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● *Original Contribution*

THERMAL DOSE DETERMINATION IN CANCER THERAPY

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With the rapid development of clinical hyperthermia for the treatment of cancer either alone or in conjunction with other modalities, a means of measuring a thermal dose in terms which are clinically relevant to the biological effect is needed. A comparison of published data empirically suggests a basic relationship that may be used to calculate a "thermal dose." From a knowledge of the temperature during treatment as a function of time combined with a mathematical description of the time-temperature relationship, an estimate of the actual treatment calculated as an exposure time at some reference temperature can be determined. This could be of great benefit in providing a real-time accumulated dose during actual patient treatment. For the purpose of this study, a reference temperature of 43°C has been arbitrarily chosen to convert all thermal exposures to "equivalent-minutes" at this temperature. This dose calculation can be compared to an integrated calculation of the "degree-minutes" to determine its prognostic ability. The time-temperature relationship upon which this equivalent dose calculation is based does not predict, nor does it require, that different tissues have the same sensitivity to heat. A computer program written in FORTRAN is included for performing calculations of both equivalent-minutes (t_{43}) and degree-minutes (t_{dm43}). Means are provided to alter the reference temperature, the Arrhenius "break" temperature and the time-temperature relationship both above and below the "break" temperature. In addition, the effect of factors such as step-down heating, thermotolerance, and physiological conditions on thermal dose calculations are discussed. The equations and methods described in this report are not intended to represent the only approach for thermal dose estimation; instead, they are intended to provide a simple but effective means for such calculations for clinical use and to stimulate efforts to evaluate data in terms of therapeutically useful thermal units.

Hyperthermia, Thermal dosimetry, Arrhenius analysis, Equivalent-minutes.

INTRODUCTION

With the rapid development of clinical hyperthermia for the treatment of cancer either alone or in conjunction with other modalities, a means of measuring a thermal dose in terms which are clinically relevant to the biological effect is needed. Clinical trials for local hyperthermia treatment have been reported;[4,25,33] however, there has been little consistency in protocols. The temperatures used have varied from 42 to 50° Celsius, and the duration of treatment and the frequency and number of multiple fractions have also varied. The difficulties in assessing and comparing these treatments are obvious.

A plethora of data on the effect of heat on both cells in culture and in tumors is available. A comparison of these data empirically suggests a basic relationship that may be used to calculate a "thermal dose." In clinical situations, the time required to achieve a predetermined hyperthermic exposure temperature can be a significant part of the total treatment time. Furthermore, in some instances, it may not be possible to achieve a pre-chosen temperature because of such limitations as patient discomfort, insufficient power, tumor location, high tumor blood flow, or a combination of these factors. Therefore, it is essential to determine some sort of comparative dose estimate for the actual treatment given. From a knowledge of the temperature during treatment as a function of time combined with a mathematical description of the time-temperature relationship for thermal inactivation or damage, an estimate of the actual treatment calculated as an exposure time at some reference temperature can be determined. For the purpose of this report, a reference temperature of 43°C has been arbitrarily chosen.

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The importance of this technique can be seen in its application to determining the dose accumulated in real time during actual exposure, in order that hyperthermic treatment could be adjusted for temperature variations during the actual treatment. For example, in a case where the measured temperature exceeded the proposed treatment temperature, the actual treatment could be shortened during the exposure to correct for the "extra" damage occurring during the period of excessive temperature.

Other methods of calculating thermal dose have also been proposed.[1,8] These methods are based also on a thermodynamic or "Arrhenius-type" relationship which has been empirically determined. The equations and methods described in this report are not intended to represent the only approach for thermal dose calculation; instead, they are intended to provide a simple but effective means for such estimations for clinical use and to stimulate efforts in evaluating clinical results in terms which are practical and prognostically relevant.

THEORETICAL MODEL

Equivalent-minutes calculation

The relationship between temperature and exposure time during hyperthermic treatments has been reported for a variety of biological systems.[5,6,15] The evidence clearly indicates that, for both *in vitro* and *in vivo* systems, an exponential relationship exists between temperature and exposure time. In most systems, this relationship can be simply stated: a one degree increase in temperature requires a two-fold decrease in time for the same effect above 43°C and a three-to-four fold decrease in time for an iso-effect below 43°C. Investigators have attempted to describe this relationship mathematically;[5,15,18,19] however, these analyses have been directed primarily toward the mechanisms of heat killing, and little effort has been put into the clinical application of this mathematical approach.

