ON THE POSSIBILITY OF NONTHERMAL BIOLOGICAL EFFECTS OF PULSED ELECTROMAGNETIC RADIATION

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ABSTRACT Two mechanisms for the interaction of alternating electrical fields with biological tissue are the development of heat, via i^2R losses, and field-induced force effects, via differences in passive electrical properties. It has been shown that for continuous wave (CW) fields in media of physiologic electrical conductivity, the development of heat ($>1°C$) always precedes the possible appearance of a field-induced force effect. Using pearl-chain formation as a model effect and experimentally demonstrating that its time constant varies inversely as the square of the electrical field strength, we show that a pulsed field has no greater ability than a CW field of equal rms field strength to produce a field-induced force effect. Thus, the statement above for CW fields can be broadened to include pulsed fields of any description. By relating incident power density to electric field strength in tissue, we show that the American National Standards Institute's radiation protection guide obviates the production of genetic effects in man, if they exist, via field-induced force effects.

INTRODUCTION

The primary interaction of alternating electrical fields with biological materials can be classified conveniently as thermal or nonthermal. The thermal interaction is well understood presently, even though the biological manifestations are often unpredicted, and with poor experimental technique, unexpected. In contrast, the nonthermal interaction is still controversial, although, to date, there is only one mechanism of demonstrated validity — field-induced force effects. A field-induced force effect is any movement or rearrangement, on a size scale from molecular to macroscopic, which is the direct result of the presence of an AC or DC electric and/or magnetic field. It has been shown that field-induced force effects cannot occur in a CW field and in media of physiological electrical conductivity in the absence of gross heating (1, 2). Therefore, in the analysis of possible biological effects, the interesting question is whether a pulsed field of any description can be more effective than a CW field of the same rms field strength in producing a field-induced force effect.

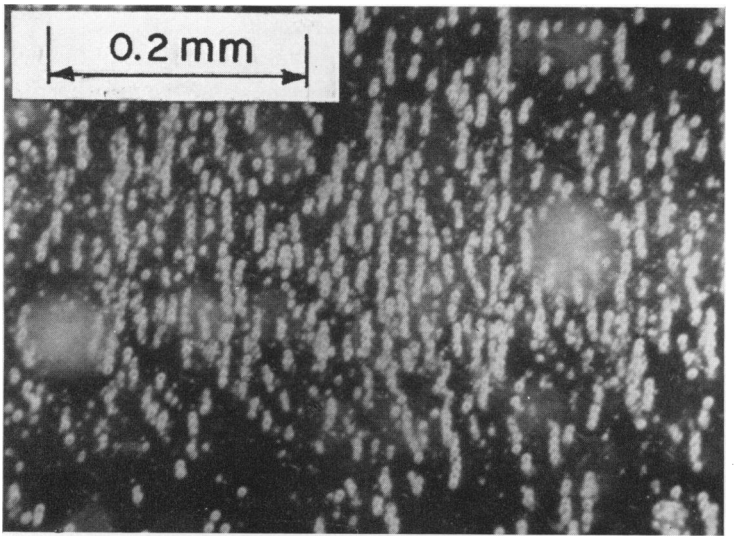

FIGURE 1 Optical micrograph of pearl-chain formation with red blood cells in physiologic saline. Field strength is 50 v/cm (rms).

We here show that the question has a negative answer, and that consequently, in media of physiological electrical conductivity, field-induced force effects cannot account for a presently unknown nonthermal effect.

As a model of a field-induced force effect, we use here the phenomenon known as pearl-chain formation. Pearl-chain formation is the alignment into chainlike structures of suspended, electrically polarizable, microscopic particles under the influence of a DC or AC electrical field. The name is derived from the appearance, which, for micron-sized particles in a sufficiently strong field, closely resembles the formation of a trembling chain of pearls. The forces which cause this linear assemblage are most easily visualized as forces between the dipoles induced on each particle by the impressed electrical field. Competing with these electrical ordering forces are the Brownian randomizing forces, so that pearl chains formed under marginal conditions tremble as if they were breaking up momentarily. A typical pearl chain is shown in Fig. 1.

