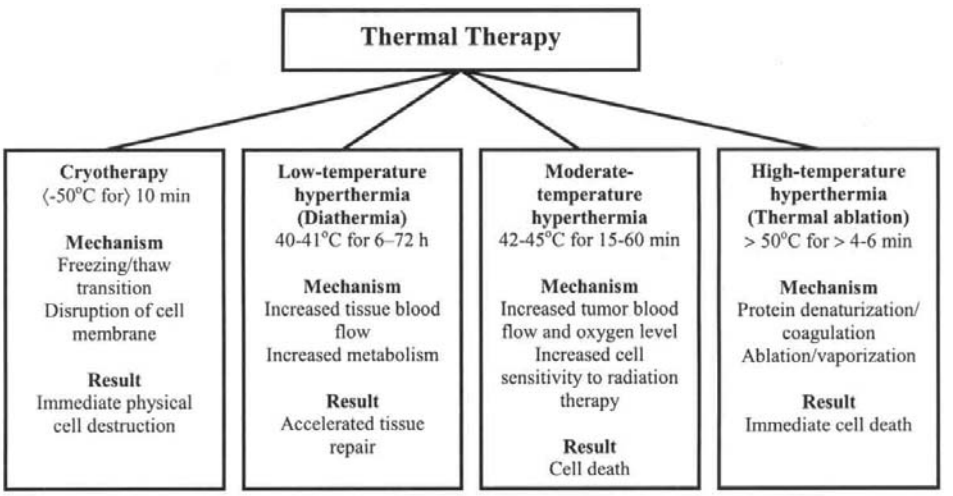

FIGURE 2. Schematic ranges of thermal therapy.

1. Cryoablation (T ⟨–50°C for ⟩ 10 min)
2. Hyperthermia
   a. Long-term low-temperature hyperthermia (40–41°C for 6–72 hr).
   b. Moderate-temperature hyperthermia (42–45°C for 15–60 min).
3. High-temperature hyperthermia or thermal ablation (> 50°C for > 4–6 min).

It is important to stress that thermal ablation and moderate-temperature hyperthermia should be viewed as complementary forms of thermal therapy. Based on realistic limitations of each approach, neither form of therapy is likely to replace the other. The beauty of thermal ablation is the ability to treat a tumor with a defined volume in sites where surgery itself is difficult (e.g., liver) or where organ function preservation is needed or desired (e.g., prostate, uterus). However, this form of therapy will find little use for large bulky tumors such as colorectal cancer primaries, soft tissue sarcomas, head and neck nodules, and superficial disease involving the skin. Whether a consequence of tumor size or infiltrative disease with borders that is difficult to define, there are applications that require more subtle moderate-temperature hyperthermia as opposed to complete ablation in order to preserve surrounding critical normal tissue structures.[5] Figure 3 shows the challenges to the development of thermal therapy.

IV. POSSIBLE SIDE EFFECTS OF EM ENERGY AND HEAT

It has been known for some time that high intensities of nonionizing radiation can be harmful due to the ability of its energy to heat biological tissue rapidly. This is the principle by which microwave ovens cook food, and exposure to high EM power densities, i.e., on the order of 100 mW/cm² or more, can result in heating of the human body. Tissue damage can result primarily because of the body's inability to cope with or dissipate the excessive heat. The amount of damage in tissue as a result of heating is dependent on both temperature and time. On a different note, Osepchuk and Petersen[69] have noted that millions of people experienced strong EM exposures via clinical diathermy during the last century, and with only beneficial consequences.

