# HYPERTHERMIA DOSE DEFINITION

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## Abstract

In vitro thermal cytotoxicity data are consistent with the simple picture of chemical reaction kinetics governed by an activation energy. These kinetics are used to calculate, for any arbitrary heating profile used in clinical hyperthermia, the corresponding percent of cells killed by such treatment in in vitro tissue culture. The quantity calculated, which incorporates biological response to thermodynamic parameters, is suggested as a measure of hyperthermia 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 cytoxicity basis for dosage measurement.

## Introduction

When antibiotics were first introduced, physical and chemical assays for 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 which would be cleared of a trial organism after innoculation with a measured quantity of a given batch of "penicillin". The problems of assessing hyperthermia efficacy and toxicity are similarly plagued by the lack of a definition of hyperthermia dosage. In the absence of a dose-response measurement procedure, hyperthermia 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 hyperthermia 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 the avoidance of the specific adverse reaction chosen.

Another class of hyperthermia 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 hyperthermia dosage.

## 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 (10,11,12). Likewise, the rate of decline of viable cell population varies with temperature in the same manner as a Boltzmann factor containing a thermal activation energy determinant of cell death (12,13,14). 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 hyperthermia dosage. In order to arrive a 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 non-linear reaction kinetics of tissue viability.

Assume that the surviving fraction of cells at time "t" to be given by: $\exp(-at)$, where "a" is a reaction rate constant related to temperature via: $a = \alpha \exp(E/kT)$, where "$\alpha$" is the temperature independent rate constant, "E" is an activation energy and "k" is the Boltzmann constant equal to $8.62 \times 10^{-5}$ 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 non-viable by this hyperthermia 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 hyperthermia 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

a given temperature. With this interpretation "a" may be taken as a measure of the intensity of a hyperthermia treatment at a given time.

The time integral of the cellular lethality rate, "a", could, itself, be taken as a measure of hyperthermia dose. There is, of course, a simple logarithmic relationship between these alternative dose definitions and so they are related by a simple look-up 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 which cannot exceed 100 for a treatment, however, may well out-weigh this small theoretical advantage.

The hyperthermia dose unit definition amounts simply to incorporating a non-linear weighting factor in the procedure, already in use (5) for computing hyperthermia exposure in degree-hours above an arbitrary temperature. It may loosely be interpreted as the percent of cells killed by such a treatment applied to in vitro tissue culture. Without the non-linear, 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 non-linear weighting factor makes long exposure to low temperatures entirely equivalent to brief exposures to high temperatures, in direct contradiction to experience.

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

## A Specific Example

Using kinetic data obtained from non-synchronized 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 figure 1. It is seen that a characteristic "threshold for hyperthermic effect" at 41.5°C is clearly reflected in the changing magnitude of D. So, too, is the result of the clinically determined combination of exposure to temperatures, in whole body hyperthermia, in excess of 41.5°C for times on the order of four or five hours.*

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 of from 41.5 to 42.0°C 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 hyperthermia treatments lasting on the order of days, during which 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 non-vital tissues, doses on the order of 50 units may be achieved with temperatures of from 42.5°C 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 hyperthermia dose defined by the quantity D, the rectal temperature profile of two patients receiving whole body hyperthermia (17), figure 2, may be taken as equivalent to a hyperthermia exposure to 30 minutes at 42.0°C or 50 minutes at 41.8°C, since all these conditions produce a dose of about 20 units.

## References


1. R. T. Pettigrew, J. M. Galt, C. M. Ludgate, D. B. Horne, and A. N. Smith, Circulatory and biochemical effects of whole body hyperthermia. Br. J. Surg. 61, 727 (1974).

2. J. E. Robinson, M. J. Wizenberg, and W. A. McCready, Radiation and hyperthermal response of normal tissue "in situ". Radiology 113, 195 (1974).

3. Y. Okamura and H. S. Reinhold, Heat sensitivity of rat skin. Br. J. Radiol. 49 (585) 806 (1976).

4. S. W. Edwards, Personal Communication. Department of Surgery, The University of New Mexico, School of Medicine, Albuquerque, New Mexico 87131 USA (1976).

5. R. T. Pettigrew, J. M. Galt, C. M. Ludgate, and A. N. Smith, Clinical effects of whole-body hyperthermia in advanced malignancy. Br. Med J. 4, 679 (1974).

6. J. S. Stehlin, Jr., B. C. Giovanella, P. D. de Ipolyi, L. R. Muenz, and R. F. Anderson, Results of hyperthermic perfusion for melanoma of the extremities. Surg. Gynec. Obstet. 140, 338 (1975).


*For a review of times and temperatures used for hyperthermia up to 1940 see Johnson (15) and for an update from 1940 to 1975 see Dickson (16).

7. J. Mendecki, E. Friedenthal, and C. Botstein, Effects of microwave-induced local hyperthermia on mammary adenocarcinoma in C3H mice. Cancer Res. 36, 2113 (1976).

8. H. H. LeVeen, S. Wapnick, V. Picone, G. Folk, and N. Ahmed, Tumor eradication by radiofrequency therapy. JAMA 235, 2198 (1976).

9. G. M. Hahn, and M. L. Boone, Editorial correspondence. JAMA 236, 2286 (1976).

10. B. C. Giovanella and C. Heidelberger, Biochemical and biilogical effects of heat on normal and neoplastic cells. Cancer Res. 9, 24 (1968).

11. N. Schulman, and E. J. Hall, Hyperthermia: its effect on proliferative and plateau phase cell cultures. Radiology 113, 207 (1974).