Current interest in pearl-chain formation is related to its candidacy as a significant, nonthermal, biological effect of microwave radiation. An assessment of this potential biological hazard has been made for CW fields and for usual pulsed fields, i.e., those arising from usual radar systems (1, 2, 3). It was found that for continuous, whole-body irradiation, pearl-chain formation of biological particles, such as blood cells or subcellular components, could not occur in human tissue under CW or usual pulsed-field conditions if the person was observing, even loosely, the safety precautions established to prevent thermal hazards.[1] This conclusion unfortunately

[1] For periods of 0.1 hr or more: 10 mw/cm^2; during any 0.1 hr period: 1 mw-hr/cm^2. From the American National Standards Institute, Inc., New York. USASI-C95.1-1966.

does not exclude the possibility that for an unusual pulsed system, the field might be more effective in producing pearl chains than its rms value, i.e., its thermal potential, would indicate.

To evaluate the likelihood of pearl-chain formation under any pulsed-field condition, one needs to know (*a*) the threshold CW field strength for pearl-chain formation using the particles under investigation, (*b*) the time constant characterizing the rate of formation of a pearl chain under the high field strength conditions prevailing during the on time of the pulse, and (*c*) the time constant characterizing the rate of dissolution of a pearl chain under zero field strength conditions, i.e., between pulses. Since (*a*) is known (1, 2), what is needed is a knowledge of the relationship between time constant and field strength.

The following symbols (and units) will be used:

E = rms value of electric field strength (v/cm).

E_c = rms value of that critical electric field strength for which pearl-chain formation is just apparent to the microscope-aided eye (v/cm).

m = a measure of the enlistment of available particles in pearl chains ($m = 0$ represents no pearl-chain formation, and $m = 1$ represents that state in which all available particles of the size being considered are in chains) (dimensionless).

m_c = that value of m which corresponds to E_c in the steady state (dimensionless).

τ = time constant for pearl-chain formation (defined below) (sec).

τ_c = that value of τ which corresponds to E_c (sec).

d = diameter of a particle, assumed to be a sphere (μm).

It has been shown by Saito (4) that a good description for the predominant mode of behavior of $m(t)$ is exponential. Accordingly, if the suspension has some measure m_0 at time $t = 0$, and, at this time an electric field of value E is applied, then

$$m = \begin{cases} m_0 e^{-t/\tau}, & E < E_c \qquad (1\,a) \\ 1 - (1 - m_0)e^{-t/\tau}, & E > E_c, \qquad (1\,b) \end{cases}$$

where $\tau = \tau(E)$ is called the time constant of the pearl-chain formation. In the special case where a suspension of particles is allowed to equilibrate with no field applied, and then, at $t = 0$, an electric field E is applied, where $E > E_c$, the rise of m from zero is described by:

$$m = 1 - e^{-t/\tau}. \qquad (2)$$

It should be emphasized here that we make no distinction between the meanings of τ as defined by equation 1 *a* and τ as defined by equations 1 *b* or 2. In both cases, the time constant is used as a theoretical measure of the time required for the suspension to "complete" its response to an abrupt change from one constant E to another. There is an inherent distinction, however, between the theoretical τ of equation 2 and the experimenter's estimate of the rate constant for an observed relaxation process. Therefore, although the following descriptions of experimental determinations of the

time constant make no distinction between a theoretical τ and an experimental τ, these values differ by an unknown, and probably systematic, factor which is very likely to be between 0.5 and 2.0.