As stated above, the overwhelming majority of biological systems exhibit the same exponential relationship between time and temperature for a given isoeffect. For cells in culture, this is most clearly observed in an Arrhenius plot of the logarithm of the reciprocal of D_0 versus the reciprocal of temperature.[3,5,15,35] This plot is linear and of approximately the same slope above 43°C for almost all cell lines.[3,15] Of course, this is not to say that all cells exhibit the same sensitivity to heat, as evidenced by the vertical displacement between lines on an Arrhenius plot,[15,35] but only that for many cell lines, a consistent relationship describes how the slope of the survival curve changes with temperature.

This same relationship is also seen for many *in vivo* systems[26] and mathematically has been described[5] as a relationship between time (t) and temperature (T) by:

$$t_1 = t_2 R^{(T_1 - T_2)} \quad (1)$$

where R can be calculated as a function of ΔH, the activation energy (cal/mol), and absolute temperature (°K) from an Arrhenius plot by:

$$R = e^{-\Delta H/(2T(T+1))} \quad (2)$$

The constant 2 is an approximation for the universal gas constant (1.98 cal/°K-mol) and the numerator of the exponent contains a constant of 1°K which cancels the unit of °K in the denominator, thus providing the correct dimensions. Although R is a function of temperature, for the range of interest (37–46°C), assuming that R is constant will give an error of less than 2%. The selection of R values can significantly affect the calculated dose; however, this occurs only when the actual temperature is different from the reference temperature. A change in R of 10% will cause approximately a 10% error in the calculated dose per degree difference between the actual temperature and the reference temperature. Determinations of R have been reported for a number of biological systems and endpoints (see review in reference 5). The values reported range from 0.4 to 0.8 above 43°C, with 0.5 being the most common value. There have been fewer studies below 43°C; however, in general the R value is approximately a factor of 2 smaller than that above 43°C.[3,5,26,29] Thus, we have assumed R = 0.5 for temperatures greater than 43.0°C, and R = 0.25 for temperatures below 43.0°C.

The choice of the "break" temperature at 43°C has also been arbitrarily chosen as a best estimate from all available data. However, there is evidence that this temperature may vary[2,20] and that it may be a relative temperature related to the normal physiological temperature of the tissue rather than an absolute value.

For the simple case of equating a time at one temperature with an equivalent time for the same effect at another temperature, a nomogram can be drawn (Figure 1). This nomogram has a reference temperature of 43°C and can be used in two ways. First, if a preselected treatment at the reference temperature is chosen, the appropriate time at any other temperature to achieve the same effect can be calculated. Conversely, if a treatment at some temperature is given, this may be equated with an equivalent treatment time at 43°C. Therefore, comparisons between treatments at different temperatures can be made by converting each treatment to an equivalent time at 43°C.

An important extension of the use of this relationship is the determination of the equivalent time at 43°C for a complex temperature history. As shown in Figure 2, a typical temperature profile for a treatment would consist of three components: 1) an initial warm-up period (often exponentially approaching the treatment temperature), followed by 2) a period of more or less constant temperature, and ended by 3) a cool-down period (also typically exponential). Ideally, the least complicated temperature history would have instantaneous temperature transitions and a period of constant temperature mainte-

