

Review of Major Directions in Non-Equilibrium Atmospheric Plasma Treatments in Medical, Biological, and Bioengineering Applications

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ABSTRACT: Plasma Medicine is the newest and rapidly expanding area of engineering medicine and bioengineering focused on direct applications of plasma for treatment of different diseases, blood coagulation control, wound management, and wound healing, as well as improving patient care through sterilization, medical implants, biomaterial engineering, and tissue engineering. The number of medical engineering professionals, researchers, upper undergraduate, and graduate university students involved today in plasma medicine is already large and growing; there is also an exponentially growing number of publications in this new field. All these students and professionals need the ability to find these publications to aid them in getting started and to advance in their research in plasma medicine. This determines the main purpose of this review, focused on, first of all, summarizing the major directions of fundamental plasma medicine and providing an extensive guide to specific diseases with current plasma-bioengineering solutions, as well as providing a relevant, up-to-date bibliography.

KEY WORDS: plasma medicine; nonequilibrium atmospheric plasma

I. INTRODUCTION

A. What Is Plasma and Which Medical Challenges Can It Address

There are many examples of plasma in current technologies and sciences, including examples of plasma in nature and plasma in the laboratory, composition of plasma, concept of plasma electroneutrality, description of major charged particles in plasma, descriptions of types of plasma neutrals, major parameters of plasmalike plasma temperatures, plasma density, and gas pressure, as well as a general introduction to physics and engineering of principal plasma sources operating at low pressures and high pressures. Specific features of plasma, which can be of interest to biological and medical applications, are discussed in this review. Special attention is paid to the possible medical effects of plasma-generated active neutral and charged species, different types of radiation from plasma, plasma-related electric fields, and plasma-related mechanical effects like shock waves. Discussion of which specific medical challenges may be addressed using plasma devices is discussed in some

recent reviews.¹⁻⁷

B. From Cauterization of Blood to Treatment of Cancer

Plasma medicine can be subdivided into several sub-disciplines, including plasma-medical discharge devices and their characterization,⁸⁻¹² plasma-medical chemistry in gas phase and medium,^{6,13-15} biochemistry of plasma-medical treatment of cells and tissues,^{13,14,16-18} and finally, applied plasma medicine.^{1-3,6,7} Applied plasma medicine is focused on medical and bioengineering aspects of the subject, on practical issues related to medical sterilization,¹⁹⁻²² treatment of wounds,^{12,23-26} and healing different diseases.²⁷⁻³¹ Applied plasma medicine also includes multiple issues related to animal and human clinical trials, toxicity, safety, and other aspects related to application of plasma devices in hospitals, and other types of medical environment.

C. Nonequilibrium Chemistry

Principal concepts of nonequilibrium chemistry of charged and neutral species generated in plasma are of great importance in the field of Plasma Medicine. The special importance of nonequilibrium plasma chemistry to biological and medical applications is explained in a few recent reviews.^{1,14} The nonequilibrium nature of plasma is discussed, focusing on differences in electron temperature and gas temperature, as well as on differences of temperature corresponding to different degrees of freedom of atoms and molecules.³² Principal electronically and vibrationally excited states are especially important for plasma applications in biology and medicine. General principles of nonequilibrium plasma chemical kinetics are introduced, including those for reaction of charged particles, radicals, as well as electronically and vibrationally excited species. Relations between nonequilibrium plasma-chemical kinetics and biochemical kinetics define the core foundation of chemistry-driven understanding of plasma-medical mechanisms.^{14,20}

D. Bioactive Plasma Components

General concepts related to bioactive plasma components (chemical and nonchemical) were introduced primarily due to their importance in plasma-medical treatments.¹⁴ Major plasma features, which can be interesting and important to biological and medical applications, are discussed.^{14,20,33-35} Special attention is paid to possible medical effects of plasma-generated active neutral and charged species (the so-called chemical bioactive components), as well as the so-called nonchemical bioactive plasma components, including different types of radiation from plasma (UV-A, B, C, and X-rays), plasma-re-

lated electric fields (local and global), and plasma-related mechanical effects like shock waves.^{14,20,36}

E. Plasma Devices in Medicine: Achievements, Challenges, and Aspirations

There are a few families of major electric discharges applied in plasma medicine.^{1,2,7,37} They are classified into thermal, nonthermal, and “warm” (transitional) discharges. The more conventional, nonthermal plasma-medical discharges are represented by dielectric barrier discharge (DBD, including floating electrode DBD, FE-DBD) and different modifications of plasma jets, as well as coronas and atmospheric-pressure glow discharges (APG). Major thermal and “warm” discharges applied in plasma medicine are represented by arc discharges (including gliding arc discharges), microwave discharges, and spark discharges. Major toxicity and safety issues related to applications of plasma discharges in medicine are frequently considered.^{15,18,38,39} Ideas of combination of plasma discharges with medical robots are discussed and applications in telemedicine mentioned.^{40–43}

F. Physics of Cold, Warm, and Hot Plasmas

Plasma medicine is obviously based on physics, chemistry, and engineering of plasma.³² Keeping that in mind, there is a prevalent focus on some general fundamentals of plasma physics, plasma chemistry, and plasma engineering, which are then used for the description and explanation of different aspects of plasma medicine. Consideration is frequently subdivided into analysis of cold, warm, and hot plasmas, depending on the specifics of the discharge used for a specific application.^{7,20,21,32,42,44–49}

G. Fundamental and Applied Plasma Medicine

Fundamental aspects of plasma medicine include plasma-medical discharge devices and their characterization, plasma-medical chemistry in gas phase and medium, and biochemistry of plasma-medical treatment of cells and tissues.^{1,32} Applied plasma medicine includes medical and bioengineering aspects of medical applications of plasma on practical issues related to medical sterilization, especially sterilization of living tissues, sterilization during surgeries, treatment of wounds, and healing different diseases. Applied plasma medicine also includes multiple issues related to clinical trials, toxicity, safety, and other aspects related to application of plasma devices in hospitals, and other types of medical environment.^{1,4,7,8}

H. Biochemical Basis of Applied Plasma Medicine

Understanding of applied aspects of plasma medicine is impossible without understanding of related issues in biology and especially biochemistry.^{13,14,17,18,50} Plasma-medical physics is frequently focused on what is going on in plasma itself and in the special medium; at the same time plasma-medical biochemistry is focused on what is going on inside of cells and tissues.^{4,51–54} A clear need exists to understand the plasma-medical biology and biochemistry; therefore there is a presentation of general biochemical schematic of plasma interaction with cells and living tissues, introduction of some major terms and concepts, as well as experimental methods and approaches usually used analyzing the biological and especially biochemical aspects of plasma medicine.¹⁴

I. Classification of Diseases Reachable by Plasma and Meeting Unmet Medical Needs

Plasma processes, usually, take place in the gas phase; therefore plasma-medical treatment is usually related to medical treatment of various types of surfaces.^{55–61} There is a focus on the discussion of what kind of specific diseases can be, in principle, treated by plasma, and how plasma treatment can reach tissues located not on the surface, but deep in the body. Specific classification of diseases that can be reached by plasma treatment is occasionally mentioned.^{38,40,62,63} Plasma medicine is especially interesting for medical practitioners because of its chance to treat diseases not treatable before, in other words to meet the so-called “unmet medical needs.”

II. PLASMA-MEDICAL DEVICES: FUNDAMENTALS AND ENGINEERING

A. Elementary Plasma Processes: Charged and Excited Particles and Reactions Between Them

It is important to focus on the basic science principles and fundamentals required to understand operation of major plasma-medical devices, especially dielectric barrier discharges (DBD),^{64–68} different types of plasma jets,^{69–76} radio-frequency (RF) discharges,^{77–81} and atmospheric-pressure glow (APG) discharges.^{66,82–90} Physical kinetics of ionization, recombination, electron attachment/detachment and ion-molecular processes, and atomic and molecular excitation process, as well as plasma reactions of atoms, radicals, and excited species are described concisely but sufficiently for further description of the physical basis of plasma medicine.

B. Quasiequilibrium and Nonequilibrium Plasmas: Statistics and Thermodynamics

The Principal concepts of plasma equilibrium (complete and local) as well as classification of different levels of plasma nonequilibrium are frequently discussed, specifying important relations for chemical and ionization equilibrium (Saha Equation).^{91–95} Major statistical distributions are considered for different internal degrees of freedom of atoms and molecules in quasiequilibrium and strongly nonequilibrium plasmas, including nonequilibrium statistics of vibrationally excited molecules, and Treanor distribution.^{96–100} Principal thermodynamic functions of thermal plasma systems relevant to thermal plasma-medical devices are often introduced in the literature.

C. Nonequilibrium Plasma Kinetics

Energy distribution functions, including those of plasma electrons, vibrationally excited molecules, electronically excited species, and high-energy atoms are in the focus of plasma kinetics discussions.^{101–105} Electron energy distribution functions (EEDFs) for major electric discharges applied for medicine are considered. EEDFs are analyzed using general plasma kinetic equations (especially the Boltzmann equation and Fokker-Planck equation).^{106–110} Applicability of Maxwell distribution, Druyvesteyn distribution, Margenau, and other specific EEDFs in plasma are discussed, together with modern experimental methods of EEDF characterization. Theoretical and experimental characterization of kinetics of vibrationally excited molecules and electronically excited atoms/molecules in plasmas are considered, as well as the effect of “hot” energetic atoms relevant to medical applications.^{111–113}

D. Transfer Processes in Plasmas Used for Medical Applications

Heat and mass transfer processes in thermal and nonthermal plasma-medical systems are important to understand to describe the relevant application mechanisms.^{12,114,115} Specifics of the contribution of conduction, convection, and radiation to heat transfer in plasma systems are analyzed, especially keeping in mind dissociation/recombination and ionization/recombination processes.^{116–119} The effect of plasma nonequilibrium on vibrational and electronic energy transfer is analyzed (Treanor effect in vibrational energy transfer).^{120–122} Radiation heat transfer in plasma is considered depending on specific organization of plasma processes (optically thin and optically thick plasmas). Diffusion is discussed paying special attention to that of charged particles, including ambipolar diffusion and diffusion in the presence of magnetic field.

E. Electrodynamics of Plasmas Used for Medical Applications

Plasma electrodynamics covers the subjects of motion of electrons and ions in external fields, as well as plasma ideality, collective motion of charged particles, plasma polarization and effect of sheaths, plasma oscillations, plasma interaction with electromagnetic waves (absorption and reflection), and propagation of electromagnetic waves in plasma (high-frequency plasma conductivity and dielectric permittivity of plasma).^{123–127} Elements of plasma magnetohydrodynamics are discussed in relation with possible plasma-medical applications. More attention seems to be focused on analysis of drift of charged particles in electric and magnetic fields, mobility of electrons and ions, and plasma conductivity of the thermal and nonthermal discharges, as well as plasma interaction with complex flows (plasma electrodynamics and fluid mechanics).^{128–131}

F. Electric Breakdown and Steady-state Plasma Regimes

Fundamentals of electric breakdown in form of both uniform discharge development and streamers are frequently discussed, as well as analysis of major steady-state regimes of nonequilibrium electric discharges in different pressure ranges.^{132–135} Discussion of Paschen curves is related to consideration of the Townsend breakdown mechanism. Introduction of the streamer concept is concluded by consideration of the spark breakdown mechanism.^{136–139} Cathode- and anode-directed streamers are discussed, as well as the physics of microdischarges, filaments, and their interaction and structuring. Steady-state regimes of nonequilibrium electric discharges are considered, including those controlled by volume and surface recombination processes (including Engel-Steenbeck relation), as well as electron attachment/detachment processes and negative ions.^{140–144}

G. Glow Discharge and Arcs: NonThermal vs. Thermal Plasma Sources

Physics and engineering of glow and arc discharges are considered and compared in particular to demonstrate qualitative differences between thermal and nonthermal plasma sources.^{145–147} Consideration of glow discharges includes, in particular, their structure and major configurations, physics of cathode layer and positive column, and current-voltage characteristics, as well as normal and different abnormal glow regimes.^{148–152} Specifics of hollow-cathode glow discharges and atmospheric-pressure glow discharges (APG) are especially discussed. Consideration of arc discharges includes, in particular, their structure and current-voltage characteristics, physics and engineering of electrode processes, cathode spots, and physics of positive column: Steenbeck-Raizer channel model and Elenbaas-Heller equation. Specifics of gliding arc discharges applied in plasma medicine and plasma biology are especially discussed.^{34,153–157}

H. Key Plasma-Medical Discharges in Atmospheric Air: Dielectric Barrier Discharge (DBD), Corona, and Atmospheric-pressure Glow (APG)

Principal features and comparison of major atmospheric-pressure air discharges are applied today in plasma medicine: dielectric barrier discharges (DBDs).^{21,104} continuous and pulse coronas,^{130,158,159} as well as atmospheric-pressure glow (APG) discharges.^{136,160,161} Consideration of these atmospheric-pressure cold air discharges includes, in particular, general features of their physics, and plasma parameters, discussion of the direct and indirect approaches to plasma-medical treatment, plasma uniformity of the atmospheric-pressure cold air discharges, engineering peculiarities of their design, and specifics of their applications in plasma medicine.^{1,6,7,162–165}

I. Fundamentals and Engineering of Continuous Wave, Microsecond-, and Nanosecond-pulsed DBDs

Different modes of dielectric barrier discharges (DBDs) widely applied in plasma medicine are discussed widely in the literature, and one needs to especially pay attention to older literature since these discharges have been under development since the times of Dr. Siemens in the 1800s.^{108,166–170} Direct and indirect modes of DBD application in plasma medicine are compared¹⁷¹ to analyze the physics and engineering of floating electrode–dielectric barrier discharge (FE-DBD). Consideration of continuous wave, microsecond-, and nanosecond-pulsed DBDs include, in particular, physics of DBD plasma at different modes of applied voltage, DBD overvoltage depending on characteristics of the applied voltage, physics of the DBD streamers, filaments, and uniformity, depending on characteristics of the applied voltage, concept of “blind” streamers, and peculiarities of the nanosecond-pulsed DBD application for treatment of living tissue.^{172–177} Engineering of different FE-DBD configurations for special applications in plasma medicine and plasma biology are often a topic of important discussions.