EXPERIMENTS

The suspension used in these measurements was an emulsion of silicone globules in water (SM-70 silicone emulsion [General Electric Co., Silicone Products Department, Waterford, N. Y.]) with an electrical conductivity (in the diluted state used) of about $10^{-4}\ \Omega^{-1}\ cm^{-1}$ and

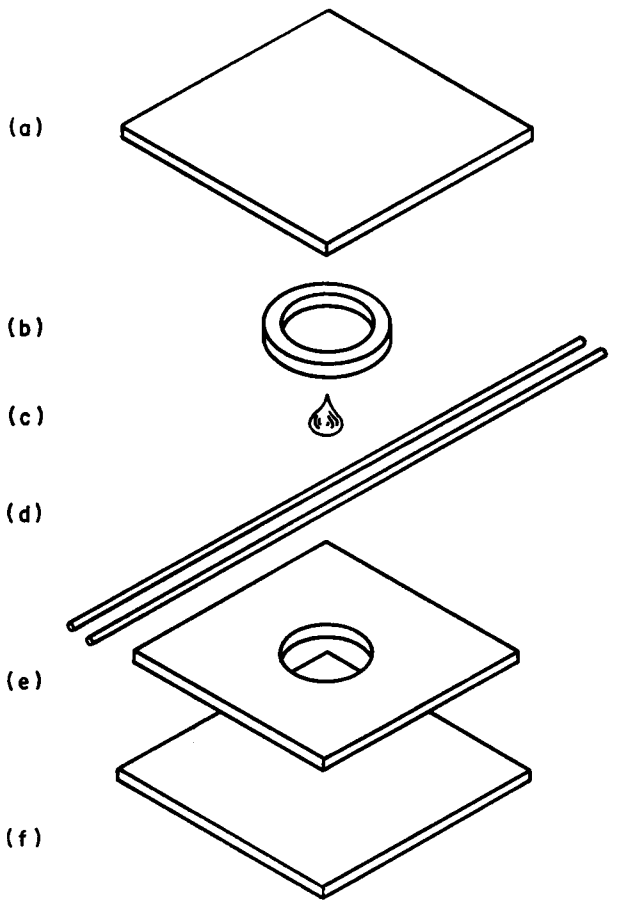

FIGURE 2 Exploded view of the cell, not to scale. (*a*) Top cover glass, No. 0, 100 μm thick, 18 mm square; (*b*) annulus of Parafilm; (*c*) sample fluid, 4 mm^3 required; (*d*) two parallel Pt wires, 65 μm diameter; (*e*) sheet of Parafilm, 16 mm square, with a 7 mm diameter hole for sample; (*f*) bottom cover glass, No. 0, 100 μm thick, 18 mm square. Assembly is done in a jig in the following order. Onto (*f*) is pressed (*e*), then (*d*); (*c*) is introduced from a dropping pipette; (*b*) is pressed onto (*a*), then (*a*) + (*b*) is laid onto (*c*) + (*d*) + (*e*) + (*f*). The sandwich is then "grilled" shut by laying onto the assembly a metal block at 100°C for a few seconds. A hole in the block is used to prevent heating of the sample chamber.

a spread of particle size from about 1.8 to 2.6 μm. The average particle size was about 2.3 μm and conscious effort was made to ignore the effects observed in the few particles of larger size. This emulsion was used because it is adequately stable in the diluted state in which the individual globules can be seen and the thresholds for pearl-chain formation compare with those found in biological cell suspensions (1, 2).

The cell (1), shown in Fig. 2, is a sandwich of two 18 mm square microscope cover glasses between which is a layer of Parafilm (American Can Company, Marathon Division, Menasha, Wis.) containing both sample and electrodes in a hollowed out chamber. The electrodes, two parallel platinum wires, each 60 μm in diameter, are sufficiently close together so that 1 v applied between them provides about 20 v/cm in the sample. With the above mentioned sili-