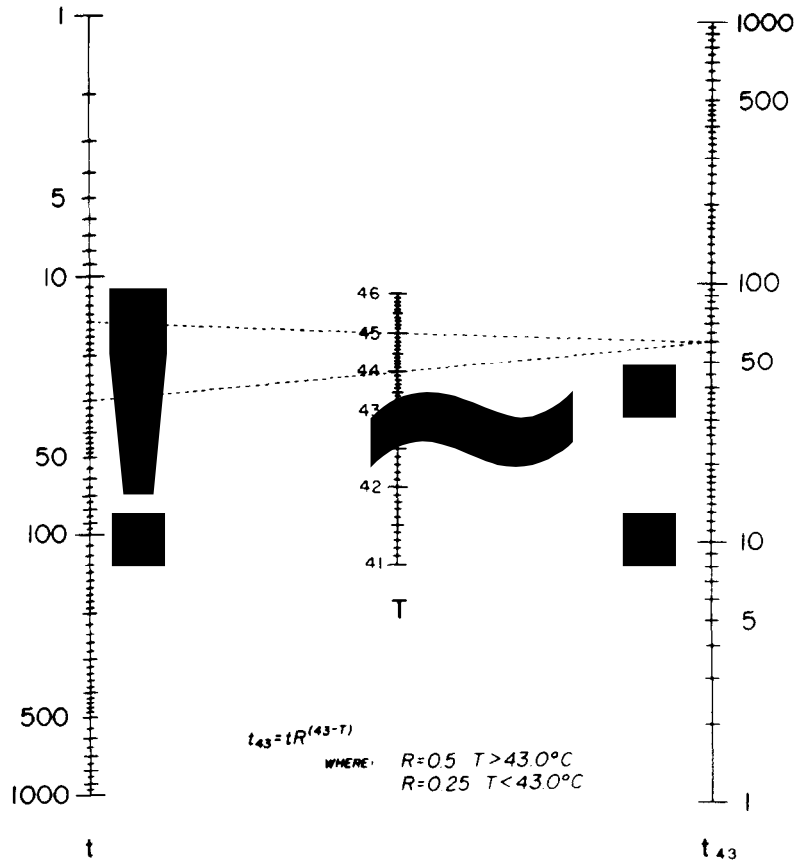

Fig. 1. A nomogram relating time at any temperature to an equivalent time at 43°C (t_{43}). Two examples of use are shown by dashed lines; a 30 minute treatment at 44°C is equivalent to 60 minutes at 43°C which is also equivalent to 15 minutes at 45°C.

nance as also shown in Figure 2. For ease of comparison, this is the temperature profile to which all complex profiles should be reduced.

By mathematically describing the change in temperature as a function of time, it is possible to calculate the equivalent time at any chosen reference temperature. A

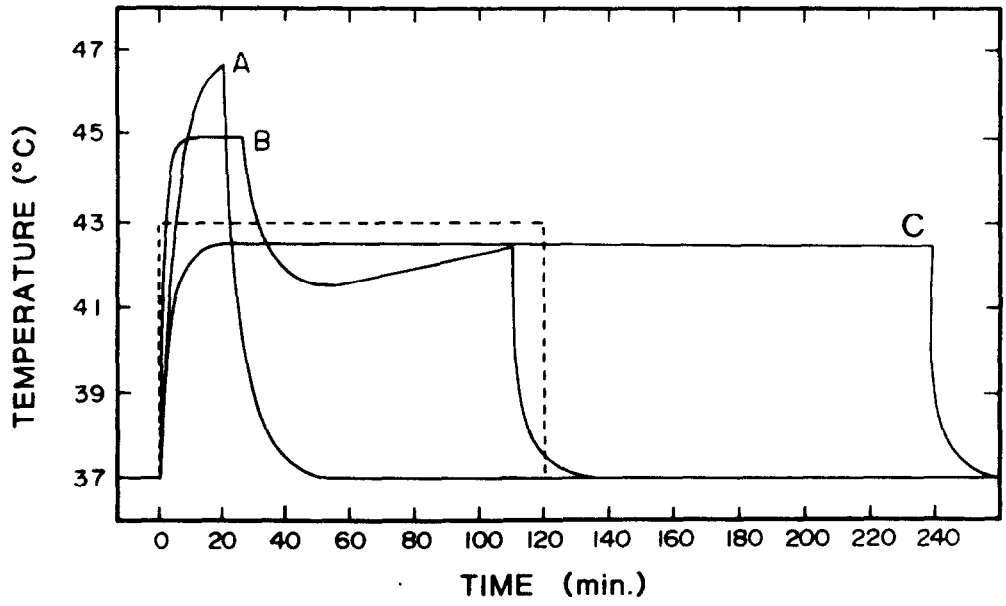

Fig. 2. Theoretically generated temperature profiles as a function of time. The ideal temperature profile is shown by the dashed line and represents 120 minutes at 43°C. The three additional profiles (A–C) are all equivalent to 120 minutes at 43°C by equivalent-minute calculation. As can be seen, the areas under each curve are *not* equal.

common case is that of an exponential change in temperature of the form:

$$T(t) = T_f - \Delta T e^{-\lambda t} \quad (3)$$

where T_f is the final temperature, ΔT is the difference between the final and initial temperatures, and $\lambda = 0.693/t_{1/2}$, with $t_{1/2}$ being the half-time for the temperature change.

Henle and Roti Roti[18] have evaluated the equivalent treatment time for the type of exponential warm-up described in equation 3. To determine the total exposure time, it is necessary to integrate the time-temperature relationship as a function of time. Since, in this case, the equation to be integrated is an indefinite integral of the form e^x/x, the authors used an approximation by series expansion limited to the first 10 terms.

A more general approach to a changing temperature exposure would be to calculate the accumulated exposure by numerical integration using a computer. This provides a method for calculating the accumulated dose at a reference temperature under a variety of heating profiles, including temperature histories that cannot be easily described mathematically.

For sufficiently small Δt, the equation can be described mathematically as:

$$t_{43} = \sum_{t=0}^{t=\text{final}} R^{(43-\bar{T})}\Delta t \quad (4)$$

where t_{43} is the equivalent time at 43°C, $\bar{T}$ is the average temperature during time Δt, R = 0.5 above 43°C and R = 0.25 below 42°C.