A. Tissue Physiology and Response to Heat

Heat causes numerous subtle changes in tissue physiology such as increased blood perfusion, vascular permeability, and metabolic activity. The most important physiological parameter in this context is blood flow. When any tissue is heated, various physiological changes occur, the majority of which are secondary to changes in blood flow.[70–72] Blood flow is also one of the major vehicles by which heat is dissipated from tissues; thus, the tissue blood supply will have a significant influence on the ability to heat tissues.[73] The lower the rate of blood

flow, the easier it is to heat. Although solid tumors can have blood flow values that can be greater than that of certain normal tissues, when compared to normal tissues the tumor blood supply is generally primitive and chaotic in nature, which can result in areas that are nutrient deprived, low in oxygen, and highly acidic, and cells that exist in these adverse conditions are generally more sensitive to the cytotoxic effect of heat.[72]

Toxicity of heat generated during thermal therapy in general is low. Burns represent typical thermal-therapy-associated toxicity with low incidence[74] that can be avoided via correct heating techniques. The primary hazards of thermal therapy are due to either increased body core temperature or increased temperature in specific organs. Regulation of the body core is critical in humans because numerous cellular structures and metabolic pathways are affected by changes in temperature. Body core temperatures range from 36°C to 38°C, but may increase during, for example, exercise and/or humid weather. Normally, in healthy persons such excursions seldom exceed 39°C. Compared with other species, humans are especially adept at dissipating heat through increased blood flow and increased sweating over most of the body surface.[75] Most healthy people can tolerate body core temperature excursions up to 40°C when adequately hydrated. At higher temperatures (42°C to 43°C) cellular death begins.

The molecular-biological mechanisms of health effects are still under investigation. Increases in temperature result in increases in molecular motion in cells,

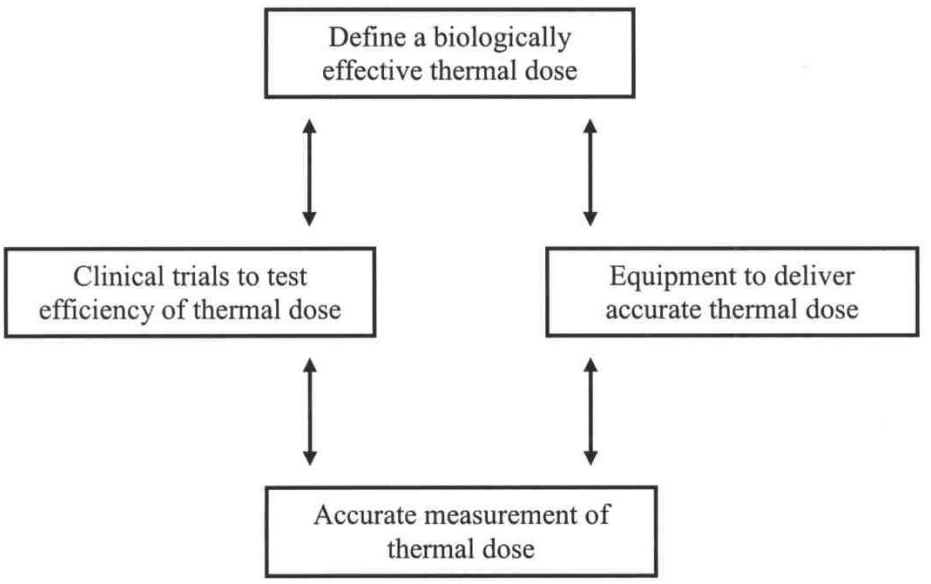

FIGURE 3. Challenges to the development of thermal therapy.

tissues, and organisms. The increased molecular motion in turn increases chemical reaction rates. If reaction rates within steps of a metabolic process become unbalanced, metabolism may be altered. The activation energies of metabolic reactions are low, on the order of 3–20 kcal/mole. For short-duration heat exposures, it was thought that unbalanced metabolism would be transitory, and therefore unlikely to cause permanent damage. Long periods of unbalanced metabolism could cause permanent, irreversible damage, but there is currently no scientific evidence for this hypothesis.[75]

Because EM exposure may produce hyperthermia, it is necessary to delineate whether any observed effects are specific to EM exposure, or if they were simply a result of the hyperthermia attendant on EM exposure.[76]

B. Cellular Responses

Various targets in the cell affected by rises in temperature have been found, such as cell activity, growth rate, membranes, the cytoskeleton, synthesis of macromolecules, the cell cycle, regulating molecular functions such as apoptosis, and DNA repair.[77–80] Another potential harmful effect of hyperthermia is the triggering of programmed cell death; for example, apoptosis in both normal and tumor cells.[79]