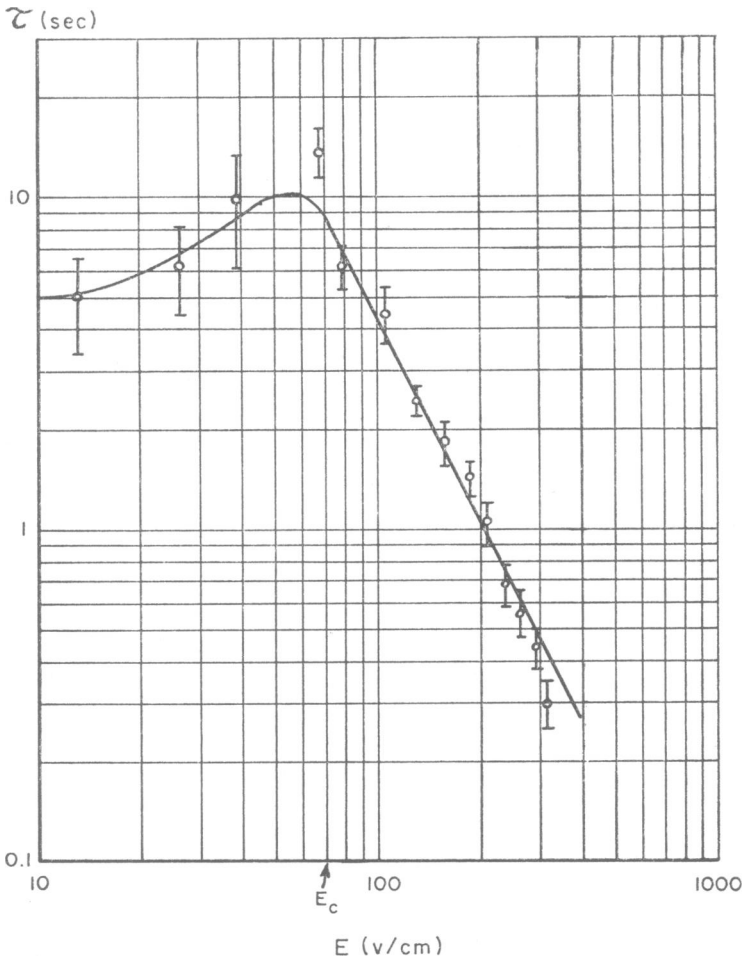

FIGURE 3 Experimental determination of the time constant for pearl-chain formation vs. the applied rms electric field strength at 100 kHz. For $E > E_c$, the data shows that $\tau \propto E^{-4}$. For $E \ll E_c$, the data shows that $\tau \approx$ constant. For $E \approx E_c$, the time constant elevation is apparently due to the tendency of the weak field to delay pearl-chain dissolution. Bars indicate ± 1 SD of the data.

cone emulsion as the sample material, and employing frequencies not less than about 10 kHz, it was found from the frequency independence of the filled cell's apparent resistance that electrode polarization could be neglected (5). Field uniformity is fairly good, E varying not more than about $\pm 3\%$ over the microscopic field of view, as determined by field plotting in a macroscopic model of a cross-section through the cell (1). The cell is refabricated with all new materials for each new sample, an operation which takes about 15 min. The picture (Fig. 1) was taken using this cell.

The voltage source used in these measurements was operated at 100 kHz, a choice dictated by convenience and the knowledge that the time constant, if measured in terms of E/E_c, must be frequency independent (cf. equations 6 *a* and 6 *b*). A transformer was used at the output when voltages as high as 40 v were necessary. An electric stop clock was wired to the oscillator so that when the voltage was applied to the cell, the clock started, and vice versa.

To measure the time constant for $E > E_c$, the voltage and clock were started out of sight and hearing from the person at the microscope, who had the job of stopping the clock when pearl chains first became apparent. For each value of E, this measurement was repeated 20–30 times and the results were averaged. These averages appear in Fig. 3 as the 11 right-most data points.

When $E < E_c$, a new method for measuring the time consant had to be devised, because of the absence of an easily observable end point. Its description follows (refer to Fig. 4).

Let E_d be a value of electric field, where $E_d > E_c$, for which the time constant, τ_d, has been determined. Then, the procedure was the following.

