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Microwave-Induced Hyperthermia Dose Definition

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Abstract—*In vitro* thermal data on cytotoxicity are consistent with the simple picture of chemical reaction kinetics as governed by an activation energy. These kinetics are used to calculate, for any arbitrary heating profile used in clinical hyperthermia, the corresponding percentage of cells killed by such treatment in *in vitro* tissue cultures. The quantity calculated, which incorporates biological response to thermodynamic parameters, is suggested as a measure of hyperthermal dosage. Alternative dosage measures are discussed. Doses, defined by thermal cytokinetics, are derived for current clinical practice in whole-body and local hyperthermia. Both types of treatment, although superficially very different, are shown to employ comparable dose magnitudes, and these magnitudes are found to be in quantitative accord with the thermal cytotoxic basis for dosage measurement.

I. INTRODUCTION

WHEN ANTIBIOTICS were first introduced, physical and chemical assays of their potency were found to be poorly correlated with treatment efficacy. The

problem, of course, was that it was not until years afterward that it was discovered which of the closely related derivatives and isomers were effective. In order to quantitate dose for research and clinical trials, a system of "units" was adopted. The units of penicillin, for example, were related to the area of a petri dish that would be cleared of a trial organism after inoculation with a measured quantity of a given batch of "penicillin." The problems of assessing efficacy and toxicity of hyperthermia are similarly plagued by the lack of a definition of hyperthermal dosage. In the absence of a dose-response measurement procedure, hyperthermal dosage has been assigned by a variety of schemes.

One class of methods is based upon observed sequelae to hyperthermia. To this class belong such units as dose to produce a certain percentage decrease in liver function [1], dose to produce an arbitrary erythema score [2], [3], dose to produce various serum enzyme elevations [1], [4], etc. Although these methods beg the question of hyper-

Manuscript received July 14, 1977; revised March 16, 1978.

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thermal dosage, they do provide convenient milestones in specific treatment protocols. No comparison between treatment protocols giving rise to different sequelae is rendered possible, however, nor is it possible to gauge protocol improvement except for avoidance of the specific adverse reaction.

Another class of hyperthermal dosage schemes is based upon measurement of some combination of thermodynamic parameters. Such quantities have been used as total heat transferred or confined to the patient [5], duration of exposure above some baseline temperature [6], power level administered [7], highest temperature achieved [6], [8], lowest temperature achieved [9], etc. These methods are capable of very precise quantification but are of doubtful relevance as measures of biological response except under very restrictive conditions.

It would appear to be desirable to find an easily and precisely measurable thermodynamic parameter which could be associated with general tissue response to hyperthermia for use as a measure of hyperthermal dosage.

II. CELLULAR LETHALITY

Mammalian cells grown in *in vitro* tissue culture exhibit short-term kinetics with a characteristic temporal dependence of viability, or plating efficiency, upon ambient temperatures. The viable cell population decreases exponentially with increasing exposure time to a given elevated temperature [10]–[12]. Likewise, the rate of decline of viable cells varies with temperature in the same manner as a Boltzmann factor containing a thermal activation energy determinant of cell death [12]–[14]. As might be expected for an entropy increase accompanying an order-disorder transition, such as a change in tertiary molecular structure accompanying denaturation, this activation energy appears to be quite high, i.e., on the order of ten electron volts [14].

It is suggested that the simple short-term reaction kinetics of cell viability as a function of time and temperature be employed to quantitate hyperthermal dosage. In order to arrive at a dosage figure by this means, it is merely necessary to interpret the time and temperature measurements, already ordinarily monitored in clinical hyperthermia, in terms of the nonlinear reaction kinetics of tissue viability.

Assume that the surviving fraction of cells at time t are given by $\exp(-at)$ where a is a reaction rate constant related to temperature via $a = \alpha \exp(E/kT)$, where α is the temperature independent rate constant, E is an activation energy, k is the Boltzmann constant equal to 8.62×10^{-5} electron volts per degree, and T is the absolute temperature. Then, in a tissue caused to vary in temperature along the heating curve $T(t)$, the percent D of cells rendered nonviable by this hyperthermal treatment will be given by $D = 100 - 100 \exp(-\int a(t) dt)$ where the integration is carried out over the course of the treatment. For long times and/or high temperatures, the quantity D approaches the value 100, and for short times and/or low temperatures, the quantity D approaches the value 0. It is

proposed that this quantity D calculated from time, temperature, and somewhat arbitrary assumptions regarding cytotoxicity and chemical reaction kinetics, be employed as a unit of hyperthermal dosage. The quantity a derived from temperature, cytotoxicity data, and chemical reaction kinetics, has the dimensions of reciprocal time. It may be interpreted as a measure of cellular lethality rate associated with given temperature. With this interpretation, a may be taken as a measure of the intensity of a hyperthermal treatment at a given time.