J. Plasma Jets as a Popular and Effective Device in Plasma Medicine

Different types of plasma jets widely applied in plasma medicine are often employed in plasma medicine.^{39,41,71,136,178–187} Jets are classified based on plasma sources (DBD, RF, etc.) applied for generation of the jets, gas or gas mixture used, on the presence or absence of plasma bullets, plasma-surface interaction effects, jet temperature, and level of electric field in the jet. Physical and chemical composition characterization of different types of plasma jets is often argued. Physical and plasma-medical modeling of different types of plasma jets are considered, with the simulation results compared with relevant diagnostics. Different configurations of the plasma jets designed for plasma-medical applications are discussed. Gas-dynamic effects in jets are discussed. Special discussion is dedicated to consideration of “warm” and quasi-thermal plasma jets (including those

sustained by microwave and radio-frequency RF ICP discharges), and their comparison with strongly nonequilibrium cold plasma jets.^{12,188–192}

K. Plasma Bullets: Physics and Plasma-Medical Applications

There is a recent focus on physics, plasma chemistry, and biomedical aspects of plasma bullets.^{91,108,178,179,184,188,192–194} Experimental data on plasma bullets observed in different types of plasma jets are considered. Physical and chemical kinetics models are presented in comparison with experimental data. Contributions of different factors important for propagation of plasma bullets in dielectric tubes are presented, explaining, in particular, effects of branching of the plasma bullets. Special attention is paid to the influence of possible surface conductivity on the propagation of plasma bullets inside of tubes. Propagation of plasma bullets in slightly conductive biological orifices is discussed, which can be of importance for treating of multiple diseases including, for example, colon and lung cancer.^{27,29,31,167,195–197}

L. Gliding Arcs as Plasma Sources for Biological and Medical Applications

Relevant physics of gliding arc discharges is often discussed, as well as applications of these powerful nonequilibrium discharges to biology and medicine.^{153,155,156,198–202} Regimes of the discharges corresponding to the FENETRe (fast equilibrium-to-nonequilibrium transition) effect are specified. Results of diagnostics of the gliding arc discharges are presented. Gliding arcs can be organized in different configurations corresponding to different applications. Applications of the flat gliding arcs are considered, especially those related to biology and medicine. The major focus of the recent research is the organization of the nonequilibrium gliding arcs in reverse-vortex (tornado) flow, including plasma physics, plasma chemistry, and fluid dynamics of the discharge, diagnostics of the discharge, simulation of gas flow in the system, short- and long-lifetime active species generated by the discharge, as well results of application of the reverse-vortex (tornado) gliding arcs in biology (especially in generation of biologically active liquids) and medicine.^{203–209}

M. Pin-to-Hole Spark Discharge (PHD) for Biological and Medical Applications

Physics, plasma chemistry, and gas dynamics of the pin-to-hole discharge (PHD) is the

focus of a few recent papers.^{15,50,210–214} Results of diagnostics of the PHD discharge are compared with results of physical and plasma chemical modeling. Specific attention is paid to generation of UV, charged, and different kind of active neutrals in the PHD discharge. Different configurations of the PHD discharge are discussed in relation to their applications in medicine.

N. Radio Frequency (RF) and Microwave (MW) Discharges in Plasma Medicine

Physics and engineering of multiple types of RF and microwave discharges, as well as general features of their applications in plasma biology and plasma medicine are discussed. Comparison of RF discharges with RF-activated jets, and comparison of low-pressure and high-pressure RF discharges are provided, as well as comparison of CCP- and ICP-based discharges. Direct medical applications of RF-based plasma discharges vs. applications of the discharges in tissue engineering and material treatment for further applications in biology and medicine are also discussed, as well as physics, engineering, and applications of microwave discharges in different pressure ranges: low-pressure, moderate-pressure, and high-pressure microwave plasma systems. Finally, microwave plasma-based devices in plasma medicine, and engineering aspects of microwave discharges effectively used in clinical tests are reported.^{20,215–220}

O. Plasma Discharges in Liquids: Fundamentals, Engineering, and Biological and Medical Applications

Classification of plasma discharges inside of liquids and in contact with liquids is part of a recent and rather interesting development in plasma science.^{118,146,155,221–223} Ionization physics inside of liquids and in two-phase mixtures is analyzed; ionization of liquid with bubbles is compared with ionization characteristics of aerosols. Effect of bubble size on ionization is considered; the concept of critical bubble size is introduced. Different mechanisms of bubble formation during breakdown of liquids are compared. Possibilities of ionization inside of liquid phase without bubbles are discussed: experimental results are compared with relevant modeling. The contribution of electroporation to ionization of liquids is analyzed. Plasma chemistry on the liquid surface and relevant chemistry induced by plasma inside of different liquids are considered. Specifics of plasma/liquid systems for plasma-medical applications are analyzed. Chemistry and especially chemical kinetics of plasma liquids are discussed. The concept of plasma acid is introduced, as well as the concept of plasma pharmacology. Medical applications of plasma treated water, and plasma treated medium are discussed.^{73,77,222,224–228}

III. EFFECTS OF BIOACTIVE PLASMA COMPONENTS ON PATHOGENS, CELLS, TISSUES, AND SYSTEMIC SIGNALING

A. Major Bioactive Plasma Components: Specific (Radicals, Ions, etc.) vs. Global (Applied Electric Field, Temperature, etc.)

Major bioactive plasma components, chemical and nonchemical, are the key ingredients of plasmas.^{38,62,118,198,229–231} Special attention is paid to possible medical effects of plasma-generated active neutral and charged species (the so-called chemical bioactive components), as well as to possible medical effects of the so-called nonchemical bioactive plasma components, including different types of radiation from plasma (UV-A, B, C, and X-rays), plasma related electric fields (local and global), plasma related mechanical effects like shock waves, and finally temperature (global and local). Specific (radicals, ions, excited chemical species, streamer electric fields, etc.) and global (applied electric field, temperature, etc.) plasma-medical effects are frequently compared.

B. Plasma Generation of Atoms, Radicals, and Electronically and Vibrationally Excited Species

Plasma chemistry of chemically active atoms and radicals, electronically excited atoms, and electronically and vibrationally excited molecules in nonequilibrium plasma are often considered in plasma-medical biochemical activity analysis.^{118,200,232} Elementary processes of generation and quenching of active species, of excitation and relaxation of excited states of atoms and molecules are presented.^{233–236} Physical and chemical kinetics of generation, losses, and reactions of the active species are considered as a function of reduced electric field in discharge systems. Specific attention is paid to those elementary plasma-chemical reactions, which play a significant role in plasma-medical processes.

C. Plasma-Medical Effects of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS)

Between multiple medically relevant plasma-generated and plasma-induced chemically active species, the most special role belongs to reactive oxygen (ROS) and reactive nitrogen (RNS) species [sometimes RONS (reactive oxygen/nitrogen species) are considered separately].^{4,237–239} The crucial contribution of ROS/RNS biochemistry to functioning of cells and tissues is often discussed. The special role of nitrogen oxide (NO) in biology and medicine is reported. The roles of intracellular and extracellular ROS and RNS are compared (interaction between physical and biochemical mechanisms, between intracellular and extracellular effects). Specific biochemical pathways are stimulated by specific ROS and RNS.^{17,240,241}

D. Plasma-Medical Effects of Positive and Negative Ions, Plasma Catalytic Processes

Chemical kinetics of ion-molecular processes is considered in many recent papers.^{1,165,240–244} Absence of activation barriers in kinetics of exothermal ion-molecular reactions is explained as the basis of the effect of plasma catalysis. Examples of plasma catalysis in organic plasma chemistry are considered. The specific contribution of plasma catalysis in plasma-medical processes is indicated and demonstrated. Contributions of positive and negative ions to plasma catalytic effect in plasma medicine are compared. Local electric fields of ions are considered both as a source of electroporation and source of removal of activation energy barriers (plasma catalytic effect).¹⁴

E. Global Effects of Temperature and Applied Electric Field; Effects of Plasma Gas Composition

The global effect of gas temperature in plasma is analyzed; average and local temperature effects are compared.¹⁴ Thermal plasma sources are compared with nonthermal and “warm” plasma sources. The global effect of applied electric field (electroporation) on cells and tissue is considered.^{245–247} Electroporation effects induced by different plasma-medical devices are compared. Possible synergy between electroporation and plasma chemical effects is discussed. The effect of plasma gas composition on plasma-medical treatment is discussed; the special role of oxygen and water is analyzed.¹⁴

F. Local Plasma-Medical Effects of High Electric Field in DBD Streamer Head

Local electric fields in the streamer heads (in particular, in DBD and streamer corona discharges) can be significantly greater than the applied electric fields analyzed above. These electric fields in streamer heads are able to provide strong electroporation effects as well as other electric field induced biological and biochemical effects.^{14,238,239,248} Medical effects of local and global electric fields are compared. Possible significant contribution of the electric field effects (both global, and local related to DBD and corona streamer heads) on plasma-medical treatment is considered, keeping in mind the depth of penetration of the electric field effects.

G. Direct and Indirect Plasma-Medical Treatment

Concepts of direct, indirect, and “separated” plasma-medical treatments were recently introduced in the literature.¹⁷¹ The difference in major treatment factors in the cases of

the direct, indirect, and “separated” plasma-medical treatments is discussed. The contribution of electric fields, radiation, and short- and long-living active species are discussed from this point of view. Experimental data comparing the cases of the direct, indirect, and “separated” plasma-medical treatments are presented and discussed.^{241,249} Concepts of the direct, indirect, and “separated” plasma-medical treatment of wounds and different diseases are considered from the prospective of medical safety, toxicity, and effectiveness.

H. Biomedical Effects of UV and other Types of Plasma Radiation, as well as Plasma-Generated Shock Waves

Biological and medical effects of ultraviolet radiation are considered in the recent literature.^{16,162,163,200,211,250,251} Effects of UV-A, UV-B, and UV-C are compared. UV generation by different plasma-medical devices is compared. The medical toxicity effect is analyzed in comparison with UV-treatment efficiency. Especially, the contribution of UV radiation in medical and biological sterilization is discussed. Contribution of possible X-ray generation in plasma-medical devices is analyzed. Effects of plasma-generated shock waves on sterilization and medical treatment are considered. Especially, attention is paid to the influence of the mechanical effects on depth of penetration of plasma-medical treatment.

I. Biochemical Mechanisms of Plasma Interaction with Bacteria, Viruses, and Other Pathogens

Biochemical mechanisms of plasma interaction with bacteria, viruses, and other pathogens are considered and compared.^{1,165,194,252–254} Different effects on cell membranes are presented and analyzed. Special attention is paid to membrane peroxidation, membrane percolation, and signaling mechanisms. Experimental data are presented for multiple types and groups of the microorganisms. Kinetics of deactivation is analyzed. The contribution of different plasma-generated factors on deactivation of the microorganisms is analyzed.^{10,155,158,255,256}

J. Biochemical Mechanisms of Plasma Interaction with Mammalian and Other Types of Cells

Biochemical mechanisms of plasma interaction with mammalian and other types of cells are considered.^{39,240,257–259} Differences between biochemical mechanisms of plasma interaction with mammalian cells and bacteria are discussed based on existing experimental data. Different effects on mammalian cell membranes are presented and analyzed. Different effects on mammalian cell DNA are presented and analyzed.^{260–262} DNA analy-

sis methods are discussed. Special attention is paid to cellular membrane peroxidation, membrane percolation, and signaling mechanisms across the membranes. Experimental data are presented for multiple types of mammalian cells.

