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Atmospheric pressure plasmas have shown considerable, although still preliminary, clinical success to date for a variety of biomedical applications. For example, atmospheric pressure plasma jets (APPJs) have widespread use in plasma medicine. Key challenges in advanced control of APPJs arise from: (i) the multivariable, nonlinear nature of system dynamics, (ii) the need to constrain the system operation within an operating region that ensures safe plasma treatment, and (iii) the cumulative, non-decreasing nature of dose metrics. However, the mechanisms through which plasma biomedical devices function are still a matter of considerable uncertainty. One consequence of this uncertainty is difficulty in defining and quantifying dose. In addition to immediate and local effects such as fluxes of heat, current, charge, photons and chemically active species, plasma devices generally induce a set of coupled biological responses that have a range of time and length scales. In this talk I will review the likely mechanisms based on current understanding of plasma biomedical devices. In addition, although not well known, historical high frequency current devices, used over 100 years ago, have similar characteristics to some modern plasma medical devices. These early pioneers had a surprisingly modern view of some aspects of the therapeutic mechanisms of high frequency currents that clearly overlap with recent results. The perspective of this community was that the most important physiological effects are associated with the high frequency currents rather than the gas phase plasma. Some early work, such as the analgesic effects of dielectric barrier air plasma on tissue, is not well known today. The range of afflictions that early practitioners treated successfully is remarkable. This body of work, in some cases almost 130 years old, might have important lessons for current investigations into plasma medicine. Finally, I will briefly outline the advantages of exploiting modern advanced control theories for future plasma biomedical devices and applications.