The time integral of the cellular lethality rate a could, itself, be taken as a measure of hyperthermal dose. There is, of course, a simple logarithmic relationship between these alternative dose definitions, and so they are related by a simple lookup table. The D dose unit is based upon the somewhat more theoretically appealing idea that the overall fraction of cells killed over a certain period of time is multiplicatively, rather than additively, related to the fraction of cells killed in each of the subintervals of time making up the period. The disadvantage of a novel dose unit that cannot exceed 100 for a treatment, however, may well outweigh this small theoretical advantage. The hyperthermal dose administered in a given heating procedure may, of course, be expressed as an equivalent time duration of exposure to some constant temperature which would result in the same D value.

The hyperthermal dose-unit definition amounts simply to incorporating a nonlinear weighting factor in the procedure, already in use [5] for computing hyperthermal exposure in degree hours above an arbitrary temperature. It may loosely be interpreted as the percentage of cells killed by such a treatment applied to *in vitro* tissue culture. Without the nonlinear temperature-dependent weighting factor, the degree-hour figure is simply proportional to the total energy transferred or confined to the patient during treatment. The absence of a nonlinear weighting factor makes long exposure to low temperatures entirely equivalent to brief exposures to high temperatures, in direct contradiction to experience.

III. DISCUSSION

It must be recognized that the dose defined by D units will not, in general, be linearly cumulative over times comparable to cell cycle duration and will be strictly interpretable as a surviving fraction only for the cell subpopulation, and under the growth conditions for which the numerical values of cytotoxicity are determined. It must also be recognized that the simple assumptions of chemical reaction kinetics, used in arriving at the expression for D , ignore more sophisticated considerations of cell kinetics. It is felt, however, that in a typical clinical situation, insufficient data will be available to incorporate these refinements while the functional form of D will remain unchanged over sufficiently narrow ranges of applicability. If more refined data should be available, the model proposed may be easily modified accordingly. As clinical experience accumulates, it is to be expected that numerical values for cytotoxicity will improve. Ideally,

TABLE I
HYPERTHERMAL DOSE OBTAINED BY EXPOSURE TO VARIOUS TEMPERATURES FOR VARYING DURATIONS. NUMERICAL VALUES OBTAINED FROM CHO TISSUE CULTURE DATA [14]

D	42.0	41.8	41.5	41.0	40.5	40.0	39.5°C
1 hr	35	23	12	4	1	0	0
2 hr	58	41	22	7	2	1	0
3 hr	73	55	32	10	3	1	0
4 hr	83	66	40	14	3	1	0
5 hr	89	74	47	17	5	2	0

TABLE II
TIMES REQUIRED TO ACHIEVE A HYPERTHERMIA DOSE OF 50 UNITS BY EXPOSURE TO VARIOUS TEMPERATURES. NUMERICAL VALUES EXTRAPOLATED FROM CHO TISSUE CULTURE DATA [14]

TEMPERATURE (°C)	TIME
41.5	5.5 hrs.
41.8	2.5 hrs.
42.0	1.5 hrs.
42.5	28 min.
43.0	8 min.
43.5	2.5 min.

these values would be determined from biopsy specimens for individual patients, cultured under conditions of growth simulating tissues in clinical hyperthermia.

IV. A SPECIFIC EXAMPLE

Using kinetic data extrapolated from nonsynchronized CHO cells in tissue culture [14], the quantity D obtained for conditions of hyperthermia at various temperatures as a function of exposure time is given in Table I and plotted in Fig. 1. It is seen that a characteristic "threshold for hyperthermic effect" at 41.5°C is clearly reflected in the changing magnitude of D . The rapid change in the magnitude of D with temperature is also reflected in the empirically determined treatment procedure widely used in whole-body hyperthermia, i.e., elevation of body temperature to 41.5–42.0°C for times on the order of four or five hours.¹

The time required to achieve a dose of 50 units by exposure to various tissue temperatures, clinically, is given in Table II. It is reasonable to assume that a dose on the order of 50 units is required to produce measurable short-term tumor regression. As may be seen from Table II, temperatures from 41.5 to 42.0°C that are sustained for a matter of hours would suffice to produce this dose. This intensity and duration of hyperthermia is consistent with current clinical practice in whole-body hyperthermia [16]. To produce the same dose by sustaining tissue temperatures between 40 and 41.5°C would require hyperthermal treatments lasting on the order of days, during which

¹For a review of times and temperatures used for hyperthermia up to 1940, see Johnson [15], and for an update from 1940 to 1977, see Giovannella [16].