K. Effect of Extracellular Medium on Plasma Biochemistry; Plasma Interaction with Complex Biomolecules in Solution: Nucleic Acids (DNA, RNA), Proteins, Enzymes, and Others

Plasma is usually separated from cells and/or tissues by special biological extracellular medium, which plays very important role in plasma-medical treatment of cells and living tissues.^{77,224,241} Kinetics of plasma interaction with the biological medium as well as the medium interaction with cells and tissues are in focus of many of recent discussions in literature and at the conferences. Special attention is paid to depth of penetration of different plasma related effects in the depth of the biological medium. Experimental methods applied for this analysis are discussed. Different types of plasma interaction with complex biomolecules in solution are also discussed in the literature. Specifically, the behavior of nucleic acids (DNA, RNA), proteins, and enzymes in solution under different types of plasma treatment is discussed.^{260,262}

L. Plasma Effects on Intracellular DNA: Single- and Double-strand Breaks; Plasma Activation of Apoptotic Pathways

Plasma effects on intracellular DNA and activation of apoptotic pathways are in focus due to the great importance of these processes in biology and medicine.^{16,262} Consideration of the plasma effects on DNA behavior inside cells is oriented to analysis of single-strand breaks and double-strand breaks in the DNA molecules. Both effects are considered as a function of the plasma treatment dose. Definition of the dose is discussed in application to different types of plasma-medical discharges. Plasma activation of apoptotic pathways is discussed for different cell lines, and different types of electric discharges; multiple groups of experimental data are presented, compared, and discussed.^{240,257,263–265}

M. Specifics of Plasma Interaction with Living Tissues: Depth of Penetration of Plasma Effects

Plasma processes take place in the gas phase; therefore, plasma-medical treatment is usually related to medical treatment of surfaces.^{1,15,251} Only very limited types of diseases can be, in principal, plasma-treated from the “surface.” The crucial question therefore is the depth of penetration of plasma effects, or, in other words, how does the plasma treatment reach tissues located not on the surface, but deep in the body? This chal-

lenging question is often discussed. Physical effects, able to provide deep penetration of plasma effect, include electric fields, some special diffusion mechanisms, radiation, and mechanical effects like shock waves. Biological effects, able to provide deep penetration of plasma effect, include, in particular, bystander effect, intercellular signaling pathways, stimulation of immune system response, and others.^{266,267}

N. Plasma Stimulation of Immune System Response, and Intercellular Signaling Pathways

As it was discussed above, the crucial question for plasma medicine is the depth of penetration of plasma effects, or in other words, how can plasma treatment can reach tissues located not on the surface, but deep in the body? Much of the recent research is focused on the major biological effects, which are able to provide deep penetration of the plasma effect including intercellular signaling pathways, and especially plasma stimulation of the immune system response. Experimental data are to be presented comparing different plasma stimulated pathways. Special attention is paid to discussion of possibilities of plasma treatment of various cancers.^{268–273}

O. Concept of Plasma Pharmacology: Plasma-activated Water (PAW), Plasma-activated Solutions; Biological and Medical Effects of Plasma-activated Cell Growth Media (PAM)

The Plasma-medical effect can be strong, not necessarily in a direct way—effective plasma-medical treatment can be in some cases “separated.” In this case different kinds of plasma (nonthermal, like DBD or jets, but also transitional or “warm” like gliding arcs) are activating water—different solutions, in particular biological medium, which later on can be applied to different biological or medical applications, including sterilization, as well as treatment of wounds and different diseases. This approach is sometimes called plasma pharmacology. The general concept, major devices, and applications of the plasma pharmacology are discussed. Specific examples are related to the physics and chemistry of the plasma-activated water (kinetics of plasma acid is presented), plasma-activated solutions [*n*-acetyl cysteine (NAC), etc.], as well as to biological and medical effects of plasma-activated cell growth media.^{274–280}

IV. INFECTIOUS DISEASE CONTROL AND PREVENTION

A. Plasma Approaches to Disinfection and Sterilization of Different Surfaces and Living Tissues

There are a multitude of different plasma sources for disinfection, sanitization, and ster-

ilization of all possible surfaces,⁴⁸ starting from dielectric barrier discharge treatment of simple flat metal surfaces,⁴⁹ to the three-dimensional surface of heat-sensitive lettuce leaves treated by low-pressure radio-frequency discharge,⁶² and finally plasma sterilization of a complex wound surface on a live patient using floating electrode–dielectric barrier discharge (FE-DBD),²¹ helium plasma jet,⁶³ and other sources. During plasma treatment, special attention is given to various approaches that minimize or eliminate entirely any damage to the surface being treated and minimize generation of toxic by-products following plasma treatment; for example, reduction of toxic peroxynitrite radical production during wound treatment.²⁸¹

B. Surface Sterilization in Low-pressure Plasmas

Approaches to surface sterilization include removal of pathogenic organisms such as bacteria, viruses, and fungi using reduced-pressure pulsed,²⁸² radio-frequency,²³¹ and DC plasmas in different gas atmospheres, e.g., RF discharge in 1 Torr argon with the addition of a few percent of oxygen. In the current sterilization systems the pressures range from slightly above atmospheric to plasmas at pressures significantly below 1 Torr.²⁸³ A few organisms are of special interest, such as, for example, *Deinococcus radiodurans*,²⁸⁴ which are able to safely survive low pressure without significant loss in viability.²⁸⁵ Differential pressure systems, where pressure is varied during the treatment process, are also frequently discussed as well as plasma systems with pulsed pressure²⁸⁶ and gas additives, such as ethylene oxide. Plasma is frequently used in combination with alcohol vapor, hydrogen peroxide vapor, and other chemicals. Antipathogen effects of ultraviolet and other radiation, active neutral species, charged species, and thermal effects of plasma are discussed in the literature as it applies at reduced pressures.

C. Specifics of Microorganism Inactivation by NonThermal High-pressure Plasmas

High-pressure plasmas, such as atmospheric pressure and higher, are quite different from low-pressure discharges and special attention needs to be given to reduction or elimination of thermal effects.⁴⁷ Especially when we are dealing with sanitization of biological objects thermal effects lead to significant surface damage and thus need to be reduced to a minimum.²¹ Special attention is given to plasmas currently used for nondamaging sterilization of living objects, such as low-energy ultraviolet radiation sources in UVB and UVC range, dielectric barrier discharges (both in jet mode and in direct contact with living skin) where pulses are kept quite short to reduce or prevent local overheating, short-pulsed spark discharges generating both reactive oxygen and nitrogen species and UV, and others.

D. Physical and Biochemical Mechanisms of Atmospheric-pressure Air Plasma Sterilization

In general, plasmas generate radiation, active neutral species, charged species, local thermal effects, high electric fields, and mechanical effects such as local vibration. Physical and biochemical mechanisms of atmospheric-pressure plasmas interacting with living biological objects such as bacteria, fungi, and viruses are often discussed.¹⁴ Specifics of different discharges are also addressed; for example, pin-to-hole spark discharge (PHD)²¹⁰ generates higher ultraviolet radiation and shock waves than dielectric barrier discharge, while plasma jets tend to carry only reactive neutral species to the surface being treated. Special consideration is given to discharges, such as floating electrode–dielectric barrier discharge where plasma is generated between the dielectric-covered electrode and the surface being treated^{21,287} in comparison with discharges where only the plasma afterglow is used, e.g., helium plasma jets,¹⁸⁵ charges and short-living species do not contact the surface being treated.

E. Plasma Suppression of Methicillin-resistant *Staphylococcus aureus* (MRSA) and Other Antibiotic-resistant Microorganisms

Special attention needs to be given to various antibiotic-resistant organisms in vegetative, spore, and biofilm form, for example, methicillin-resistant *Staphylococcus aureus*, or antibiotic-resistant strains of *Acinetobacter*.⁴¹ Some issues are specific to these organisms and to how plasma is used to effectively and efficiently inactivate and remove these pathogens. As, for example, *Staphylococcus aureus* developed resistance to methicillin, a common antibiotic, so it is possible, though unlikely, that pathogens may develop resistance to plasma treatment.²⁸⁸ The possibility of pathogens developing immunity to various plasma components is often discussed along with recommendations of how this could be circumvented in the future. Multiple studies performed globally in various research laboratories on the possibility of resistance to plasma treatment, especially plasma sources where the primary mode of action is ultraviolet radiation, are continually reported on.

F. Plasma Suppression of Bacterial Spores

Bacterial spores, such as *Bacillus subtilis* or *Clostridium difficile*, are well known to be especially resistant to antimicrobial agents.²⁸⁹ Plasma inactivation of dry spores on a dry surface as well as spores in liquid, in air stream, and in other media are being effectively addressed by plasma treatment.^{45,290} Ranging from inactivation to complete removal and full oxidation to CO₂ and water is possible with plasma and examples of inactivation of various common spores are discussed. The special case of spore removal from the surface of a spacecraft to prevent forward contamination of other planets and eliminate

false detection of life on other planets presents an interesting challenge to plasma²⁹¹; there is also a discussion of various organisms that can service extreme environments. Both physical mechanisms by which plasma inactivates spores, similar to those above, and biochemical mechanisms specific to spores, for example, activation of the death receptor (DR), are discussed.

G. Plasma Suppression of Fungi and Yeasts

Fungi, unlike bacteria, frequently have a rather strong cell wall and are prone to form connected colonies, e.g., *Candida albicans*, a common opportunistic human pathogen. These organisms tend to be more resistant to sanitization agents and cleaning products, much like biofilms. Successful and effective sterilization was shown with specific examples of plasma interaction with single-cell fungi as well as multicell colonies on various surfaces,³⁸ including living tissues such as colonized burn wounds, oral cavity, and other surfaces. Specifics of plasma interaction with fungi and fungal colonies are also discussed.

H. Challenges of Plasma Suppression of Mature Biofilms

When allowed to thrive, biofilm-forming bacteria can build an intricate and complex network for themselves, consisting of multiple cell types that are able to carry different functions. If a wound is colonized to the extent of biofilm formation the antibiotic intervention is likely to go unnoticed by the pathogens. Plasma jets, direct application of dielectric barrier discharge to tissue, pin-to-hole spark discharge (PHD), and other plasmas have been shown to effectively inactivate biofilms and even prevent biofilms from forming on various living and nonliving surfaces.^{50,292,293} Specifics of plasma application to a biofilm, mechanisms of interaction, and specific medical examples of plasma application in dentistry for dental caries removal, wound bed cleaning, and removal of biofilms from other surfaces are addressed.

I. Plasma Suppression of Viruses

Viruses exist in two main forms, as far as plasma treatment is concerned: (a) free-floating in air (most likely surrounded by single or multiple layers of water molecules), on surfaces, in liquid (could be blood or intracellular fluid), and (b) inside of a host cell. Plasmas have been shown to successfully inactivate viruses for both cases. Most challenging, of course, is the inactivation of the virus inside of a host cell. Plasma inactivation and/or complete destruction of viral pathogens in air, in water, and on surfaces as well as *in vitro* studies showing successful removal of herpes simplex virus (HSV) in human corneal epithelial cells and others have been

reported on. Specific discharges used in such cases include various versions of helium plasma jets and floating electrode–dielectric barrier discharge. Challenges of controlling plasma dose and dose rate to keep delicate cells alive while inactivating the virus are discussed.

J. Plasma Suppression of Prions

Prions are quite similar to viruses in their infective nature but are, essentially, a protein rather than an amino acid-based pathogen. There are two separate issues with prions: removing them from a surface to prevent transmission of infection, and inactivating this misfolded protein inside of a host cell. Results were obtained in different discharges, both low and atmospheric pressure, where prion removal from medical instruments was shown to be quite effective, e.g., helium plasma jets²⁹⁴ and low-pressure RF plasma in argon with oxygen addition.²⁸³ There are some preliminary studies *in vivo* in a mouse model where floating electrode–dielectric barrier discharge plasma was shown to effectively inactivate prion activity while the animal survived the treatment. Challenges of such applications in human medicine are often brought up with no clear solution surfacing just yet.

K. Plasma Suppression of *Bacillus anthracis* (Anthrax) and Other Highly Dangerous Pathogens

Anthrax is effectively controlled by vaccination in domesticized animals with but a few cases reported yearly. However, recently anthrax was used, in a spore form, as a biological weapon and continues to be a threat along with other dangerous pathogens.²⁹⁵ For this reason, special plasma systems, based on dielectric barrier discharge⁴⁵ or nanosecond-pulsed powerful coronas,³⁶ have been developed to address these issues. Plasmas were successfully demonstrated to effectively inactivate anthrax spores inside of an envelope as well as in air and in liquid. Special consideration is given to atmospheric-pressure discharges addressing decontamination of especially dangerous and infective pathogens.

L. Animal and Human Living Tissue Sterilization

Plasma-assisted sterilization and pathogen inactivation on live animals and human patients has been gaining significant traction recently. Both plasma treatment alone, and in combination with various antimicrobial agents, a common practice in medicine, is often discussed. There are three key discharges used in medical sterilization: (a) thermal plasma jets, where only downstream plasma afterglow is used, especially argon and nitrogen jets with and without oxygen addition²⁹⁶; (b) nonthermal plasma jets where long-living

and shorter-living active species are able to reach the tissue, such as RF helium jets²⁹⁷]; and (c) direct discharges where plasma itself contacts the tissue or the tissue is used as a second active electrode, e.g., floating electrode–dielectric barrier discharge²¹ or pin-to-hole spark discharge.²¹⁰ Plasma application to intact skin for pre-surgery sterilization, treatment of surface wounds, treatment of burn wounds, and plasma treatment of various ulcers are discussed.

M. Plasma Treatment of Leishmaniasis, Malaria, and Other Parasitic Diseases

Leishmaniasis is a typical example of a parasitic disease where a carrier (a sand fly, in the case of Leishmaniasis) injects a parasite into the host organism and the parasite thrives, invading the host. In a way, the problems associated with parasitic disease treatment are similar to the issues arising in the case of viruses and prions. There is a recent focus on inactivation of parasites by plasma outside of the host cells and inside of the cell. In the case of cutaneous Leishmaniasis, for example, promastigote form of the parasite is injected by the sand fly under the skin and attacks macrophages. Once inside the macrophage, the parasite transforms to amastigote form and multiplies. Inactivation of parasitic diseases by plasma is discussed with illustration of specific plasma treatment examples, e.g., floating electrode–dielectric barrier discharge treatment of *Leishmania* promastigotes *in vitro*, a co-culture model with macrophages, where promastigotes are inactivated by plasma before they can enter the cell while the cells remain reasonably intact, and finally an *in vivo* mouse air model where plasma is shown to eliminate progression of the disease.²⁹⁸

N. Food-related Pathogen Management by Plasma

Fresh produce, meat, fish, poultry, beans, powders, and other food products are all prone to pathogen invasion, including bacteria, fungi, viruses, and various parasites (single- and multicell). There are key specifics related to sterilization of food items with focus on specifics related to sterilization of foods preserving colors, taste, and other properties of the products while reducing or eliminating pathogen load.²⁹⁹ Plasma-treated water for fresh produce wash, an important food safety application, and produce misting is one of such examples.¹⁹⁸ Issues specific to the farm environment, transportation from the farm to the food processing facility, handling, packaging, and transportation sanitization issues, and finally food safety issues in the store environment are addressed.³⁰⁰ Separately there is a discussion on some issues specific to the in-home storage and handling of foodstuffs; e.g., reduction of ethylene inside the refrigerator³⁰¹ and cleaning of food-contacting surfaces.³⁰² Issues associated with air cleaning, water treatment, and direct treatment of foodstuffs and food-contacting surfaces are also of importance in produce infection control.