The cell growth rate increases with increasing temperature to some maximum temperature above which growth is sharply inhibited.[47,48,81] In the hyperthermic region above the maximum growth temperature, there are three significant cellular responses for thermal therapy, which are cytotoxicity, radiosensitization, and thermotolerance.[82,83] These changes at the cellular level must be due to temperature-induced alterations in molecular pathways. These usually involve inhibition of DNA, RNA, and protein synthesis.[82] While protein synthesis is inhibited during heating at higher temperatures, at milder temperatures and after return to normal growth temperature the induction of heat-shock protein (HSP) occurs.[84] This is an inducing event and is closely associated with the induction of thermotolerance. The role of these proteins in neurodegenerative disease and in suppression of neuronal apoptosis led to a strongly enhanced interest in these proteins.[85,86]

Hyperthermia may induce both regional and systematic production of cytokines through activation of inflammatory cells. The release of tumor necrosis factor (TNF) is well described after whole-body hyperthermia (WBH).[87] Increased levels of TNF have direct cytotoxic effects, can induce tumor endothelial injury, and sensitize tumor cells to heat-induced damage.[88,89]

A number of studies have documented the adverse effects of hyperthermia on the normal adult testis in several species, including mouse,[90] rat,[91] and human.[92,93] The reported effects include a temporary reduction in relative testis weight accompanied by a temporary period of partial or complete infertility.[94,95] Sperm quality has also been shown to suffer, with a reduction in progressive sperm mo-

tility and a significantly lower in vitro fertilization rate of oocytes by sperm from heat-shocked males.[94,96]

Studies have shown heat-dependent immunological reactions of human leucocytes,[97] and effects on natural killer cells and cytokine depletion.[98]

C. Immunological Effects

The possibility of hyperthermia-induced inhibition of the host immune system must be considered when heat is used clinically for cancer treatment.[99] WBH appears to enhance the synergistic and antiproliferative activities of gamma-interferon leading to an upgrading of immune surveillance.[100,101] However, this effect is reversed at temperatures greater than 42°C.[102] Studies have also shown heat-dependent immunological reactions of human leucocytes.[97] Whether some of the changes described in WBH occur with focal hyperthermia remains unknown.[1]

HSPs are the most abundant and ubiquitous soluble intracellular proteins. They are recognized as significant participants in immune reactions. Hyperthermia induces overexpression of HSP at the expense of inhibiting the synthesis of many other proteins, including cytosketetal and regulatory proteins that may be crucial for normal cellular functions. For example, heat may alter the normal body immunoresponse by altering thymocyte[103] and leukocyte[100] production as well as inducing T-lymphocyte propagation.[104] Ito et al.[105] suggested that HSP70 is an important modulator of tumor cell immunogenicity, and that hyperthermic treatment of tumor cells can induce the host antitumor immunity via the expression of HSP70. These results may benefit further efforts on developing novel cancer immunotherapies based on hyperthermia. Other studies demonstrated a dual role of thermotolerance and immune stimulation of HSPs.[106,107] Ivarsson et al.[108] used an implantation model of colorectal liver metastases to identify increased expression and change in the localization of HSP70 at 10 to 15 hr after laser ablation. It is postulated that increased HSP tumor petite complexes following focal hyperthermia are involved in tumor antigen presentation to macrophages and other antigen presenting cells. The immunological properties of HSPs enable them to be used in new immunotherapies of cancers and infections.[109,110]

Milani and Noessner[111] reviewed the topic and concluded that: "We emphasize that the response to thermal stress is not a one-time point event, but rather a time period starting with the heat exposure and extending over several days of recovery. In addition, the response of tumor cells and their susceptibility to immune effector cells is strongly dependent on the model system, on the magnitude and duration of the thermal stress and on the time of recovery after heat exposure." Consideration of these aspects might help to explain some of the conflicting results that are reported in the field of thermal stress response.