(*a*) Let the system equilibrate at zero electric field strength. This step insures that the system is in a state for which $m = 0$.

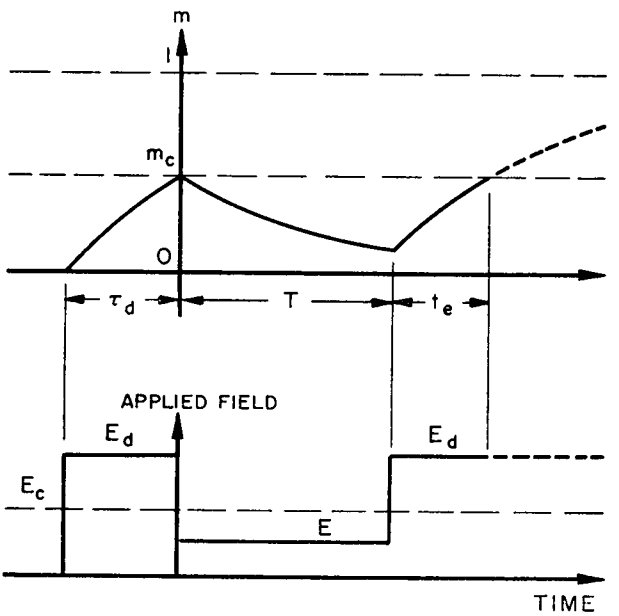

FIGURE 4 The enlistment, m, of available particles into pearl-chain formation vs. time. The graph further describes a technique described in the text for making experimental determinations of the time constant for pearl-chain dissolution when weak fields are applied.

(*b*) Apply the field E_d for a period of τ_d sec, thereby putting the system into a state for which $m = m_c$.

(*c*) Apply the field in question, E, for T sec, where the value of T is arbitrary and will be discussed below. This field application is the actual beginning of the experimental procedure, and so, from equation 1 *a*, for $t = 0, m_0 = m_c$. After T sec, the system is in a state m_1 given by

$$m_1 = m_c e^{-T/\tau}, \tag{3}$$

where τ, to be determined, is the time constant at electric field strength E.

(*d*) Apply the field E_d again until $m = m_c$ and note the time, t_e, needed for this reordering process to occur. Equation 1 *b* applies, where $m_0 = m_1$, and after a time t_e,

$$m_c = 1 - (1 - m_1) \exp(-t_e/\tau_d). \tag{4}$$

(*e*) Calculate the time constant, τ, by taking equations 3 and 4 to form a set of two simultaneous equations in the two unknowns m_1 and τ ($m_c = 1 - e^{-1}$, from equation 2). These equations can be solved for τ:

$$\tau = \frac{T}{\ln \{[e - 1]/[e - \exp(t_e/\tau_d)]\}}. \tag{5}$$

From Fig. 4, guidelines for the choice of T can be found. If T is very small, the system will be just barely below threshold, making t_e too small to measure. If T is very large, the system will have effectively reached a randomized state, and the time t_e will be of no experimental value. Therefore, T should approximate τ, which is to be determined. Since τ was not known, a series of values for T were used, and those which were most appropriate for the calculation were chosen. In the experimental measurements, for each value of electric field, four values of the time, T, were found suitable: $T = 1$, 2, 3, and 4 sec. For each of these four values of T, six trials were carried out. The time constant, τ, was computed for each trial using equation 5, giving 24 values of τ for each electric field strength. These values were then averaged. The results are shown in Fig. 3 as the three left-most data points.

DISCUSSION AND CONCLUSIONS

Saito and Schwan had formulated scaling laws for particle size and field strength as they affect the time constant for pearl-chain formation (3):

$$\tau \propto d^3, E \ll E_c \tag{6 a}$$

$$\tau \propto d^3 E^{-2}, E > E_c. \tag{6 b}$$

Clearly, the data of Fig. 3 support the field independence of τ in equation 6 *a* and the E^{-2} dependence of τ in equation 6 *b*. The data also show that $\tau \mid_{E \approx E_c} \approx 2\tau \mid_{E=0}$. The increase in τ for $E \approx E_c$ is a result of the protracted competition between the electrical ordering forces and the Brownian randomizing forces. This competition is resolved more quickly when the antagonists are less equally matched.