O. Antimicrobial Liquids and Surfaces Produced by Plasma

Preparation of temporarily or permanently antimicrobial liquids, gels, and surfaces by plasma treatment is another important issue in infectious disease control and prevention applications. Active species produced in plasma can be dissolved in liquid or gel to produce a lasting effect, from a few minutes to a few years of antipathogen activity. For example, floating electrode–dielectric barrier discharge (FE-DBD) was shown to increase reactive oxygen and reactive nitrogen species concentration as well as decrease pH of the treated liquid.³⁰³ Specifically, FE-DBD treatment of water was shown to generate H₂O₂, HO₂, NO₃⁻, NO₂⁻, and HONOO in concentrations sufficient to inactivate >99.99999% (7-log reduction) of bacteria. Similarly, alginate gel, an alginic-acid-based hydrogel, gains strong antimicrobial properties following FE-DBD treatment and was shown effective in inactivating wound pathogens *in vitro* and in a mouse model. FE-DBD treated water was shown to be nontoxic to animal tissues and was even injected into live mice without immediate adverse effects (mice were observed for one week following intravenous FE-DBD treated water injection). Similarly, various surfaces and fibers can be peroxidized or similarly processed in plasma resulting in an antipathogen coating. Specifically, if normal-acetylcysteine (NAC), a common antioxidant, is added to treated water it is readily peroxidized and can offer long-term stable antimicrobial properties to this water. Surfaces can be modified to have a microscopic structure not favored by microorganisms for attachment and chemicals, such as Ag, TiO₂, or antibiotics, may be deposited on the surface of an implant for permanent anti-microbial properties. Details of preparation of antimicrobial liquids, solutions, and surfaces are discussed in the referenced literature.

P. NonThermal Plasma Sterilization and Pathogen Inactivation in Air Streams

Oxidation and removal of organic contaminants, smells, viruses, bacteria in spore and vegetative form, and other pathogens from air streams is yet another infectious disease control and prevention challenge. Air sterility is an important issue in, for example, intensive care units where currently the high-efficiency particulate absorption (HEPA) filters are utilized. Two key issues with HEPA filters are that (1) they have a limit on the size of the particles they can trap, allowing viruses and volatile toxins through; and (2) HEPA filters create a significant pressure drop increasing the cost of the air conditioning systems. Both problems are effectively and efficiently addressed by dielectric barrier grading discharge (DBGD),³⁰⁴ pulsed corona,⁴⁶ transitional forward or reverse-vortex gliding arc discharge, and other plasmas.

Q. Plasma Disinfection and Sterilization of Water and Other Liquids

Sanitization and sterilization results and issues related to plasma cleaning of water

streams is another challenge in a hospital environment or at a nursing home. *Legionella*, for example, thrives in hot water and it is known to infect hospital water supplies. Pulsed spark discharge, generated in water, creates a high concentration of ultraviolet radiation coupled with reactive oxygen species (OH and H₂O₂, mainly) that lead to fast and effective removal of *Legionella pneumophila* from water. Similarly, corona discharges were employed in Japan to reduce or eliminate algae infestation of lakes.³⁰⁵ Other examples include sterilization of conductive water, for example in-line sterilization of saline for surgical irrigation.

R. Plasma Disinfection of Fracking and Produced Water, Ballast Sea Water, and Other Industrial Waste Waters

While not directly related to medicine, it is important to point out advancements in industrial applications of plasma for water treatment, as they are likely to find their way into the hospital water supply and handling systems as well. Large-scale plasma systems are being developed for (a) desalinization and removal of organic contaminants from fracking and produced water, resulting from the water used in hydraulic fracturing (fracking) in oil and gas industries³⁰⁶; (b) sterilization of conductive and dirty sea water used as ballast in large cargo ships leaving the United States⁴⁴; and (c) various other industrial waste waters such as softening of hard water resulting from water use in cooling towers of power plants. Discussed are the issues related to plasma generation and control specifics associated with dielectric barrier discharges of various configurations, pulsed and DC coronas, and transitional nonequilibrium gliding and pulsed arc generated in water or near the water surface.

S. Pathogens Developing Resistance to Plasma Treatment: Partial Inactivation, Viable-But-Not-Culturable (VBNC) State of Microorganisms

Infectious disease control and prevention using plasma requires a discussion of resistance development by the pathogens to the plasma treatment. Pathogens are well known to develop resistance to antibiotics as fast as we come up with new ones and plasma may not be an exception. For this reason, understanding of the specifics of the mechanisms of resistance development, viable-but-not-culturable (VBNC) or active-but-not-culturable (ABNC) states, and effects of partial inactivation are all rather important in the medical field where plasmas are beginning to take hold. Special examples are given with plasma treatment by floating electrode–dielectric barrier discharge, pulsed and DC corona, gliding arc discharge, and other plasma treatment of especially resistant organisms like *Deinococcus radiodurans* that survives extreme radiation doses, *Bacillus stratosphericus* which survives low pressure and extreme ultraviolet environment of the stratosphere, and other pathogens.^{174,307}

V. HEMORRHAGE CONTROL, HEMATOLOGY, AND CARDIOVASCULAR DISEASES

A. General Biochemical and Medical Aspects of Whole Blood, Blood Plasma, Blood Cells, and Blood Coagulation Processes

Fundamentals of blood coagulation processes required to understand the basis of hematology and hemorrhage control in medicine are discussed. Intrinsic and extrinsic blood coagulation cascades are discussed. During surgery, most bleeding issues can be predicted by a surgeon while this is not the case during trauma: there are some important differences between minor surgeries, like vocal cord polyp removal or treatment of epistaxis, compared with larger-scale surgeries, like liver resection surgery, where larger blood vessels are affected. Key medical aspects of small surgeries are discussed and compared with those for larger-scale surgeries. Basic concepts of different types of hemorrhage include mainly controlled, e.g., surgical wounds, and uncontrolled bleeding, e.g., trauma. Specific focus is also given to the medical aspects of profuse noncompressible hemorrhage.

B. Blood Cauterization by Thermal Plasma

High temperature has been used to cauterize wounds since the ancient times where warriors heated their swords in the fire and applied hot metal to the wound to stop bleeding and create a protective layer of charred tissue/cells/blood; basically, a mesh of coagulated proteins³⁰⁸ There are many plasma-medical devices currently available to medical professionals for blood cauterization by temperature. One such example is a Bovie® electrosurgical tool that utilizes a jet of argon gas passed through thermal arc, resulting in tissue-contact temperatures of over a thousand degrees Celsius.³⁰⁹ Another example is the Plasma Surgical PlasmaJet® system which is also thermal in nature but arguably delivers less damage to the tissues.³¹⁰ While thermal plasma tools can be made rather small with minimal damage to the surrounding tissue, further investigation of the mechanism behind thermal plasma interaction with blood is still needed.³¹¹

C. Non-Thermal Plasma-assisted *In Vitro* Blood Coagulation

Plasma temperature is not always the main mechanism of action for *in vitro* studies of blood coagulation control. For example, there are blood coagulation using direct application of floating electrode–dielectric barrier discharge to blood, blood cells, and blood plasma; and indirect plasma delivery have been investigated through various jet configurations (with helium, argon, nitrogen, air, and other carrier gases), sparks (that are kept

in nonthermal regime by keeping voltage pulses to extremely short duration to prevent gas temperature raise above ambient; e.g., pin-to-hole spark discharge system), and other nonthermal plasma sources.

D. Biochemical Mechanisms of Plasma-assisted Intrinsic and Extrinsic Coagulation Cascade Activation

Depending on the type of plasma used, the mechanisms of blood coagulation, both intrinsic and extrinsic, can be drastically different. The key mechanisms of different types of plasmas with respect to blood and blood-contacting cells (extrinsic) and blood proteins (intrinsic) are discussed. Nitrogen plasma jet, for example, was shown to significantly reduce the kinetic rate of fibrin filament formation and platelet activation, effectively slowing down the coagulation process, or “anti-coagulating” the blood; while floating electrode–dielectric barrier discharge in open air was shown to create the exact opposite effect with fast fibrin cross-linking and platelet activation.²¹ Chemical kinetic models of blood coagulation focus on the combined kinetic models where plasma-coagulation-catalysis is added to the biochemical kinetic model of coagulation. Reactive neutral species, charged species, radiation, and the biochemical effects are specific to different plasma discharges.

E. Plasma-assisted Coagulation of Capillary Bleeding and Hemorrhage Control in Microsurgeries

Plasma coagulation of capillary bleeding include small cuts, scrapes, and surface wounds, and hemorrhage during controlled microsurgical incisions and other microsurgical wounds. Specific applications of various nonthermal discharges are discussed as pertinent to the specific medical cases. Epistaxis (nose bleeds): while not fatal or particularly harmful, epistaxis frequently becomes chronic in children, leading to frequent visits to the emergency room where coagulation agents (such as silver nitrate) are used and frequently cause more harm than good by destroying excessive amounts of tissue around the bleeding capillary. Plasma in epistaxis is used to controllably coagulate small capillaries in the nose without damage to surrounding tissue.³¹² Capillary bleeding also remains a concern in small-scale surgeries.

F. Plasma-assisted Hemostasis of Profuse Noncompressible Hemorrhage

Profuse noncompressible hemorrhage accounts for over 40% of deaths in the forward surgical units in a war zone; similar statistics apply to major car accidents, gunshot wounds, and other times of massive trauma involving noncompressible hemorrhage. Stopping massive bleeding is an important medical challenge. Thermal plasmas can,

in theory, coagulate large volumes of flowing blood but the damage to tissues may be too excessive for the patient to recover from this treatment. Similarly, many surgical procedures are not undertaken due to risk of excessive bleeding; e.g., direct surgery on the heart, excessive spleen resection, or liver resection surgeries. The ability of plasma to stop profuse hemorrhage may lead to a novel set of surgeries, not to mention saving severe trauma and military patients.

G. Plasma Control of Rheological Properties of Blood

Blood can be treated as a viscous non-Newtonian flowing fluid in order to assess plasma influence on its rheological properties, primarily on blood viscosity. Introduction of the 2D and 3D chemical fluid dynamics (CFD) models of blood flowing in a vessel is important in discussing the fundamentals of rheology as it applies to blood. This CFD model can be coupled to the chemical kinetic model discussed above resulting in a full model of blood coagulation by direct plasma treatment.

H. Plasma Control of Low-density Lipoprotein (LDL) Cholesterol

While blood viscosity depends on many biological factors, increase in the concentration of low-density lipoproteins (LDL cholesterol) is one of the major contributors to blood viscosity increase. Direct floating electrode–dielectric barrier discharge treatment of blood plasma cross-links LDL molecules allowing for them to be easily filtered out of blood, decreasing viscosity and making blood more fluid. This was successfully demonstrated *ex vivo* with dielectric barrier discharge and pulsed spark treatment of whole blood and blood plasma. Reduction of LDL can be effectively achieved without coagulating the blood by controlling plasma dose and dose rate.

I. Plasma Control of Ischemic Diseases

Fundamental medical issues arise in ischemic diseases where blood supply to a certain area is somehow restricted. Based on these basic medical concepts, areas are formulated where plasma treatment can significantly improve progress of the disease. Specific examples include ischemic diabetic ulcers where plasma treatment, through release of nitric oxide into tissues, acts as a vasodilator, widening blood vessels and decreasing resistance to flow. Plasma treatment also decreases blood viscosity, again to allow for better blood flow. Finally, plasma treatment has been shown to increase blood oxygenation near the area of treatment so even in ischemic wounds, where the blood flow is significantly impeded, the necessary oxygen can be delivered to tissues with increased oxygenation.

J. Plasma Improvement of Biocompatibility of Stents, Heart Valves, and Other Blood-contacting Implants

Blood biocompatibility of implants has always been a major issue for various blood-contacting medical implants, especially intravenous catheters, stents, and heart valves. Low-pressure and atmospheric-pressure discharges, such as capacitively coupled plasma, inductively coupled plasmas, and higher-pressure DC discharges, coronas, and dielectric barrier discharges, for plasma-enhanced chemical vapor deposition (PE-CVD), plasma etching and modification of various surfaces, and other plasma systems can address issues specific to blood biocompatibility of polymer, ceramic, and metal surfaces.

K. Plasma Sterilization of Blood *In Vivo*, *Ex Vivo*, and in Blood Storage Applications

A multitude of issues related to pathogen inactivation, including sterilization of wounds on a live patient have previously been addressed. There is a focus on plasma application specific to treatment of whole blood and blood plasma for pathogen inactivation inside of blood without coagulating the blood or otherwise adversely affecting it. Examples include dielectric barrier discharge jets in helium and in nitrogen, used for blood sterilization, as well as floating electrode–dielectric barrier discharge applied directly to the surface of blood and short-pulsed spark discharge plasma applied inside of flowing blood or blood plasma. Key issues include choosing plasma system and settings such that viruses, bacteria, and other pathogens are inactivated inside of blood while its rheological, biochemical, and biological properties are unaffected. Blood sterilization is an important medical application of plasmas inside the patient, during transfusion between patients, and for storage in blood banks.

L. Plasma-assisted Tissue Engineering of Blood Vessels

Plasma can also play a role in tissue engineering of blood vessels. *In vitro*, artificial blood vessels are frequently grown, in the lab, in various scaffold models and plasma treatment has been widely shown to have a positive effect on the rate of cell proliferation and growth inside of these scaffolds. Low-pressure capacitively coupled plasma can be used for scaffold surface modification as well as atmospheric-pressure short-pulsed uniform dielectric barrier discharge and other plasmas. Both *in vitro* and *in vivo*, plasma treatment was shown to enhance the rate of endothelial cell proliferation, migration, growth factor release, and even the rate of new blood vessel formation.