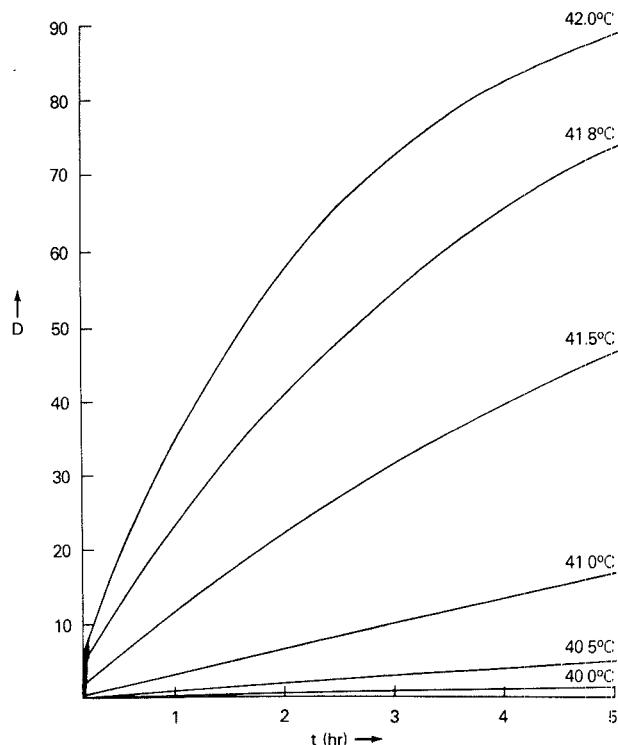
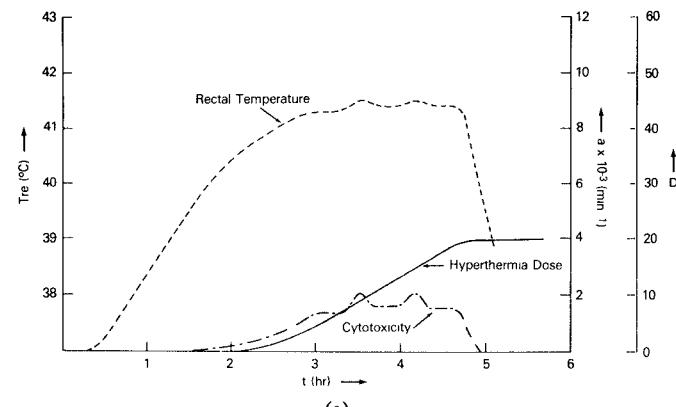
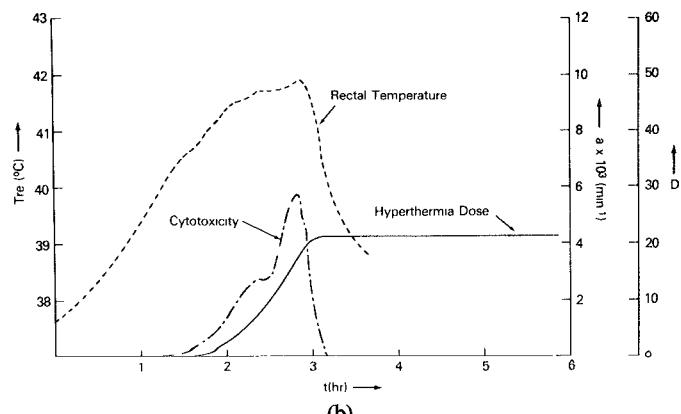


Fig. 1. Hyperthermal dose units produced by exposure to various temperatures as a function of exposure time. Numerical data for CHO cells [14] were used to obtain the formula $D = 100 (1 - \exp(755.3 - 21.19/kTdt))$.



(a)



(b)

Fig. 2. Profile of rectal temperature as a function of time for two patients receiving whole-body hyperthermia [17]. The cellular lethality rate a at each temperature is shown, as is the cumulative hyperthermia dose based on CHO tissue culture data [14]. Both patients received approximately the same dose although one was treated for five hours and the other for three hours.

times consideration of tumor regrowth at elevated temperatures would have to be made. This dose-level argument may explain why therapeutic benefit from exposure to temperatures below 41.5°C has not been reported in the cancer treatment literature. On the other hand, in local hyperthermia, where higher tissue temperatures may be produced by restriction of the tissue volume heated to nonvital tissues, doses on the order of 50 units may be achieved with temperatures from 42.5 to 44°C within minutes. This is again in accord with clinical experience [16]. Above 44°C, dose rises very rapidly with increasing temperature; exposure times only on the order of seconds are required to produce a dose of 50 units. This is to be expected and corresponds to clinical thermal cautery.

As an example of clinical applicability of the hyperthermal dose defined by the quantity D , the rectal temperature profile of two patients receiving whole body hyperthermia [17], Fig. 2, may be taken as equivalent to a hyperthermal exposure to 30 min at 42.0°C or 50 min at 41.8°C, since all these conditions produce a dose of about 20 units.

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