D. Cardiovascular Responses

Cardiovascular strain and heat-related disorders are quite common, especially in people unaccustomed to heat. Some people are particularly susceptible to the adverse effects of heat, especially the elderly, who are at increased risk of coronary thrombosis in these circumstances, but also infants and people with certain medical conditions and/or who are taking certain medications.[75]

When body temperature rises, heat balance of the body is normally restored by increased blood flow to the skin and by sweating. These responses increase the work of the heart and cause loss of salt and water from the body. They impair working efficiency and can overload the heart and cause hemoconcentration, which can lead to coronary and cerebral thrombosis, particularly in elderly people with atheromatous arteries. These adverse effects of thermoregulatory adjustments occur with even mild heat loads and account for a great majority of incidences of heat-related illness and death. Donaldson et al.[112] reviewed the basic thermoregulatory physiology of healthy people in relation to hazards from external heat stress and internal heat loads generated by physical exercise or RF radiation. The authors concluded that exposure to RF exposure levels currently recommended as safe for the general population, equivalent to heat loads of about one tenth of the basal metabolic rate, could continue to be regarded as trivial in this context, but that prolonged exposures of the general population to RF exposure levels higher than that could not be regarded as safe in all circumstances.

Gong et al.[113] found that WBH promotes cardiac protection against ischemia-reperfusion injury, in part by upregulation of HSP. Their experiments on rats subjected to WBH at 42°C for 15 min show that sublethal heat stress can lead to upregulation of both vascular endothelial growth factor (VEGF) and HSP70 in cardiac tissue and promote focal endothelial proliferation in the heart. The above finding is supported by a previous study.[114]

Compared with animals, humans are exceptionally well adapted to dissipate excess heat; in addition to a well-developed ability to sweat, which in humans can be effected over most of the body surface, the dynamic range of blood flow rates in the skin is much higher than in other species.[22] Most deaths caused by heat are not due to hyperthermia, but to loss of water and salt in sweat, leading to hemoconcentration. This makes the blood more prone to clot and therefore leads to increased incidence of coronary and cerebral artery thrombosis in elderly people. The importance of this is that any degree of heat exposure sufficient to cause sweating, from any source, will carry a risk to humans.[75]

E. Nervous System Responses

The nervous tissues appear critically sensitive to heat with a possibility of damage and changes in nerve morphology for nerve conduction and nerve function.[13] Most studies on the effects of hyperthermia on the nervous system have focused

on the heat-shock response, characterized by the transient induction of HSPs, which play roles in repair and protective mechanisms.[115] Although interspecies variations may play a role, the data indicate that the maximum heat dose without obvious complications after localized hyperthermia in regions of the central nervous system (CNS) lies in the range of 40–60 min at 42–42.5°C or 10–30 min at 43°C.[116]

A review of the literature on the effects of intermediate- and low-level EM radiation shows that exposure at relatively low SAR (less than 2 W/kg) under certain conditions could affect the nervous system.[17–20] This includes effects on the BBB, morphology, electrophysiology, neurotransmitter activity, and metabolism.

Takahashi et al.[117] induced WBH in dogs by extracorporeal heating of blood in order to determine the effects seven days after hyperthermia on the canine brain and spinal cord. The thermal dose resulted in neither microscopic damage to the CNS nor neurological symptoms, as determined by comparison of microscopic and neurological findings with those of dogs whose brain and spinal cord temperatures were maintained at 37.0°C for 60 min. The findings suggest that, for medical purposes, WBH appears promising for application at a thermal dose of up to 42°C for 60 min.

Histopathological data show that the myelin sheath, which is important for nerve conduction, is the most vulnerable part of the nerve fiber. Hoogenveen et al.[118] observed many demyelinated axons one week after a heat treatment for 30 min at 44°C. Sasaki and Ide[119] observed demyelinated axons after heating a part of the rat spinal cord.

Studies on nerve conduction 1 hr after 30 min[120] or 60 min[121] treatment at 45°C showed a significant decrease in amplitudes and conduction velocities, possibly because of edema and early demyelination. Hogenveen et al.[122] showed that nerve function remained normal the first hours after treatment for 30 min at 45°C.