The frequency with which temperature measurements are made (Δt) can affect the accuracy of the thermal dose calculation. Obviously, the more frequently the measurements (or the smaller the Δt), especially during rapid temperature changes, the more accurate the calculated dose. On the other hand, in situations where the temperature is changing very slowly, less frequent measurements may provide sufficient accuracy. For the theoretical curves used to generate the results in this report, Δt was less than 0.2% of the total treatment time. Thus, at least 500 temperature measurement points per treatment were used.

In order to completely describe a thermal dose, several new terms must be defined. These terms must be easily identifiable treatment parameters. First, t_{total} is defined as the time from the start of thermal power input until the end of power input. Thus, t_{total} includes the warm-up but does not include the cool-down to normal temperature. Second, t_{corr} is defined as the correction time to be added to the total time (t_{total}) to account for either the warm-up or cool-down periods. Hence, warm-up corrections are negative in value and cool-down corrections are positive. Conversion of t_{total} or t_{corr} to equivalent times at 43°C may be made by use of Figure 1 and would then be designated as $t_{total43}$ or t_{corr43}, respectively.

The importance of correcting for the warm-up period is clearly demonstrated in Figure 3. This figure represents theoretical temperature histories for a 30 minute (t_{total}) treatment at 45°C with various exponential warm-up half-times. Using Figure 1, the equivalent total time ($t_{total43}$) of this treatment with instantaneous warm-up and cool-down would be 120 minutes. As shown, a 10 second half-time warm-up causes a negligible reduction of the equivalent treatment time to 117.7 minutes (t_{corr43} = −2.3

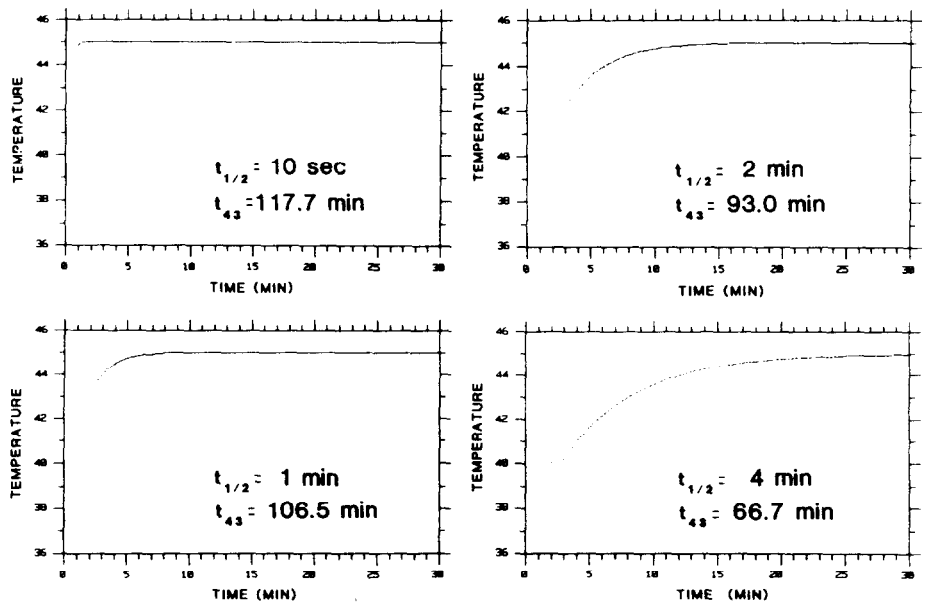

Fig. 3. Theoretically generated temperature profiles as a function time for a treatment temperature of 45°C. Each represents an equivalent total time at 43°C ($t_{total43}$) of 120 minutes with different half-times for warm-up. Half-times and equivalent-minutes at 43° (t_{43}) are indicated.

minutes). However, for a four-minute half-time warm-up, which is a quite likely clinical occurrence, the equivalent treatment is reduced to 56% of the total time (t_{corr43} = −53.3 min). Note that a rough estimate from Figure 3 of the actual time at the final temperature (e.g. 15 min at 45° for $t_{1/2}$ = 4 min is a reasonable approximation of the dose when converted to equivalent-minutes (t_{43} = 60 min). Thus, the common clinical practice of determining the duration of treatment based on the time spent at the treatment temperature may not be too unreasonable.

An empirically-derived relationship between t_{corr43} and the half-time for warm-up or cool-down, where the half-time is converted into an equivalent half-time at 43°C ($t_{1/2\,43}$), can be estimated as shown in Figure 4 for half-times of less than 15% of the total time. As can be seen, the warm-up correction is an order of magnitude greater than the cool-down correction for a given transition half-time. This occurs because during warm-up, the temperature rises slowly through the higher, more toxic temperatures before reaching the treatment temperature, while during cool-down, the temperature drops rapidly to the lower, less toxic temperatures.