12. M. Harris, Temperature-resistant variants in clonal populations of pig kidney cells. Expt'l Cell Res. 46, 301 (1967).

13. A. Westra, A. and W. C. Dewey, Variation in sensitivity to heat shock during the cell-cycle of Chinese hamster cells "in vitro". Int. J. Radiat. Biol. 19, 467 (1971).

14. S. Sapareto, Response of CHO cells to hyperthermia and hyperthermia plus radiation below 43.5°C. Proc. Int. Symp. on Cancer Therapy by Hyperthermia and Radiation, 231. American College of Radiology (1976).

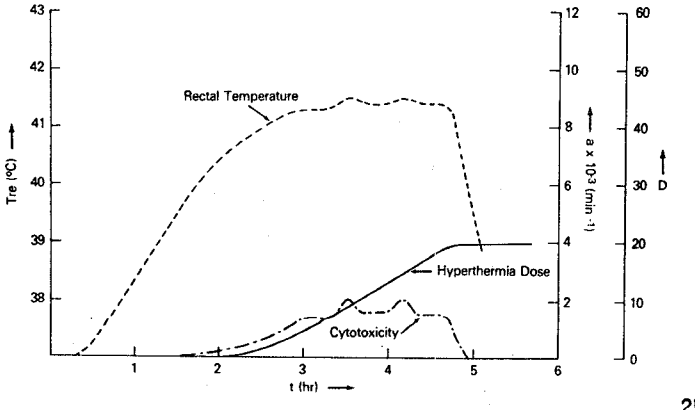
15. H. J. Johnson, The action of short radio waves on tissues III a comparison of the thermal sensitivities of transplantable tumors "in vivo" and "in vitro". Amer. J. Cancer 38, 533 (1940).

16. J. A. Dickson, Hazards and potentiators of hyperthermia. Proc. Int. Symp. on Cancer Therapy by Hyperthermia and Radiation, 134. American College of Radiology (1976).

17. J. M. C. Bull, Personal Communication. National Cancer Institute, Division of Cancer Treatment, Bethesda, Maryland 20014 USA (1977).

| 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 I - Hyperthermia dose obtained by exposure to various temperatures for varying durations. Numerical values obtained from CHO tissue culture data (14).




| TEMPERATURE | TIME | TEMPERATURE | TIME |
|---|---|---|---|
| 37.0°C | 53 yrs | 41.8 | 2.5 hrs |
| 38.0 | 4 yrs | 42.0 | 1.5 hrs |
| 39.0 | 120 days | 42.5 | 27.5 min |
| 40.0 | 10 days | 43.0 | 8 min |
| 41.0 | 19 hrs | 43.5 | 2.5 min |
| 41.5 | 5.5 hrs | 44.0 | 42 sec |

Table II - Times required to achieve a hyperthermia dose of 50 units by exposure to various temperatures. Numerical values obtained from CHO tissue culture data (14).

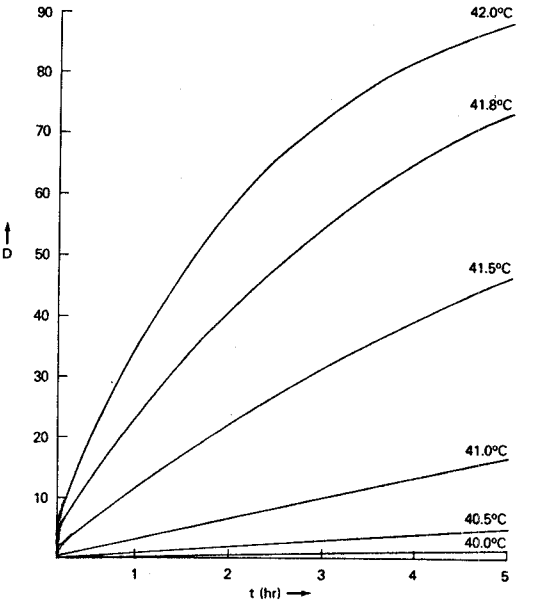



Figure 1. Hyperthermia dose units produced by exposure to various temperatures as a function of exposure time. Numerical data for CHO cells (14) were used to obtain the formula $D=100(1-\exp\int(\exp(775.3-21.19/kTdt)))$.

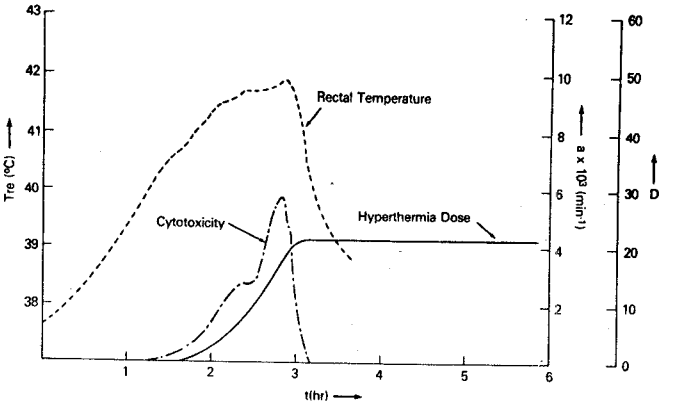



Figure 2. Profile of rectal temperature as a function of time for two patients receiving whole body hyperthermia (17). The cellular lethality rate, "a", at each temperature is shown, as is the cumulative hyperthermia dose based upon CHO tissue culture data (14). Both patients received approximately the same dose although one was treated for 5 hours and the other for 3 hours.