For the CNS, irreversible damage was found after treatment at 42–42.5°C for longer than 40–60 min.[123] Exposure of rats at 38°C for 4 hr results in cellular damage in several parts of the brain.[75] Effects of whole-body and localized heating on the CNS are discussed by Sharma HS, Hoopes.[124]

Clinically, Bull et al.[125] studied nerve conduction in four patients with a neuropathy after WBH and observed a pattern of scattered demyelination.

Haveman et al.[116] indicated in an overview that there are no clear experimental data pointing out an increase in adverse effects specific to the CNS after localized or WBH as a result of combined treatment with chemotherapy.

F. Behavioral Effects

With respect to the behavioral effects of heat in humans, it has been shown that cognitive performance is affected well before the physiological tolerance limits

are reached. Data from laboratory animals describe the disruption of ongoing vigilance behavior by imposed EM fields.[75] D'Andrea et al.[126] reviewed the literature concerning EM exposure and behavioral and cognitive effects. They conclude: "Reports of change of cognitive function (memory and learning) in humans and laboratory animals are in the scientific literature. Mostly, these are thermally mediated effects, but other low level effects are not so easily explained by thermal mechanisms. The phenomenon of behavioral disruption by microwave exposure, an operationally defined rate decrease (or rate increase), has served as the basis for human exposure guidelines since the early 1980s and still appears to be a very sensitive EM briefest."

G. Carcinogenic Effects

Prior to discussing the problems associated with thermal therapy, it should be pointed out that unlike ionizing radiation and toxic drug therapy, nonionizing radiation such as EM fields has not been found to have mutagenic effect.[127,128]

It is now widely agreed that cancer is initiated by alterations in the genetic material (DNA) in the cell (geotaxis effects), although some nongeotaxis chemicals and processes (called epigamic carcinogens) have been recognized. Alterations in genetic material can occur if there is breakage in the DNA, leading to single- or double-stranded breaks. Studies to investigate whether EM radiation produces genetic effects have been performed on various animal cells and tissue cultures. The results of the studies did not yield any reliable or systematic evidence that RF or microwaves can induce any mutation in living systems other than through induction of heat; it is known that the rate of induction of mutations increases with increasing temperature.

Carcinogenesis is known to follow a multistep process that can be categorized into four main steps, namely, initiation, promotion, malignant conversion, and tumor progression.[12,129] Although hyperthermia alone is not carcinogenic, hyperthermia may enhance the development of tumors induced by ionizing radiation.[130–132] However, several investigators have examined whether or not hyperthermia alone can cause cancer by causing chromosomal aberrations,[133–136] DNA double-strand breaks,[137–139] or mutation.[140–143]

The controversy over whether EM radiation might initiate or promote cancer continues to receive a great deal of attention, both in the popular press and in the biomedical literature.[144] Conflicting reports appear in the literature, suggesting that hyperthermia treatment (via a water bath) can either serve as an antipromoter[145,146] or as a promoter,[147] depending on the treatment regimen.

Studies of possible genotoxic effects of EM exposure, enhanced cell proliferation, and inappropriate gene expression have been carried out at the cellular level. In addition, there have been a number of long-term studies of cancer induction in animals, including tests of epigenetic interaction with known carcinogens.[148] Over the years, several studies have investigated potential carcinogenic

effects of EM exposure on mammary cancer,[149,150] liver cancer,[151] lymphoma,[152] and brain cancer.[153]

V. CONCLUDING REMARKS

The primary goal of this article was to introduce current concepts of thermal therapy as generally as possible with a collection of topics that will further expand the usefulness of this therapy and translate thermal technology into clinical practice. It was necessary, however, to provide superficial coverage of the topics, while leaving in-depth discussions to the following articles of this series.