EXPERIMENTAL DATA

Equivalent-minutes calculation

The applicability of equivalent-minute calculations is shown in Figure 5 where the *in vitro* survival of cells exposed to temperatures from 41.5 to 46.5°C for various times are plotted as a function of equivalent-minutes at 43°C. The data fit a single curve (r^2 = 0.87) with the exception of prolonged heating durations of 3 hours or more at temperatures of 42.5°C and below. At these temperatures, survival follows the curve initially, but then deviates from the single curve because of the development of increased thermal tolerance during the heat treatment.[29] Furthermore, as temperature decreases from 42.5 to 41.5, the data appear to deviate from the single curve at earlier equivalent times, which reflects the fact that maximum thermotolerance develops at different survival levels,[29] because the rate of killing increases with temperature.

The calculation of equivalent-minutes at 43°C does, in fact, partially correct for thermotolerance, since the "break" in the Arrhenius plot at 43.0°C is most likely due to the development of thermotolerance during heating.[22,29] However, this correction does not sufficiently account for thermotolerance (Figure 5) as maximum tolerance is reached, i.e., a plateau in the survival curve.[29] Since the rate of the development of thermal tolerance is probably temperature dependent, the assumption of a constant value for R below 43.0°C may not be valid, and certainly does not apply when maximum thermotolerance occurs, where R would become infinite. Indeed, these relationships require further investigation.

Degree-minutes calculation

While the approach described above is based on extensive empirical data, an appropriate model for com-

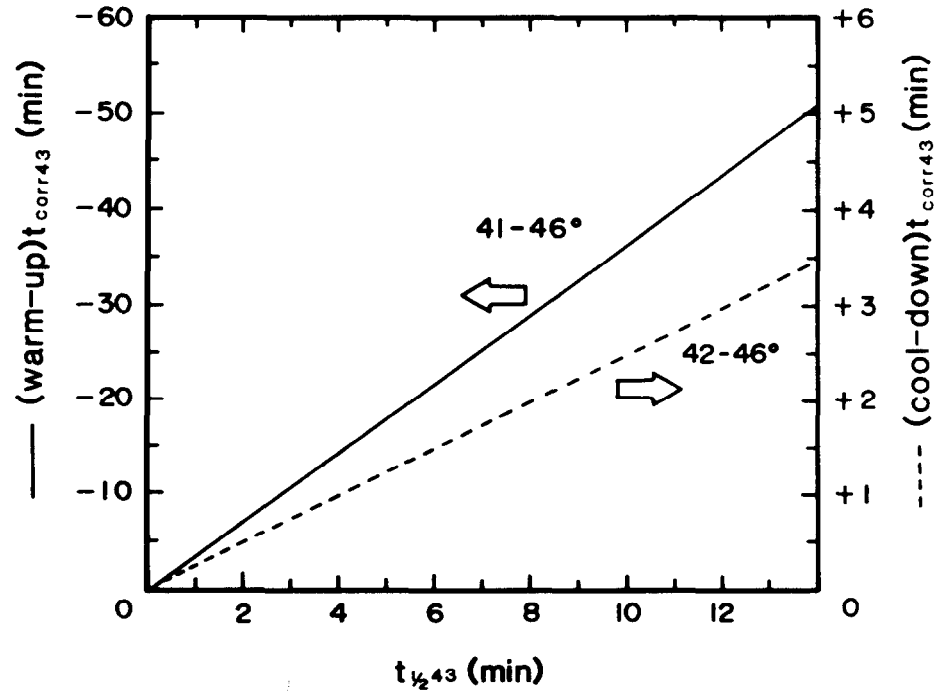

Fig. 4. An empirically-derived graph of warm-up (solid line, left ordinate) and cool-down (dashed line, right ordinate) correction times at 43°C as a function of equivalent half-time at 43°C. The correction time (t_{corr43}) can be determined by converting the warm-up half-time for the actual treatment temperature to an equivalent half-time at 43°C by the nomogram in Figure 1 (e.g. 10 sec. half-time to reach 45°C equals a 40 second half-time to reach 43°C). The straight lines are valid for half-times up to 15% of the total treatment time and each line is valid over the temperature range indicated in the figure.