VI. PLASMA IN GENERAL SURGERY AS A SURGICAL SCALPEL

A. Medical Aspects of General Surgery

Aside from medical scrubs and gloves, the scalpel is probably the most used medical device during surgery and a large number of such devices have been designed since the times of Hippocrates and before. Plasma-medical scalpels are beginning to take hold in types of surgical procedures where cutting or sectioning is used. It is important to take note of tissues with profuse vs. minimal bleeding, and cutting through tissues with different presumed level of bacterial load: organs where we can assume zero bacterial load, skin where unknown pathogens are present in low concentration, and stomach where a high concentration of known types of bacteria are abundant.

B. Thermal Plasma for Tissue Cutting, Resection, and Other Surgeries

There are two basic types of thermal plasmas: (a) where tissue is used as one of the active electrodes and the thermal arc directly connects to tissue; and (b) where the arc is removed from the tissue and only a stream of hot gas is directed toward the surface being cut.³¹³ Specific plasma systems have been developed and illustrated by Bovie® and PlasmaSurgical® for tissue cutting applications.^{309,314,315} Both systems are currently approved by the Food and Drug Administration and are available for use at the hospital.

C. Multimode Plasma Surgical Tools: Cut/Coagulate Modes

Recently there have been new developments in multimode plasmas (both plasma jets and full-contact plasmas) where the same electrode offers one “mode” where it is used to cut the tissue, and a separate mode, either controlled by electronics or by simply varying the distance to tissue, where a plasma stream is used to coagulate blood right after cutting the tissue.³¹⁶ Examples of commercially available multimode plasma include tools sold by Bovie®, PlasmaSurgical®, and other companies. These plasmas are significantly different from their older counterparts discussed previously in the mechanism of action, plasma temperature, carrier gas, etc.

D. Specifics of Spark Plasma Scalpels in Ophthalmology and Other Delicate Surgeries

Spark plasma-based discharges, e.g., pulsed electron avalanche knife (PEAK), while thermal in nature, are sufficiently short-pulsed to not raise the tissue temperature and

therefore minimize thermal damage to the surface being cut.³¹⁷ These plasmas are too “weak” to cut through significant layers of skin to be useful in general surgery; however, they are ideal for delicate surgeries like corneal resections or brain surgeries.³¹⁸ Special attention is often given to the differences in the mechanism of action between these pulsed quasi-thermal plasmas and the thermal plasmas discussed above.

E. Nonthermal Plasma Scalpels

Scalpels can be based on nonthermal atmospheric-pressure discharges. Similarly to PEAK system, nonthermal plasma scalpels are too “delicate” for general surgery but may be useful in microsurgies where each layer of cells is accounted for; e.g., in vocal cord and ear drum surgeries. Focused high-flow capillary RF-coupled plasma jets in nitrogen, argon, and helium with oxygen additions are applicable, along with dielectric barrier discharge based systems. Specifics of the mechanisms related to nonthermal tissue cutting are important to address.³¹⁹

VII. CANCER

A. General Biochemical and Medical Aspects of Cancer and Cancer Treatment

Malignant neoplasia, otherwise known as “cancer,” represents a multitude of diseases involving unregulated cell growth. Cancers can grow, spread, and affect all parts of the body. A general medical and biochemical overview of the many types of cancers and general overview of approaches medical professionals take is important in order to consider for treatment and/or removal of these tumors. While the medical field of cancer treatment seems rather broad it can be narrowed down to a few treatment modalities like resection surgery, chemotherapy, and radiation therapy. Plasma treatment may play a role either replacing some treatments or working in unison with them.

B. Apoptosis vs. Necrosis of Cancer Cells

Apoptosis is a process of natural and well-regulated programmed cell death where a cell undergoes a series of biochemical and biological processes leading to cell partitioning and shutdown.³²⁰ Necrosis, on the other hand, is an unnatural version of cell death frequently occurring from injury, overstress, or ischemia. During apoptosis all toxins contained inside of the cell are regulated, packaged, and protected from spilling into the extracellular environment, while during necrosis a cell, basically, just spills out all of its contents including some possibly toxic compounds. Necrosis frequently leads to inflammation of surrounding tissues, toxicity, internal coagulation, and other problems. Plasma-assisted removal of cancer cells not through necrosis, which can do more bad than

good, has the potential to perform through programmed apoptosis without damage to the body. Specific examples of treatment of melanoma cells *in vitro* and *in vivo* include by floating electrode–dielectric barrier discharge,³²¹ treatment of brain tumor cells in an *in vivo* mouse model by RF plasma jet in neon and in helium,³²² and many other examples with more than five different plasma systems used to selectively inactivate more than thirty cancers *in vitro* and some *in vivo* as well as specifics of application of plasmas to promote cell apoptosis in cancers.

C. Selectivity of Plasma Treatment of Cancerous Cells

Cancers occur inside and nearby the otherwise-healthy cells and tissues. The following examples focus on mechanisms of selectivity that plasma treatment exhibits during treatment of cancerous cells and tissues. Selectivity of floating electrode–dielectric barrier discharge is applicable in the treatment of breast epithelial cancerous and noncancerous cells, and results of selective treatments with helium, argon, and neon plasma jets, and other plasma systems have been published.³²³ Similar to some types of chemotherapy and radiation therapy, plasma appears to target faster-dividing cells more actively than their dormant counterparts.³²⁴ Response to cell wall peroxidation, single- and double-strand DNA breaks caused by plasma, and other mechanisms of plasma interaction with cancerous and noncancerous cells are discussed.

D. Targeting Cell Cycle

There is a recent focus on the cell cycle, or cell-division cycle, which is a complex set of biochemical events that take place, in stages, leading to cell division. The cell cycle can be divided into five major phases: G_0 , or the resting state, G_1 , synthesis (when DNA replication occurs), G_2 , and finally mitosis, or the cell division. Cancer cells can be targeted specifically in the S-phase to hinder DNA replication and cause the cell division to malfunction and put the cell in apoptotic state. Experimental results of floating electrode–dielectric barrier discharge treatment of cancer cells in different phases of the cell cycle have been demonstrated, with a stress on the importance of appropriately targeting the treatment. Various plasma jets and pulsed spark plasma used for cancer cell treatment have been reported with valuable information on dependence of the plasma-related effects on the cell cycle.

E. Targeting Immune System

There is immense importance of the immune system in fighting cancers. The immune system, a system of biological structures and processes happening within an organism to protect itself from ailment and disease, is frequently turned off or avoided entirely

by cancers. Cancers are able to “pretend” and appear to the immune system to not be diseased, significantly hindering the natural removal processes. Activating the immune system is one of the important ways to prevent cancers from spreading. Plasma can effectively activate immune cells and increase their activity, and the immune system is one of the key mechanisms by which plasma, an inherently gas-phase phenomenon, can effectively address deep-tissue cancers. Floating electrode–dielectric barrier discharge may lead to the activation of immune cells, cell migration, calcium channel activity, and other effects triggered by this treatment. Specifics related to different types of plasmas and triggering of the immune response are discussed. *In vitro* analysis of a single immune cell, like a T-lymphocyte, response to plasma treatment are relevant in discussing the systemic response of the immune system triggered by plasma treatment with specific examples of thermal plasma jets producing high concentration of nitric oxide as well as nonthermal plasmas such as floating electrode–dielectric barrier discharge and plasma jets, primarily based on helium with oxygen addition.

F. Targeting Cancer Stem Cells

Cancer stem cells (CSCs) are a particular type of cancer cell that exhibit characteristics typical to normal stem cells, specifically the ability to give rise to the many cell types found in a tumor. Targeting CSCs with plasma is the focus where plasma’s ability to force the differentiation of a CSC into a terminal cell is demonstrated. In this way CSCs are not removed by necrosis (which is dangerous, especially in or near blood) or by apoptosis; rather the CSCs are forced to specialize and then they die naturally, at a later time. Specifically, for example, inactivating leukemic cells in flowing blood can reduce activity of this cancer and impair its ability to spread to new tissues; forcing leukemic stem cells to differentiate by floating electrode–dielectric barrier discharge treatment was shown *in vitro* and serves as a positive indication in this direction. Specific details associated with plasma treatment of cancer stem cells require discussion on interaction mechanisms, and proposed medically-relevant cancer treatments.

G. Organlike Behavior of Malignant Tumors

A cancerous tumor, inside of a patient, is not simply a collection of unstructured and randomly growing cells. There are medical aspects of organlike behavior of malignant tumors, with their own dedicated blood supply network, relations with the local and global immune system and different types of cells participating in the construction and function of the tumor. If plasma is to successfully target cancers, we need to understand the interaction between the plasma, applied at the surface, and the tumor as a whole well-networked system. The interaction of floating electrode–dielectric barrier discharge and various helium, nitrogen, and argon-based plasma jets with the entire tumor is interesting when focusing on the effect of plasma treatment on cancer cells within

the tumor, blood vessel behavior, blood oxygenation level in the tumor following the plasma treatment, and other issues specific to the tumor as a whole.

H. Melanoma and Other Skin Cancers

Melanoma is a surface tumor and most accessible to plasma treatment; for this reason, perhaps, melanomas were one of the first cancers to be studied with plasma and continue to hold strong attention of both the plasma community as well as medical professionals. Specifics of the floating electrode–dielectric barrier discharge initiation of apoptosis in melanoma cell lines as well as cell response to various helium, argon, and nitrogen jets are discussed. Plasma treatment was successfully shown *in vitro* and *in vivo* in animals to inactivate melanomas.

I. Leukemia and Other Blood Cancers

Blood-borne cancers, such as leukemia, have specific medical aspects associated with tumors which are discussed along with the plasma-chemical interaction with leukemic cells. Leukemic cells are, essentially, cancer stem cells. One of the ways to address this cancer is to force these cells to differentiate and specialize into any other cell type so that it is removed by the immune system or simply dies naturally through apoptosis. *In vitro* results of plasma stimulation of leukemic cell differentiation and later apoptosis by treatment with floating electrode–dielectric barrier discharge are discussed along with the specific mechanisms of interaction of plasma with these cells inside of blood, especially flowing blood.

J. Glioblastoma and Other Brain Tumors

The focus in recent research in plasma treatment of cancers is glioblastoma, one of the most common and more aggressive malignant primary brain tumors in humans. Since the current standard of care for most brain tumors is surgery, finding new treatment options becomes essential if sections of the brain are to remain intact. Radio-frequency helium and nitrogen jets and floating electrode–dielectric barrier discharge were shown to effectively inactivate these tumors both *in vitro* and *in vivo* in an animal model. Suppression of blood vessel development in the tumor and massive apoptosis following plasma treatment has been demonstrated *in vivo*.

K. Neuroblastoma

Neuroblastoma has certain specifics of this cancer of infancy and early childhood. Plas-

ma application methodology is different in this case, compared to other head cancers due to the extracranial nature of this tumor. Although excellent results have been shown *in vitro* with neuroblastoma cell lines by radiofrequency helium plasma jet, *in vivo* validations are underway and present clear challenges compared to other tumors, primarily because the patients are typically rather young.

L. Lung Cancer

Lung cancer is a malignant tumor colonizing lung tissue that is both difficult to detect and difficult to treat. Plasmas have been successfully demonstrated *in vitro* with various lung cancer cell lines; however, the challenge is to treat deep inside the lung tissue and various plasma solutions have been recommended. Plasma-based lung cancer treatments range from long thin helium, argon, or nitrogen plasma jet catheters that can be fed into the lung, to more elegant solutions like launching ionization waves, termed plasma “bullets,” using the lung itself as the guide for plasma propagation, similar to plasma bullets propagating through a tube with conductive walls. Both solutions have been successfully demonstrated *in vitro* and *ex vivo*.

M. Pancreatic Cancer

Plasma may have applications in pancreatic cancer treatment. Plasmas have been successfully demonstrated *in vitro* to effectively initiate apoptosis in various pancreatic cancer cell lines by application of radio-frequency helium plasma jet. This treatment, however, remains an academic adventure for the moment because of the challenge of treating organs deep within tissue. However, plasma may be quite useful in pancreas resection surgeries.

N. Cervical and Ovarian Cancer

The discussion of treatment of cervical and ovarian cancers should begin with the discussion of medical specifics of these cancers and follow with specifics of plasma application techniques relevant to these types of cancers since they are more accessible with catheters than some deeper cancers. Catheter-based radio-frequency helium jets were shown *in vitro* and *ex vivo* to effectively inactivate cervical cancer cells. Significant *in vitro* and *ex vivo* advancements in antitumor studies with various plasmas have been demonstrated.

O. Prostate Cancer

Current approaches to possibilities of using plasma jets and direct plasma approach to

prostate cancer treatment are discussed. Significant results have been obtained *in vitro* with plasma initiation of apoptosis in cancer cell lines using radio-frequency helium plasma jet or the floating electrode–dielectric barrier discharge; however, the challenge of treating deep within tissue remains a major barrier for plasma-assisted prostate cancer treatment and needs to be addressed appropriately.

P. Bladder Cancer

In general, bladder cancers are a bit easier to get to with a catheter than some of the other cancers. Current *in vitro* results obtained with helium, argon, or nitrogen plasma jets and proposed *in vivo* studies of plasma treatment of bladder cancers are demonstrated. Specifics related to plasma application inside of the bladder are addressed and compared to plasma treatments of other similar cancers.

Q. Breast Cancer

While breast cancer mostly occurs in females, these cancers do occasionally appear in males as well, and the medical aspects of these are discussed as well as typical tumor locations and the current medical approaches to treat this ailment. Excellent results have been demonstrated *in vitro* where floating electrode–dielectric barrier discharge treatment showed selective initiation of apoptosis in malignant cells while noncancerous cells remain largely intact. While these results are promising, discussion is required of the challenges plasma treatments face in moving into *in vivo* human clinical treatments of breast cancers.

R. Oral Cancer

Oral cancers, while a subset of head and neck cancers, are separated in many plasma-treatment discussions due to ease of access by plasma probe. Discussed are the medical aspects, types of cancers, their typical locations, and the current treatments of oral cancers. We will then focus on discussion of current *in vitro* and limited *in vivo* data available of plasma treatments of oral cancers and the specifics of applying plasmas in the oral cavity. Provided are several examples of oral cancer treatment by helium plasma jets and other plasmas. Challenges facing plasma in advancing to full oral cancer treatment clinical trials are discussed as well as the approaches proposed by the scientific groups working in this direction.