These relationships support the following conclusions.

(*a*) We consider a pulsed field whose average field strength squared, E^2_{rms}, is the

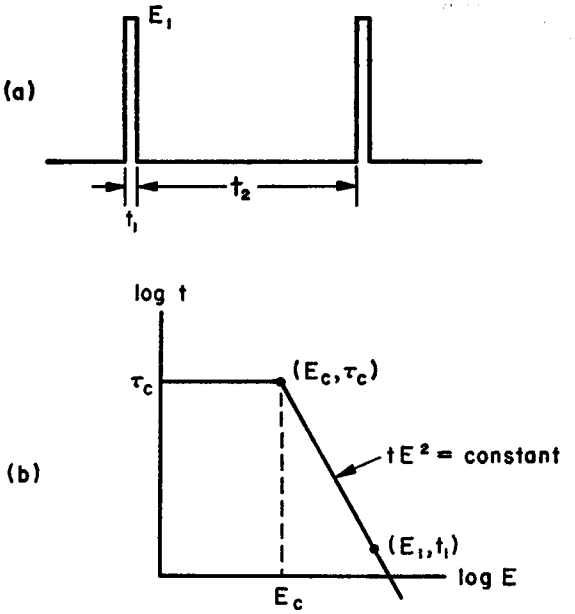

FIGURE 5 (*a*) Diagram of electric field strength vs. time for a pulsed field whose t_1 and t_2 have been chosen as the minimum and maximum values, respectively, consistent with the resultant formation of persistent pearl-chains. The value of t_1 is chosen in view of the prior choice of the peak value E_1. (*b*) Simplified graphical presentation of equations 6 *a* and 6 *b*, or Fig. 3, showing the relationships used in formulating equation 7 in the text. The hump in Fig. 3 has been neglected in view of the already rough argument surrounding equations 7 and 8.

minimum possible value for forming persistent pearl chains (chains which do not break up between pulses). Such a pulsed field (Fig. 5 *a*) is characterized by (i) some field strength E_1, where $E_1 > E_c$, (ii) pulse durations of time t_1, where t_1 is just long enough (in view of the prior choice of E_1) for pearl-chain formation to occur, and (iii) interpulse periods of time t_2, where t_2 is just long enough for breakup to begin. Clearly, we thus minimize the possibility that a significant field-induced heating will accompany the field-induced force effect. Then referring to Fig. 5 *b*, which is a schematized version of Fig. 3 and which, for simplicity, ignores the fact that $\tau_c \approx 2t_2$, we see that

$$t_1 E_1^2 = \tau_c E_c^2 \approx t_2 E_c^2 . \tag{7}$$

Then, assuming that $t_2 \gg t_1$,

$$E_{\text{rms}} = \left(\frac{t_1 E_1^2}{t_1 + t_2}\right)^{1/2} = \left(\frac{t_2 E_c^2}{t_1 + t_2}\right)^{1/2} \approx E_c . \tag{8}$$

Thus, the rms field strength of the minimum strength, pulsed field which can pro-

duce persistent pearl chains is equal to the rms field strength of a minimum strength, CW field which can produce persistent pearl chains. Alternatively, we conclude that for a given average power, a pulsed field offers no greater likelihood over a CW field for the formation of pearl chains.

(*b*) In the presence of a field $E > E_c$, any particle rearrangement to a higher state of order requires a certain amount of field-supplied energy proportional to t_1E^2. It should not matter if this work is done over a long period t_1 using a small E^2, or vice versa, provided that the end effect is the same (alignment, orientation, etc.). Furthermore, for small fields, where $E < E_c$, the time necessary for the return of particles to the random state should not depend much on E. Therefore, the conclusion stated under conclusion *a* above should apply to all field-induced force effects, including the dielectrophoretic and orientation phenomena previously analyzed by us (6, 7).