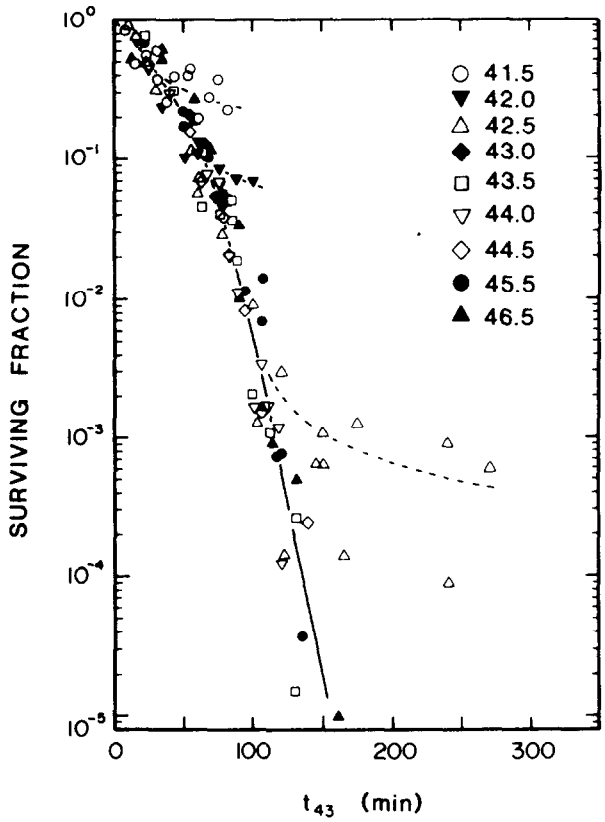

Fig. 5. The dose survival response for asynchronous Chinese hamster ovary cells at various temperatures plotted as a function of equivalent-minutes at 43°C. Error bars have been omitted for clarity. The data at 41.5, 42.0, and 42.5 deviate from a single line, as shown by the dashed lines, due to the development of thermotolerance. Actual data are taken from reference 29 and replotted.

parison would be the integral of the product of the temperature above a certain starting point multiplied by time, or the "degree-minutes." This degree-minute quantity can be reconverted back into a time as if the whole period had been at a constant temperature by dividing by the difference between the starting temperature and reference temperature. Again, using 43°C as a reference, this is expressed as:

$$t_{dm43} = \frac{\sum_{t=0}^{t=final} (\bar{T} - T_0)\Delta t}{43 - T_0} \qquad (5)$$

where t_{dm43} is the degree-minutes converted to a time at 43°C, and T_0 is the starting temperature which has been arbitrarily chosen to be 41°C since there is little evidence of cell killing below this temperature.

Computer programs

A program performing calculations of both equivalent minutes (t_{43}) and degree-minutes (t_{dm43}) is listed in Appendix I. The program, called TEQUIV, was written in FORTRAN 4 on a PDP11/23 computer* and should be sufficiently documented. Two alternate subroutines have been provided for data input either directly from an interactive terminal or from a data file. The program allows changes of R values and the Arrhenius "break" temperature; however, default values used in this report are provided. Further information about this program including test data to verify its accuracy and a version of the program written in BASIC can be obtained from the authors. In addition, a program will be available to provide real-time accumulated dose with the input of temperature values during actual treatment.

COMPLICATIONS AFFECTING THERMAL DOSE

Step-down heating

An initial exposure of cells to temperatures above 43°C causes a modification of the time-temperature relationship below 43°C. If cells are briefly exposed above 43°C and then immediately treated below 43°C, the break in the Arrhenius plot at 43°C is eliminated; thus an R value of 0.5 is maintained over the whole temperature range.[13,22] Both Sapareto *et al.*[29] and Li *et al.*[22] suggest that the development of thermotolerance causes the break in the Arrhenius plot and that exposure to temperatures above 43°C inhibits or delays the development of thermotolerance, thus allowing more rapid killing when cells are subsequently exposed to temperatures below 43°C. This phenomenon, of course, would affect the calculation of an accumulated dose as described in the model presented here by increasing the t_{43} dose accumulated during exposure to temperatures below 43°C. However, by determining the amount of high temperature exposure necessary to cause this effect, the R value below 43°C should be adjusted after the appropriate accumulated exposure necessary to reflect that this change had occurred. For example, Figure 3, curve B, represents a step-down heating situation. Following these arguments, this curve would represent a dose greater than 120 minutes at 43°. Further research is essential to develop and test these possibilities.

Multiple dose therapy

A simple calculation of equivalent time at 43°C cannot be accomplished for multiple heat doses because of the development of thermal tolerance between treatments. As has been clearly demonstrated for a variety of cells, whether normal or malignant, previous exposure to elevated temperature produces resistance to further thermal damage, for periods of up to 6 days.[9,16,27,29] The effect of the development of thermal tolerance on the Arrhenius relationship is to cause both a shift in the "break" temperature to higher temperatures and a displacement of

* Digital Equipment Corporation, Maynard, MA.

the linear relationship toward slower rates of killing (i.e., higher D_0 values).[2,20] However, the slope of the Arrhenius relationship does not appear to change.[2,20] This is demonstrated for *in vivo* normal tissue in Figure 6.