S. Thyroid Cancer

The medical aspects of treating thyroid cancers today largely remain to be a surgical

removal of the entire thyroid gland. *In vitro* data on plasma treatment of thyroid cancers is available and the mechanisms by which the cancer reduction/removal occurs. The specific challenges plasma faces in clinical applications of thyroid cancer treatment exist in possible resection surgeries, and/or removal of the gland.

T. Specifics of *In Vivo* Plasma Treatment of Cancers

There is a fundamental challenge for plasma, typically a gas-phase phenomenon, to penetrate deep into the tissue and treat a large tumor. Various configurations of the floating electrode–dielectric barrier discharge, catheter-delivered helium, argon, and nitrogen radio-frequency, dielectric barrier, and pulsed DC plasma jets, pin-to-hole spark discharge (PHD) plasma, and other plasmas have mechanisms in treatment delivery. There are possibilities for novel discharges generated directly in liquid media by ultrashort high-voltage pulses and their current achievements in cancer treatment. Based on the current knowledge in the field and the directions plasma scientists are taking, there are novel ideas of plasma treatments that have not yet been tested *in vivo* or *ex vivo*, but have some *in vitro* success, and show significant medically-relevant potential.

VIII. WOUND HEALING: TRAUMATIC WOUNDS, BURN WOUNDS, AND ULCERS

A. General Biochemical and Medical Aspects Wounds, Wound Healing, and Tissue Repair and Regeneration

General biological, biochemical, and medical aspects of wounds in general, wound healing processes and current medical methods designed to aid these processes, and specific processes related to tissue repair and regeneration, both from the single-cell view to the systemic behavior of the body during wound healing are discussed. Current approaches used in medicine stress specific areas where plasmas, due to their active oxidative nature, may play a significant role. Special focus is given to pharmaceutical agents used for specific types of wounds and their biomolecular mechanisms of aiding in improved wound healing. Biomolecular pathways used through specific pharmaceutical agents can be linked to how plasma may influence or aid in the same pathway(s). In the medical field, multiple drugs and treatments are frequently combined to improve the overall healing rate; thus, we will discuss what treatments plasma may be a good additive for, ranging from plasma-assisted drug delivery to plasma-aided activation of immune system response.

B. Mechanisms of Plasma-induced Wound Sterilization and Healing

Plasma, generated over the surface of a wound, is inherently a gas-phase phenomenon.

Active species produced in plasma, together with charged species, ultraviolet radiation, and localized thermal effects (attributed to streamers hitting the surface) only come in contact with the water, either as liquid or physisorbed on cell/protein surface.¹⁴ From that point on, only the residual effects of plasma treatment remain and are discussed in detail. Effects of direct application of plasma to the wound tissue, like in the case of floating electrode–dielectric barrier discharge, are clearly different than those of a plasma jet, where short-lived species and charges never reach the tissue surface.⁵ These differences and the biochemical mechanisms by which plasma treatment stimulates inactivation of pathogenic organisms in the wound bed and stimulates wound healing processes are discussed. Specific focus is given to the difference between the many types of plasma discharges used in medical applications and the plasma specifics and is comparable to the different medically relevant situations and the different types of wounds addressed.

C. Plasma-assisted Disinfection and Sterilization of Wounds

Virtually every single type of plasma treatment historically began with showing its antimicrobial ability.³²⁵ Different types of plasmas and their specifics are relevant when applied to disinfection and sterilization of a complex three-dimensional surface of a wound. Three major types of plasmas include noncontact thermal plasmas, noncontact nonthermal plasmas, and full-contact nonthermal plasmas. Many examples of different discharges currently exist for use in wound sterilization. Examples of thermal discharges are provided based on the data obtained from Bovie®'s J-Plasma® and similar thermal plasmas.^{309,311} Noncontact nonthermal plasmas have the most examples with the wide array of different helium, argon, nitrogen, and other plasma jets, pulsed spark discharges, and other nonthermal plasmas where plasma does not use tissue as an active electrode³²⁶ while full-contact discharges include floating electrode–dielectric barrier discharge and other similar plasmas such as hollow-cathode discharge and dielectric barrier plasma jet in a contact mode.^{287,321} There are plasma specifics for different plasmas and the mechanisms by which each individual exemplary system inactivates pathogens in a wound bed. Medically relevant *in vitro*, *in vivo* animal, and human clinical data have been generated over the last decade of use of these discharges in the medical field.

D. Plasma Sterilization of Surgical Wounds

Previously the general aspects of sterilization of different types of wounds were discussed. It is important to distinguish wounds made through surgical intervention. The medical aspects of generating surgical wounds range from opening the patient's spine up to a microsurgery performed with the aid of a Da Vinci® robotic system. There are important differences between cutting skin, which has bacteria on it which can be embedded in the skin pores, and cutting internal organs and tissues where there are no bacteria present, hopefully. Results of floating electrode–dielectric barrier discharge sterilization

of surgical wounds to skin-level wounds and to internal tissues and organs as well as studies with various plasma jets and thermal discharges (where a low level of bacterial inactivation was observed) have been demonstrated. Some issues related to “telemedicine” or robotic surgery has been addressed. Proposed are the additions to existing surgical robots (e.g., the Da Vinci® robot) where plasma sterilizer may be added to the scalpel or other cutting tool.

E. Plasma Sterilization of Infected Wounds

Previously the general aspects of sterilization of different types of wounds were discussed. A separate discussion can also be made for wounds that are already infected, such as ulcerating wounds, and those already covered by a mature biofilm. We will start our discussion with medical aspects and current methods of addressing these types of wounds.²⁶ Results obtained from clinical trials with thousands of terminal patients obtained in Germany are discussed in detail where thermal nitrogen jet plasma is used to reduce the bacterial load of ulcerating wounds. *In vivo* studies of floating electrode–dielectric barrier discharge treatment of severely infected wounds with at least 48-hour bacterial biofilm have been performed as well as other plasmas used in similar studies, as demonstrated by Alkawareek et al.³²⁷

F. Plasma-stimulated Cell Migration and Proliferation

One of the important aspects of wound healing and tissue regeneration is appropriately controlled (by the body or with medical intervention) migration of wound repair cells into the wound bed, followed by their controlled proliferation and biochemical activity. Fibroblasts, for example, are needed in the wound bed to produce collagen, closing the wound. Over-proliferation of fibroblasts in the wound frequently leads to formation of a scar and thus activity of these cells needs to be regulated. Floating electrode–dielectric barrier discharge, helium and argon radio-frequency jets, and other plasmas have been shown to significantly affect the rates of cell migration and proliferation as well as their biochemical activity (e.g., collagen release by fibroblasts) both *in vitro* with single cell line and *in vivo* in animal trials.¹⁷

G. Angiogenesis in Wound Repair

Once the integrity of the tissue is broken, the delicate network of the capillary blood supply is likely to be affected. Angiogenesis, or formation of new blood vessels by endothelial cells, is one of the key processes involved in wound healing and tissue regeneration. Biological and medical aspects of angiogenesis are discussed as well as current medical approaches to improve the rate of new vessel formation. Specific examples of

floating electrode–dielectric barrier discharge control of angiogenesis both *in vitro* in endothelial cell lines and *in vivo* in animal trials have been illustrated by Kalghatgi et al.¹⁷ Treatments with radio-frequency argon plasma jet have also been extensively studied in angiogenesis control.

H. Plasma-induced Immune Response

Immune cells play a critical role in wound repair and regeneration processes. *In vitro*, floating electrode–dielectric barrier discharge, and argon and helium radiofrequency jets have been shown to stimulate activity of T-lymphocytes and macrophages without damage to these cells. Plasma interaction exists with these and other types of immune cells, calcium channel activity following plasma treatment, cell migration, and other aspects important to immune response. Various *in vivo* applications of thermal discharges where immune cell activity is controlled primarily through nitric oxide mechanisms are discussed. Interestingly, for example, when treating a mouse paw, nitric oxide is found in the liver and other organs, suggesting a systemic response to such treatment.

I. Tissue Repair, Regeneration, and Plasma-stimulated Differentiation and Specialization of Stem Cells

Medically, or rather biologically, wound healing is a complex process recruiting stem cells in the damaged area to promote tissue repair and regeneration via specialization of these stem cells into the necessary target cells. Plasmas have been shown to play an important role in stimulating and catalyzing these processes both *in vitro* and *in vivo* in animal models. For example, floating electrode–dielectric barrier discharge (FE-DBD) treatment of mesenchymal stem cells (MSCs) has shown to increase activity, rate of differentiation, and finally specialization of these cells *in vitro*. *In vivo* experiments where Matrigel® impregnated with MSCs was injected subcutaneously into mice showed significant statistically sound increase in the rate of cartilage and bone tissue formation in the samples that were treated by FE-DBD.

J. Plasma Sterilization and Healing of Burn Wounds

Burn wounds range from superficial first-degree burns, like sunburn, to severe cases with extensive tissue damage, fourth-degree burns, frequently requiring amputation. Special attention is given to both the initial wound management at an emergency room or when the burn is first observed, and to long-term burn wound management practices. Floating electrode–dielectric barrier discharge treatment of epithelial cells, plasma-stimulated cell migration and proliferation, and *in vivo* experiments with this plasma, as well as similar examples exist with the use of cold radio-frequency helium jet and thermal plasma in ni-

trogen. Clinical cases with the use of nitric oxide-generating thermal plasma are detailed.

K. Plasma Sterilization of Infected Ulcers

The discussion of sterilization of infected ulcers can start through the medical classification of ulcers, sources and types of infections, and the current methods used to address these ailments by the medical professionals. Because the population typically affected by ulcers is generally older, permissions for clinical trials tend to be easier to obtain; and for this reason plasmas are widely investigated currently for ulcer debridement and sterilization. Plazon® is one specific example, along with other nitric oxide-generating thermal plasma sources and the results of the human clinical trials as well as mechanistic studies in animals and in cell lines. More novel discharges include the use of floating electrode–dielectric barrier discharge and radio-frequency helium, nitrogen, neon, and argon jets for ulcer sterilization.

L. Plasma Treatment of Ulcers: Wound Healing and Tissue Repair and Regeneration

Once the ulcer is free of pathogenic organisms the process of wound healing and tissue regeneration may proceed. Some of the general mechanisms of wound healing and tissue regeneration were discussed above. Current medical methods and procedures specific to ulcerating wounds are discussed. Specific examples of *in vitro* and *in vivo* studies include floating electrode–dielectric barrier discharge healing of ulcers, as well as the use of radio-frequency helium plasma jet.

M. Treatment of Wounds Using Thermal and Nitric Oxide (NO)-Producing Plasmas

Nitric oxide is an important signaling molecule involved in many physiological and pathological processes, taking the title of “Molecule of the Year” in 1992. Wound healing applications where nitric oxide treatments are currently used in medicine include NO-producing drugs. The Plazon® system has already been in use by medical professionals for a number of years. Other NO-generating plasmas include pin-to-hole spark discharge and its applications in wound healing and tissue regeneration.

N. Plasma Wound Healing: Review of Results of Current Human Clinical Trials

Many specific achievements of plasmas in clinical trials were mentioned previously and here we summarize all plasma treatments currently or recently under investigation

in the framework of human clinical trials. Discussed separately are the thermal plasma sources, such as the nitrogen arc used by AD TECH Medical Instrument Corporation in a wound healing clinical trial and Plazon[®] system, and nonthermal plasmas such as floating electrode–dielectric barrier discharge plasma and radio-frequency helium plasma jet.

IX. DERMATOLOGY AND COSMETOLOGY

A. General Biochemical and Medical Aspects of Dermatology and Cosmetology

Plasma treatments in dermatology and especially in cosmetology are rapidly increasing the number of applications, *in vitro* and *in vivo* validation studies, in animal and human trials. Cosmetology is addressed as a special and separate case from dermatological diseases and dermapathology mainly because the regulatory pathways to productize plasma treatments are quite different in dermatology and in cosmetology. Many medical and herbal treatments and their claimed mechanisms of action are currently available and can be discussed along with the biochemical mechanisms of plasma interaction with tissues and cells.

B. Sterilization of Skin: *In Vitro*, *Ex Vivo*, and *In Vivo* Results

Sterilization of intact skin is an important medical challenge, especially when it relates to the fields of dermatology and cosmetology. Specific medical treatments requiring sterilization of intact skin such as tattoo placement and/or removal, for example, and the current medical and nonmedical methods used to achieve partial or complete removal of pathogenic organisms from skin are discussed. Special attention is given to the location and the origin of the pathogens on the skin; for example, bacteria that are on the skin surface are easily removed with soap and water, unlike the pathogens that are inside of oil-filled skin pores and hair follicles. Various plasmas are currently being investigated for skin sterilization. For example, there are *in vivo* and *ex vivo* experiments with deep skin sterilization and removal of bacteria from pores using the floating electrode–dielectric barrier discharge both with and without the addition of antibiotics, surfactants, and other aids.

C. Depth of Penetration of Plasma Skin Sterilization

While the previous focus was on general aspects of sterilization, discussed here is the

depth of penetration of plasma treatment into intact skin, skin pores, and skin crevices. Mechanisms of direct penetration of plasma-generated species into skin as well as primary, secondary, and tertiary messenger system activation are relevant in plasma treatment. Specifically, floating electrode–dielectric barrier discharge *ex vivo* and *in vivo* studies of skin treatment, as well as similar studies with radiofrequency plasma jets generated in helium, argon, nitrogen, neon, and other gas mixtures have been performed.