A. Risk Assessment

Thermal therapy techniques are becoming more acceptable as a minimally invasive alternative for the treatment of some cancers and other forms of benign diseases.[39] However, evaluation of human exposure risk to EM sources or the corresponding heat, especially patients and personnel working in this field, is a difficult task because it involves many physical, biological, and chemical variables. In this article, we were largely concerned with the thermal effects of EM exposure. Thermal effects are produced by energy transfer from radiation to tissues, varying with frequency of operation, mostly governed by dielectric loss, i.e., the loss that is proportional to the intensity of radiation. In general, elevated temperatures have obvious effects on humans such as cataracts (opacity), increased blood pressure, dizziness, weakness, disorientation, nausea, or a faint pain. Heating the human body, either the whole body or part of the body, may affect physiology, particularly the heart and circulatory system. It may induce other thermoregulatory responses such as sweating or various heat-related disorders such as heat stroke.

It should be mentioned that based on the long history of EM exposure in humans, it is reasonably certain that exposures below MPE values have no credible reported adverse health effects and are medically safe.[11,154] Some epidemiological studies addressing possible links between EM exposure and excess risk of cancer have reported positive findings for leukemia and brain tumors. However, in some of these studies there are significant difficulties in assessing the relationship between disease incidence and EM exposure and with potential confounding factors such as extremely low frequency (ELF) fields and chemical exposure.[12]

When considering the impact of EM-induced heating on carcinogenesis, the problem is that there are few or no data from studies using high EM exposures to produce thermal responses, particularly with respect to the initiation, promotion, or copromotion of cancer. Studies involving higher thermal exposures from heat alone do suggest modulation of both initiating and promoting events in carcinogenesis. However, the issue is complex. Data from two published series indicate

promotion of tumor formation for heating during initiation.[147] How such data affect the establishment of standards for EM exposure is a challenge.[12] The thermogenic effects of EM energy have been well documented and are summarized as follows[155]:

1. Biological effects due to thermoregulatory response occur when a living body is thermally loaded at a rate equal to its basal metabolic rate (BMR).
2. Numerous behavioral and endocrine effects, and cardiac and respiratory changes for SARs below the BMR, are manifestations of physiological responses to mild thermal stress.
3. Thermal stress resulting from about twice the BMR, when maintained over long periods of time, leads to significant physiological effects.
4. Responses to thermal load from pulsed fields appear to be the same as responses to continuous fields of the same average power.

It is also important to mention that heat may cause a positive as well as negative effect in the integrated body system.

B. Trends in Equipment Development

Although thermal therapy requires investment in equipment and personnel training, the same is true for other types of therapies. In spite of the required investments, the economic evaluation of thermal therapy can be within an acceptable range. The most important technical areas of thermal therapy development can be specified as follows:

1. Optimization of new heating devices for more effective local, intracavitary, and regional treatment.
2. Integration of noninvasive monitoring capabilities and treatment planning for thermal therapy with the evolving heating systems to dramatically improve clinical efficacy.
3. Utilization of existing technology in clinical settings, and encouragement of equipment developers to produce devices for new clinical applications.
4. Acceleration of training programs for physicians and physics staff in order to make efficient use of the available technology.
5. Further development of fast and dynamic imaging techniques for guidance and monitoring in clinical treatment.

C. Future Research Directions

Future research should examine, in addition to the above technical advancement, various efforts including, among others,[5,64,75] the following:

1. Mechanisms of how cells react to changes in their thermal environment and clarification of thresholds for thermal damage in humans.

2. Accurate EM and thermal dosimetry including further investigations in the fields of (a) modeling power deposition and estimation of EM energy absorbed by tissues exposed to EM radiation, (b) electrical-thermal modeling for thermal therapy with various models of heat transfer in living tissues, and (c) models of EM energy deposition in humans combined with appropriate models of the human thermoregulatory responses in order to predict the potential hazards associated with specific EM exposure conditions.
3. Human and animal studies on (a) CNS changes in heat-related illnesses using quantitative immunopathological techniques at the cellular and ultrastructural levels, (b) the effect of EM exposure on cognitive performance, (c) the effect of prolonged and/or chronic exposure at ambient temperatures (less than 41°C), and (d) carcinogenic risk of heat, especially for lower-temperature hyperthermia.

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