Based on these observations, the fundamental relationship between time and temperature used in the calculation of equivalent-minutes is still valid for thermotolerant cells. However, the t_{43} dose calculated must be reduced to account for the degree of thermotolerance present. A measure of this degree of thermotolerance has been proposed by Henle and Leeper[17] as a ratio of D_0 values from survival curves for Chinese hamster ovary cells, with or without thermotolerance, and was termed the thermotolerance ratio (TTR). Thus, this phenomenon appears to be a dose-modifying factor similar to that for the oxygen effect (OER) seen with cell killing by ionizing radiation.[12]

The TTR which can be induced with acute heating treatments ranges from approximately 2.4 to 4.5.[2,14,17] Note that this is not the same as the ratio of survival levels. Figure 6[20] also shows a ratio of approximately 3 between doses in the presence and absence of thermotolerance for the same normal tissue damage. Thus, it may be possible to determine some dose correction factor if the rate and degree of thermotolerance development can be predicted. Further investigation of these dose modifying concepts are necessary to determine the feasibility of this approach.

An additional complication of thermotolerance is the development of tolerance during the warm-up period of the heat treatment. As noted previously, the R value of 0.25 below 43°C does partially account for some of this tolerance. However, slow rates of heating would also cause the development of thermotolerance to the higher temperatures finally achieved during the same treatment.[32] Although maximum thermotolerance requires several hours to develop,[29,32] the development probably begins immediately upon initiation of heating;[23] therefore, the rate of heating to treatment temperature should be kept as rapid as possible, certainly within one-half hour or less.

Physiological conditions

Several physiological factors such as pH and nutrients also modify cellular response to heat;[9,11] for example, lowering the pH, although having little effect on R, increases the cellular inactivation rate.[7] Furthermore, these factors can affect the development of thermotolerance.[10,23] However, again, these phenomena may be similar to those which affect ionizing radiation response (e.g. OER) and can be treated as dose-modifying factors. In fact, Goldin and Leeper[10] have demonstrated a simple relationship between pH and the maximum TTR achieved by 45°C exposure. These factors change appreciably in tumors,[31,33] but should be relatively constant in normal tissues; therefore, complications related to these factors should not

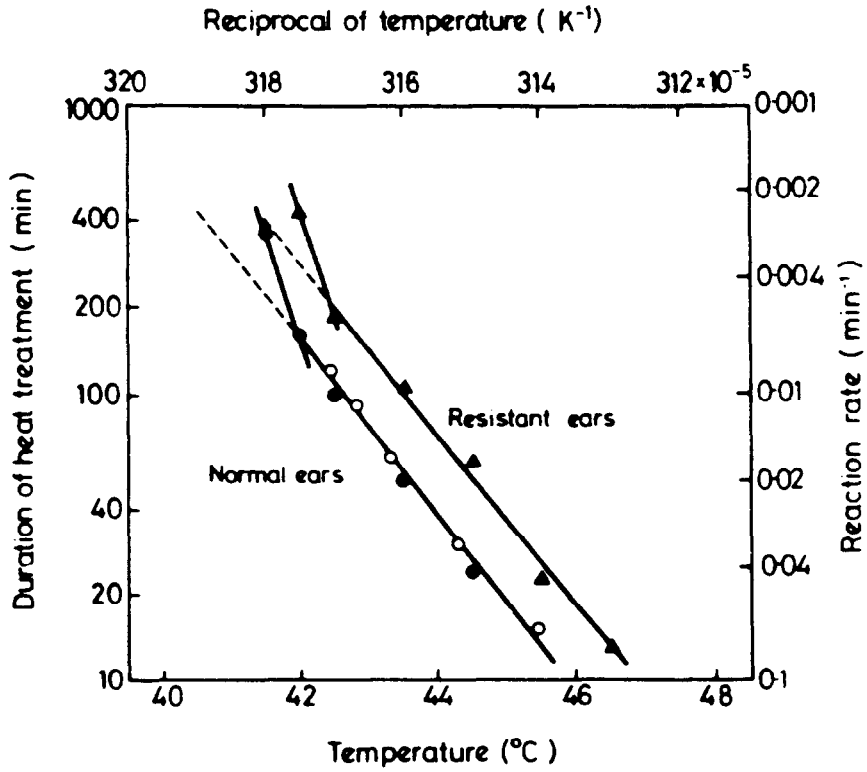

Fig. 6. An Arrhenius-like plot of the relationship between time and temperature to cause 50% necrosis in mouse ears. Resistant ears received a treatment of 43.5°C for 20 min., 24 hours prior to the test treatment. Reprinted with permission from reference 20.

pose a serious problem in establishing heat doses for normal tissues.