D. Onychomycosis, and Other Nail Diseases

Onychomycosis is a nail disease, occurring in about 10% of the population, more frequently caused by *Candida* species. Discussed are the medical specifics of this disease and we will especially focus on the growth and maturation of *Candida* under the nail. Onychomycosis presents an interesting type of a disease primarily because the pathogenic organisms tend to generate gas bubbles in the area where they are alive and metabolically active. For this reason, this presents an interesting application for plasma since the nail can serve as a dielectric and we can generate a modification of a dielectric barrier discharge inside of the human tissue with the nail serving as a dielectric and the gas bubbles generated by *Candida* as the medium for plasma.

E. Plasma Treatment of Acne

A typical skin disease cause in some cases by bacteria and in others by viruses, acne presents a medical challenge both in young adults as well as the older generation where acne “comes back.” Results of the *in vitro*, *in vivo* animal studies, and the limited human clinical data are available with plasma applications in acne treatment. Radio-frequency plasma jets in helium and argon are currently being investigated for bacterial and viral reduction of acne. Current results have also been obtained in the clinical trial of the floating electrode–dielectric barrier discharge.

F. Hair Follicle Stimulation and Hair Regrowth

Baldness is an important medical condition and large sums of money are spent on addressing this ailment; however, age-related loss of hair is not the only issue. Mechanisms of hair loss can be affected by genetic, diet-related, age-related, and other natural causes as well as issues related to hair regrowth in burn victims and other loss of hair follicle activity. Current medical practices, methods, and mechanisms employed by medical professionals and cosmetologists are discussed. Plasma may have a role in stimulation of hair follicle activity. Newer *in vitro* and *in vivo* results obtained with radio-frequency helium plasma jets and hair follicle activity stimulation and hair regrowth have been catalyzed by the floating electrode–dielectric barrier discharge.

G. Plasma-assisted Hand Disinfection and Sterilization

Although pathogen inactivation on the skin surface was already addressed above, hand disinfection and sterilization is revisited as it relates to applications in dermatology and cosmetology along with discussion of the many issues with skin sterility that medical professionals face in these fields. For example, the creation and removal of tattoos and other skin markings continually improves sterility both of the process and the skin being treated. Medical applications in dermatology and cosmetology where skin sterilization is needed is a matter of interest for potential plasma applications that are able to offer fast and effective results, such as various plasma jets and the floating electrode–dielectric barrier discharge.

X. DENTISTRY

A. General Biochemical and Medical Aspects of Dentistry

General biological, biochemical, and medical aspects of dental applications, the various diseases and medical issues, and the current pharmaceutical and device-oriented methods that the medical professionals employ are discussed. Out-of-office dental applications such as at-home tooth cleaning and whitening and some post-surgery techniques are also discussed.

B. Treatment of Gingivitis and Other Periodontal Diseases

In general, gingivitis can be characterized by the inflammation of the gum tissue. The basic medical aspects and the origins of gingivitis and other periodontal diseases are addressed alongside the discussion of the current medical practices to address these ailments.³²⁸ The biochemical action mechanisms of the pharmaceutical agents are currently employed to address gingivitis and link the Rx-reported mechanisms of action to those reported for plasma.³²⁹ Specifically, for example, there are results obtained by radio-frequency helium jet plasma treatment of gingivitis in dogs and other animal trials as well as the current human data recently reported on in Korea.³³⁰

C. Tooth Whitening

Medically, dental bleaching, commonly known as tooth whitening, is not a threatening issue like most ailments discussed here; however, with an estimated 15 billion dollars spent in the USA alone, this is a dental issue that is important to address. Plasmas, as strong oxidizers, have been reported as bleaching solutions in many industrial applications, primarily in treatments of fibers and fabrics. Recent studies with radio-frequency

helium and argon jet plasmas with oxygen addition show significant discoloration in *ex vivo* studies and animal trials.³³¹ Findings of research groups in Germany, Japan, China, and Korea focused primarily on various types of plasma jets as well as results obtained using the floating electrode–dielectric barrier discharge for dental bleaching are recently becoming available.^{332–335}

D. Sterilization of Dental Plaque: Plasma Destruction of Biofilms

Teeth offer the only surface of the human body that does not have a regulated system of renewing or shedding tissue and this allows bacteria to attach for long periods of time forming a complex biofilm matrix referred to as dental plaque. This plaque can lead to gum disease and should be promptly removed. Typically flossing and brushing can accomplish this removal but if the plaque is left undisturbed for a prolonged period of time medical intervention is needed.³³⁶ The medical aspects of dental plaque removal and prevention techniques currently applied in the dental field are discussed. The use of radio-frequency helium and nitrogen jet plasmas and floating electrode–dielectric barrier discharge sterilization and removal of dental plaque as well as proposed mechanisms of plasma interaction of this biofilm are reported in Koban et al.²⁹³ The use of plasma-treated materials in dental plaque removal—for example, plasma-assisted peroxidation of dental floss that leads to a more effective plaque removal by normal use of this floss afterwards—is another upcoming group of applications.

E. Plasma Treatment of Dental Caries

Dental caries, a bacterial infection that causes demineralization and tooth decay, is an important issue in dentistry.³³⁷ The medical aspects of addressing dental caries and the current methods employed in the practice are discussed,³³⁸ followed by a discussion of the results and mechanistic understanding of plasma treatment, sterilization, and possible prevention of caries. Specifically, the results obtained with radio-frequency argon and helium jet plasmas, treatment by floating electrode–dielectric barrier discharge, and other plasmas more thermal in nature, like pin-to-hole spark discharge and the Plazon[®] system, which both function through generation of nitrogen oxide with or without presence of reactive oxygen species, are reported.^{54,339,340}

F. Plasma-assisted Sterilization During Deep Root Canal Surgery

There are some key specifics related to root canal surgery, specifically, the issues related to bacterial invasion and the methods currently used in dentistry to eliminate these pathogens. Plasmas are used for sterilization of bacteria embedded in deep cavities under the tooth. The three specific plasma examples are (1) generation of

plasma jet in helium flow through flexible microcatheters of submillimeter diameter; (2) spark discharge plasma generated using a coaxial microcable of 450 μm diameter; and (3) launching “plasma bullets” through the root canal, using the tooth surface as the surface for the plasma ionization wave to travel on.¹⁰ The third example is the most interesting one as it utilizes the body cavity (root canal, in this case) as the plasma “guide” and thus treats all of the cavity surface, potentially leading to more effective pathogen removal.³⁴¹ The *in vitro* and *ex vivo* experimental reports as well as initial animal trial data available on plasma-assisted deep root canal sterilization are discussed.

G. Use of Ozone In Dentistry

While ozone had been receiving not very favorable coverage in the news recently, it still continues to be widely used by the dental professionals. There are many dental uses of ozone including specific applications such as ozone therapy of the oral cavity for bacteriostatic and bactericidal effects, using ozonated water as a pretreatment rinse, ozonating water in ultrasonic baths and in the water hydraulic system, using ozone directly to pretreat dental cavities for adhesion improvement, ozone insufflation of periodontal pockets, etc.³⁴² There is a clear focus on the safety implications of ozone use in the dental office setting.³⁴³ Finally, the various plasma sources are discussed, mainly based on the dielectric barrier discharge, for small-scale, midrange, and large-volume ozone generation both on-site at the dental office as well as pretreatment of water and other liquids, ozone stabilization, and packaging.^{344,345}

H. Plasma Treatment for Improved Filling Adhesion

One of the original applications of plasma surface treatment almost two decades ago was adhesion improvement and surface wettability increase via plasma treatment. Today in the printing industry and in the fabric and fiber processing industries plasmas are utilized widely and on a daily basis.³⁴⁶ The marketing terms differ by the manufacturer of the equipment but the basic science remains the same: treatment is accomplished by corona discharges, DC, AC, and pulsed and dielectric barrier discharges. There is a recent focus on the medical specifics of various dental filament materials and the surfaces they need to adhere to. Discussed are the current methods employed in the dental office setting for tooth surface preparation. There are various new plasma systems being investigated and evaluated for improved filling adhesion. Specifically, there is a focus on the uniform nanosecond-pulsed dielectric barrier discharge treatment of tooth surface, use of various helium, argon, and air plasma jets (both thermal and nonthermal in their nature), and limited use of short-pulsed corona and spark discharges.

XI. ORTHOPEDICS

A. General Biochemical and Medical Aspects of Orthopedics

The general medical aspects of various orthopedic ailments and procedures undertaken in the medical practice, both surgical intervention and nonsurgical treatments, are discussed. The biological and biochemical mechanisms associated with aging and bone and cartilage repair, synthetic joint replacements where repair is no longer possible along with antimicrobial treatments of these implants, bone and cartilage regeneration, and finally the role stem cells play in musculoskeletal tissue regeneration are addressed.

B. Plasma Materials for Synthetic Joints and Other Orthopedic Applications

Biomechanical and medical issues associated with bone and joint partial or complete replacement surgeries are of great importance in orthopedics. Although plasmas are rarely used in the preparation of the core of the implant material, they are frequently employed in treatment and preparation of the synthetic implant surface. Various plasmas, mainly thermal DC, AC, and RF plasma sprays, used for deposition of metals and metal-ceramic composites, are discussed.³⁴⁷ Separately, the low-pressure inductively or capacitively coupled systems for gentler surface modification, deposition of TiO₂ or SiO₂ films, and plasma-enhanced chemical vapor deposition are addressed in recent literature.³⁴⁸ Finally, novel atmospheric-pressure systems proposed or already used for synthetic joint material processing with specific examples of nanosecond-pulsed uniform dielectric barrier discharge system, and reverse-vortex gliding arc plasmatron are discussed.

C. Plasma Treatment of Injectable Bone Cements

With the novel developments in multimaterial bone cements for joining and anchoring prostheses there is a rising issue of material compatibility, sterility issues, cross-linking and curing of the cement, and others. There is an apparent focus on the medical aspects associated with the use of injectable bone cements in a hospital setting and the production processes for these cements. While there are many bone cement types, uses, and manufacturing practices, many are focused on plasma processing.³⁴⁹ Low-pressure inductively coupled plasma systems for powder surface modification and sterilization are a good example, as well as the use of pulsed spark discharge for ultraviolet radiation-assisted hardening of the injectable cement, and other plasma applications.

D. Plasma Deposition of Antibiotics and Other Antimicrobials on Orthopedic Implants

Medical specifics, origins, frequency, and complications associated with bacterial infections of implants along with methods currently employed by the medical professionals to both diagnose and treat such ailments are now being addressed by plasma treatments. Since cells prefer not to attach to the inanimate implant surface, bacteria find it attractive for colonization; thus, rendering implant surface permanently antimicrobial presents an excellent solution to this problem, potentially.³⁵⁰ Discussed are the different approaches taken to achieving this with plasma. For example, direct deposition of amine groups on the surface of polyether ether ketone (PEEK) of the implant in the N_2/H_2 reverse-vortex gliding arc plasmatron system was shown to promote antibiotic (vancomycin) attachment to the amines, subsequently preventing bacterial attachment to PEEK surface. Discussed are the specifics of this plasma treatment process and other similar processes.³⁵¹

E. Plasma-assisted Bone and Cartilage Regeneration

Discussed are the medical, biological, and biochemical specifics of key process of bone fracture repair: regeneration of bone and cartilage tissue. The current state of knowledge of the biological mechanisms, both intercellular and systemic, is discussed along with the current approaches taken by the medical professionals to improve and/or accelerate this process. The current accent is on the use of microsecond- and nanosecond-pulsed floating electrode–dielectric barrier discharge and radio-frequency argon plasma jet results obtained *in vitro* and *in vivo* in animal trials where both plasmas were shown to significantly improve the rate of regeneration³⁵²; the results reported *in vitro* with radio-frequency helium plasma jet and the proposed plasma-chemical mechanisms of action for these systems will also be discussed.

F. Plasma-stimulated Mesenchymal Stem Cell Differentiation and Specialization

One of the key challenges in bone and cartilage repair and regeneration is the differentiation and specialization of the mesenchymal stem cells (MSCs). Discussed are the biological and biochemical processes involved in initiation of differentiation processes as well as the cell's specialization into appropriate daughter cell.³⁵³ Discussed are the key findings on the plasma-cell interaction mechanisms and the reported increase in the MCS differentiation rate using microsecond-pulsed floating electrode–dielectric barrier discharge in *in vitro* cell studies and *in vivo* mouse model with injections of

MSC-loaded Matrigel®.

XII. OPHTHALMOLOGY

A. General Biochemical and Medical Aspects of Ophthalmology

The general medical aspects applicable to ophthalmology with specific focus on diseases of the eye rather than the overall field are addressed by plasma treatments. Discussed are the most relevant and frequent cases seen by clinicians and the medical methods currently utilized to address these issues. Special attention is given to the specifics of the plasma-ophthalmologic surgeries.

B. NonDestructive Plasma-assisted Sterilization of Cornea and Sclera

Discussed are the causes and the rate of surgical eye infections, those caused by or during the routine injections, and other types of eye infections, both bacterial and viral. Addressed are the current methods used to prevent or address these infections. Results are presented of the nondestructive sterilization of intact cornea and sclera by the floating electrode–dielectric barrier discharge as well as sterilization of the damaged corneal tissue both *ex vivo* and *in vivo* in animal trials with rabbit and pig eyes.³⁵⁴

C. Plasma Treatment of Ocular Melanoma and Other Diseases of the Eye

Discussed are the plasma treatments of various eye diseases with the focus on a surprisingly frequent case of uveal melanomas, their typical causes, and the methods and strategies employed by the medical professionals of addressing these ailments; also discussed are the mechanisms of disease healing proposed by the researchers.³⁵⁵ Floating electrode–dielectric barrier discharge has been demonstrated *ex vivo* to suppress the activity of melanoma cancer in a pig eye model. The results of these studies along with the proposed mechanisms are presented.