(*c*) If t_2 is a sufficient time for pearl-chain dissolution to occur, one can assess the probability of pearl-chain formation solely in terms of the effects from a single pulse. The fact that the heat development from a single pulse is proportional to t_1E^2 can be used to make the following simple argument: a "biologically safe" upper limit for t_1E^2 is about 1°C/0.24 σ, where σ is the electrical conductivity of the tissue being irradiated (the 0.24 changes joules to calories). On the other hand, the lower limit for t_1E^2 which will produce pearl chains is $\tau_c E_c^2$ (from equation 7). Thus a single pulse will produce pearl chains without the production of a significant temperature rise if the corresponding product of its parameters lies within these limits. If the lower limit for the product t_1E^2 exceeds the upper limit, pearl chains cannot be produced by this pulse in the absence of a simultaneous, biologically significant, temperature rise.

(*d*) The pearl-chain behavior of this experimental system, or any other system for which the parameters below are known, can be predicted in any given pulsed-field case by the following considerations.

(i) In the steady state, for a given value of CW field strength, all mobile particles above a certain size will form pearl chains. Therefore, transient considerations aside, there is a minimum size of particle which can respond to the given (peak) value of E. In general, that value is given by (2)

$$d_{\min} = 2.85 \left| \frac{\epsilon_1 + 2\epsilon_2}{\epsilon_1 - \epsilon_2} \right|^{2/3} \left(\frac{kT}{\epsilon'_2} \right)^{1/3} E^{-2/3}. \tag{9}$$

Here ϵ_1 and ϵ_2 are the *complex* dielectric constants of the particle and medium, respectively, k is Boltzmann's constant, and T is absolute temperature. (In general, $\epsilon = \epsilon' - i\epsilon''$, where ϵ' is the real dielectric constant and ϵ'' is the electrical conductivity per angular frequency.) In equation 9, a consistent set of units must be used, such as mks. In all other equations, a mixed system of units is used, as described above. In the experimental system used here, equation 9 reduces to

$$d_{\min} = 38E^{-2/3}. \tag{10}$$

(ii) The constants in the scaling laws given by equations 6 *a* and 6 *b* can be evaluated for the experimental system used by using the numerical values from Fig. 3:

$$\tau = 0.62\, d^3,\ E \ll E_c \qquad (11\,a)$$

$$\tau = 5.0 \times 10^3\, d^3 E^{-2},\ E > E_c\,. \qquad (11\,b)$$

The given pulse width will allow particles of a maximum size, d_{max}, predicted by a rearrangement of equation 11 *b* to form pearl chains. If $d_{max} < d_{min}$, pearl-chain formation is impossible under the given conditions.

(iii) The given interval between pulses will allow particles of a minimum size predicted by a rearrangement of equation 11 *a* to persist in pearl chains, if they exist, between pulses.

(*e*) The radiation protection guide[1] sets a value of 10 mw/cm^2 for the maximum permissible, average, microwave power density continuously incident on a human. This figure corresponds to an rms electric field strength in tissue given by $E^2 = (10\,\text{mw/cm}^2)\,(Z)$, where $Z = 377\,\epsilon^{-0.5}$ is the wave impedance in tissue of complex dielectric constant ϵ. Typically, for frequencies between 100 MHz and 10,000 MHz, $|\epsilon| \approx 60$ and $E_{rms} = 0.7$ v/cm. For this electric field strength, equation 10 — which predicts a d_{min} that is equal to or smaller than that predicted by equation 9 — yields $d_{min} \approx 50\ \mu$m. That is, biological structures smaller than 50 μm cannot be made to respond without an undue heat hazard, no matter how the electrical energy is applied. Thus, field-induced force effects in a physiologic tissue environment cannot be the mechanism responsible for genetic effects (8, 9), if any, nor for other physiologic responses (10).

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