D. Plasma Treatment of Herpes Simplex Virus (HSV) in Cornea and Other Viral Infections of the Eye

Discussed are the medical specifics and causes of herpes simplex virus in corneal tissue as well as current medical methodologies to control this ailment. The results of *in vitro* studies of floating electrode–dielectric barrier discharge inactivation of HSV inside of corneal cells without damage to these cells³⁵⁶ as well as similar results reported with a radio-frequency helium jet plasma³⁵⁷ and are now appearing in reports from multiple research groups.

XIII. GASTROINTESTINAL AND OTHER INFLAMMATORY DISEASES

A. General Biochemical and Medical Aspects of Gastrointestinal and Other Internal Inflammatory Diseases

There is a focus on the general medical aspects of gastrointestinal and other internal inflammatory diseases. With special attention given to the challenges associated with and arising from the fact that these diseases are *internal*, occur in a high-moisture environment of the gastrointestinal tract, and thrive in a very different gas atmosphere. Discussed are the origins and causes of these ailments as well as the current medical procedures used to address them.

B. Specifics of Plasma Devices for Treatment of *Internal* Gastrointestinal Diseases

There are specific issues associated with the nature of generating plasma in the catheter-supported internal setting. The questions of generating plasma discharge in high-humidity non-air environment of the gastrointestinal tract are addressed by, for example, the argon plasma coagulation (APC™ and APC 2™) and Bovie® Electrosurgical Pencil and they have solved the problems of feeding high-voltage electrodes, gas supply, and light source through a tight space of a catheter line.

C. Anti-inflammatory Treatment by Thermal and Other Nitric Oxide (NO)-producing Plasmas

Nitric oxide (NO) effects are quite important in addressing and controlling inflammatory diseases.³⁵⁸ There are specifics of the anti-inflammatory effects of NO gas in gastrointestinal diseases.³⁵⁹ Discussed are two specific plasmas that are designed to generate high concentration of NO: Plazon® system³⁶⁰ and pin-to-hole spark discharge (PHsD).⁵⁰ The *in vitro* results reposted for both systems, *in vivo* animal trial data collected on anti-inflammatory gastrointestinal treatments, and the extensive human clinical data available for the Plazon® system are presented.³⁶¹

D. Plasma Treatment of Crohn's Disease and Ulcerative Colitis

Ulcerative colitis and Crohn's disease, reported causes, and common medical proce-

dures used to address these are presented.³⁶² The results reported for the pin-to-hole spark discharge treatment in an *in vivo* animal trial with mice where gastrointestinal inflammation, similar to ulcerative colitis, was induced by feeding the animals with dextran sulfate-spiked water are promising.³⁶³ The reports show significant decrease in the disease activity index.

XIV. FIRST STEPS IN PULMONOLOGY, OTORHINOLARYNGOLOGY, GYNECOLOGY, DIABETES, ALZHEIMER'S DISEASE, AND NEUROLOGICAL DISORDERS

A. General Biochemical and Medical Aspects of Pulmonology, Otorhinolaryngology, Gynecology, Diabetes, and Cognitive Disorders

There are multiple neurological diseases where first successes have been achieved with plasma either *in vitro* entirely or with some initial animal data. Discussed are the general medical aspects of pulmonology, otorhinolaryngology, gynecology, diabetes, and various cognitive disorders. The discussion is split into a part related to each specific disease or a group of diseases such as diabetes. Given the current findings in plasma medicine field, discussed are the systemic problems caused by or resulting from these diseases; these will subsequently be focused on on for each individual ailment.

B. Plasma Treatment in Pulmonology

The field of pulmonology studies the physiology and function of human respiratory tract and the frequent medical problems and diseases occurring in this part of the body. One important example includes the current large-scale clinical trial involving inhaled nitric oxide (NO) for treatment of pneumonia in children.³⁶⁴ Plasma-medical devices such as Plazon[®], pin-to-hole spark discharge (PHsD), and other thermal plasmas are well known for controllable production of NO gas (combined with other reactive species in the case of PHsD).⁵⁰ Plasma-generated NO can act the same as NO coming from a gas bottle; they are, after all, the same molecule, and for this reason plasma-produced NO may become an interesting alternative and will be discussed. Helium, neon, and xenon radio-frequency plasma jets have been shown to launch self-propagating ionization waves ("bullets") through dielectric tubes and recently radio-frequency helium jet plasma was shown to be able to launch these waves through natural holes in the tissue.³⁶⁵ This interesting phenomenon may be used in treatment of, for example, lung tissues.

C. Plasma Treatment in Otorhinolaryngology

Similarly to the previous discussion, otorhinolaryngology, the study of ear, nose, and throat conditions (simply ENT), has many diseases associated with the field but the work done in plasma in this direction is, for the moment, limited. Discussed is the specific example of using focused floating electrode–dielectric barrier discharge driven by microsecond pulses for vocal cord surgery.³⁶⁶ Another example includes the use of microwave micro-plasma jet in helium for small and targeted tongue and throat surgeries primarily for coagulation of capillary bleeding. Discussed are these and other ENT plasma treatment examples.

D. Plasma Treatment in Gynecology

While the data in plasma-medical applications in gynecology is limited overall, there are studies of the use of floating electrode–dielectric barrier discharge, radio-frequency jet plasma in argon, and nitric oxide-generating thermal plasma sources. These studies are focused on treatment of ovarian cancer.^{367,368} In the medical aspect of gynecological treatments, typical problems associated with this field and standard medical treatments address these ailments. Limited *in vitro* data are available for plasma treatments in gynecology and is discussed in literature.

E. Plasma Treatment in Diabetes

Diabetes is a group of metabolic diseases affecting many areas and organs of the body presenting different manifestations in different patients. The generalized overview of diabetes and typical medical aspects associated with these ailments is frequently addressed in recent plasma-medical publications and talks. Discussed are the typical causes of diabetes, both genetic and behavioral, and medical treatments employed to address these.³⁶⁹ The *ex vivo* results of blood viscosity control in diabetic patients using nanosecond-pulsed spark discharge directly in blood plasma to control blood viscosity as well as similar results obtained using microsecond-pulsed dielectric barrier discharge is presented.³⁷⁰ Also discussed are the specifics related to wound healing rates in diabetic mice compared to healthy mice obtained with floating electrode–dielectric barrier discharge and Plazon® systems.

F. Plasma Treatment in Alzheimer's Disease

There are some medical specifics related to Alzheimer's disease (AD) and the common tools medical professionals have, if not to help, to slow down and ease the progression of the disease. Attention is paid to the current state of understanding of biological and

biochemical pathways of AD's progression and link them to the recent *in vitro* results obtained by stimulation of neuronal cells with radio-frequency jet plasma in helium and similar data obtained using the floating electrode–dielectric barrier discharge.^{371, 372}

G. Plasma Treatment in Neurological Disorders

Key specifics are discussed in plasma treatments in neurological disorders as compared to the current medical professional's methods and tools to address them. Specifically, the focus is on the mechanisms of neuronal cell repair and regeneration, growth, and proliferation and to present the *in vitro* data obtained with the radio-frequency jet plasma in argon used to promote significantly improved rate of neuron growth. Also discussed are the examples of Plazon[®]-generated nitric oxide effect on nerve tissue repair rate in human patients.

XV. PLASMA BIOENGINEERING IN DRUG DELIVERY, GENE TRANSFECTION, AGRICULTURE, AND MEDICAL IMAGING

A. Plasma-assisted Gene Transfection

Gene transfection in human cells typically is associated with the opening of temporary pores in the cell membrane, large enough for a nucleic acid to be introduced into the cell. There is a vast array of applications of this treatment modality and it is discussed in current literature. The results obtained with many different types of plasmas on formation of temporary pores in cells are reported. The *in vitro* and *in vivo* animal data obtained with radio-frequency plasma jet in helium and argon, and *in vitro* data obtained with floating electrode–dielectric barrier discharge are indicative of possible future success in gene transfection by plasma treatment.^{373,374} There are some proposed mechanisms of temporary pore formation and, more importantly, the mechanisms of their closure since that prevents cells from dying.

B. Plasma-assisted Single Cell Drug Delivery

Similar to gene transfection, drug delivery into the cell involves, in most cases, formation of temporary pores to deliver an organic molecule into the cell. Discussed are the specifics of working with one cell at a time and the medical purposes of undertaking such as endeavors ranging from research to extremely targeted medicine.³⁷⁵ Discussed are the results obtained with nanosecond- and picosecond-pulsed corona using a sub-micron- and nanometer-sized needle or a carbon nanotube placed near or inside of the cell. The plasma generated in this way appears to be nonthermal and does not create gas bubbles. Presented are the proposed mechanisms of the observed pore formation and of

the subsequent drug penetration into the cell.

C. Plasma-assisted Intradermal Drug Delivery

There are some important medical specifics, needs, and options currently available for intradermal drug delivery. These issues are relevant both in disease treatment and in cosmetic applications. Discussed is the formation of temporary large pores, or “cracks,” in the outer dead skin layers of stratum corneum by *ex vivo* treatment with microsecond- and nanosecond-pulsed floating electrode–dielectric barrier discharge followed by penetration into tissue of organic molecules as large as a few tens of thousands of daltons. The mechanisms of formation of these pores and of their closure are important to understand to further develop these treatments, and some mechanisms are addressed. The results of permanently “drilling” through the dead skin layers using higher-power pulsed floating electrode–dielectric barrier discharge with a “structured” electrode where plasma filaments of $\sim 100\ \mu\text{m}$ diameter can carry significant temperature was previously shown. Essentially this treatment is similar to fractional laser resurfacing treatment (also known as photorejuvenation) where a laser is used to make many small holes in the tissue.

D. Veterinary Applications of Plasma

Animal medicine is similar to human medicine. Discussed are some key differences between the two fields focusing on the differences in devices and pharmaceutical agents used as well as the typical medical practice differences. Most, if not all, human clinical data were obtained, first, on animals and thus the amount of data available on animals is vastly greater than that for humans. Discussed are the current findings for different diseases and conditions where animal data are available. Additionally, some of the treatment methods in veterinary medicine are quite different from human medicine and the differences are addressed; for example, application of the floating electrode–dielectric barrier discharge to skin through the thick hair of a rat.

E. Food Safety and Other Plasma Applications in Fresh Produce Treatment and Packaging

While not directly related to medicine, food safety issues and fresh produce treatment are closely related to it. The current issues related to food safety are discussed along with the applications of plasma produce management and handling, storage, etc. Specific examples include dielectric barrier discharge, reverse-vortex gliding arc discharge, pulsed spark discharge, and corona plasma for food sanitization.^{376–378} Special attention is given to the production of plasma-activated liquids and their anti-pathogen properties

as it applies to food safety.³⁷⁹

F. Plasma-stimulated Seed Germination and Early Plant Development

Seed germination and early plant development was shown to be significantly improved by plasma treatment both in direct and indirect modes. Dielectric barrier discharge, pulsed corona, DC corona, and radio-frequency jet plasma in helium and argon were all shown to increase the rate of plant seed germination. Discussed are the results of these studies and the proposed mechanisms by which plasma treatment “activates” the seeds. Another interesting way of plasma application is by indirect treatment using water as the delivery mechanism. All of the above-mentioned plasmas have been used to treat water samples, increasing the concentration of nitrates and lowering pH of the liquid and leading to higher rate of seed germination and improved early plant development as well as significant reduction in pathogen-related disease.

G. Plasma-assisted Plant Growth and Maturation

Following the seed germination discussed above, plasmas were shown to aid in following plant growth and maturation to produce fruit. For these applications, however, mostly plasma-treated water is utilized since treating maturing plant with direct plasma becomes physically impossible due to size and the three-dimensional complexity of the plant. It becomes impractical to use discharges based on noble gases so most of the data reported is produced using dielectric barrier discharge, pulsed corona, DC corona, or reverse-vortex gliding arc system. Discussed are the results showing significant improvement in plant growth rate and maturation as well as the proposed mechanisms by which plasmas are able to induce this response.

H. Specifics of Plasma Devices for Farm-scale Food and Agricultural Applications

Once outside of a lab-scale environment, many types of plasma do not scale well to real environment of a farm. There are some specifics of the farm-scale food production and the many issues associated with conveyor-like systems implemented on the farms today, especially niche farming like hydroponic farms and the like. The two plasma systems that are reported to scale to significant production rates of plasma-treated liquid are pulsed corona discharge (corona) and reverse-vortex gliding arc plasmatron (glidarc). While the two systems are drastically different in their plasma-physical nature (corona is nonthermal while glidarc is thermal) the results differ only slightly. The key important differences between the two systems are discussed, the results they yield in farm-scale food production, and the different biological and biochemical pathways of action of

these plasmas.

I. Plasma in Medical Diagnostics

Plasmas ionize the gas and produce light that differs significantly based on the chemical composition of both the gas and the electrodes used to generate plasma. Nano-second-pulsed floating electrode–dielectric barrier discharge and radiofrequency jet plasma in argon were used to treat and simultaneously diagnose the surface. Using the Swept-Wavelength Optical resonance-Raman Device (SWOrRD) in combination with plasma treatment it is possible to detect the level of bacterial contamination of skin and see when the plasma treatment had removed all of the pathogens remaining on the surface. This treatment/diagnosis system may become an interesting and powerful tool for a combined diagnostic and measurement device. Additionally, during the single-cell drug delivery by plasma, the light generated by plasma may be collected and analyzed showing changes in ion concentrations and other medically-relevant data. This is, thus far, a largely unexplored but rather interesting field.

J. Single Cell Micro- and Nano-Plasma Imaging and Other Applications in Medical Imaging

Similarly to single-cell diagnostics, plasma generated inside of or nearby a single cell may be used for imaging of this cell. The nanosecond- and picosecond-pulsed corona discharge generated on micrometer- or nanometer-curvature needle placed inside of the cell or nearby it are discussed and the imaging applications of this treatment are reported on.²²¹

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