Hyperthermia plus radiation

The calculations of thermal dose presented in this report are based on the killing effects from heat alone. When heat is combined with radiation, there are two components to the increase in cell killing: 1) killing from heat alone, and 2) increased killing from radiation due to the interaction of heat combined with radiation. Law *et al.*[21] have shown that the combination of heat plus radiation apparently alters the Arrhenius relationship, giving an R value of approximately 0.27 over the temperature range of 41 to 44.5°C. In addition, we have noted[30] that combining a single dose of radiation with different heat doses over the range of 41.5 to 45.5°C, each adjusted by an equivalent-minutes calculation to give the same killing from heat alone, had a maximum rate of inactivation at 42.5°C, i.e., about 10 to 15% greater than at 41.5 or 45.5°C. This, too, suggests that the R value chosen from heat killing data may not be the best for heat interacting with radiation. However, both of these studies, as well as others,[16,24] are of limited use because they do not take into account the effect of differences during the cell cycle in sensitivities to heat and radiation.[35] A study of homogenous populations of G1 and S phase cells heated and irradiated without such complications[28] suggests that differences in inactivation rates due to the interaction of heat and radiation at equivalent thermal doses are not large (less than 10–15%). Nevertheless, in order to truly understand the complications in calculating thermal dose for the combination of hyperthermia and radiation, further studies with homogenous populations of cells in which heat radiosensitization is clearly separated from heat killing are necessary.

CLINICAL EVALUATION

In order to determine the relevance of either equivalent-minutes or degree-minutes for measuring thermal doses in clinical treatment, it is essential to determine under which conditions the models differ. Table 1 compares the dose calculations for each of these methods with various warm-up half-times for a $t_{total43}$ dose of 120 minutes. In this case, no significant difference between the two methods can be seen. However, at a higher temperature, as shown in Table 2, for a total time of 30 minutes at 45°C or a $t_{total43}$ of 120 minutes, the two calculations differ dramatically both in absolute dose and in relative reduction in dose with longer warm-up times. Table 3 performs the same comparison for a total time of 480 minutes at 42°C which is also a $t_{total43}$ of 120 minutes, and again the two methods differ greatly in estimating the dose. Thus, only when the average treatment temperatures differ from 43°C can the two methods be compared in clinical trials to determine which is a better prognostic indicator of therapeutic effect.

The time-temperature relationship upon which this equivalent dose calculation is based does not predict, nor does it require, that different tissues have the same sensitivity to heat. These calculated doses are valid only as a means of comparing treatments on the same tissue and for the same effect. Thus, once the effect of a given treatment is known, such as the maximum tolerated thermal treatment for a given normal tissue or the minimum tumor treatment for a given probability of cure, different treatments at different temperatures can be either predicted or compared.

The importance of equivalent-minutes as a prognostic indicator of treatment response has been investigated by Dewhirst *et al.*[4] in clinical trials of spontaneous domestic pet tumors. The results clearly indicate that the thermal dose measured for the thermometer probe in the coolest part of the tumor is the best predictor of long-term response. In addition, the equivalent-minute dose (t_{43}) is a better prognostic indicator when compared to a degree-minute dose (t_{dm43}). Furthermore, the dose determined for the first treatment in multiple dose therapy was better than the total accumulated dose at predicting long-term response. This higher correlation with first heat dose is further evidence that thermotolerance may reduce the

Table 1. Comparison of calculated doses for a treatment of 120 minutes at 43°C for various warm-up half-times

$t_{1/2}$(sec)	t_{43}(min)	t_{dm43}(min)
20	118.7	119.0
40	117.4	118.0
80	114.8	116.0
160	109.6	111.9
320	99.2	103.9

Table 2. Comparison of calculated doses for a treatment of 30 minutes at 45°C for various warm-up half-times

$t_{1/2}$(sec)	t_{43}(min)	t_{dm43}(min)
20	115.5	58.4
40	111.0	56.7
80	102.0	53.5
160	84.0	47.0
320	51.3	34.6

Table 3. Comparison of calculated doses for a treatment of 480 minutes at 42°C for various warm-up half-times

$t_{1/2}$(sec)	t_{43}(min)	t_{dm43}(min)
20	119.7	239.3
40	119.4	238.7
80	118.7	257.5
160	117.5	235.0
320	114.9	230.0

effectiveness of the later treatments in multiple dose therapy, despite the separation of treatments by 72 hours or more.

The clinical usefulness of calculating an equivalent thermal dose depends on several factors. The first is that the Arrhenius relationship (ΔH and the break temperature) be valid for the tissues being treated. This linear time-temperature relationship above the break temperature has been shown to exist for the vast majority of both normal and tumor tissues studied.[3,5,15,19,20,26,35] Nevertheless, even the possibility of a variation in the Arrhenius relationships for human tumors will not lessen the usefulness of these dose calculations. In fact, even complicating factors such as changes in pH, nutrients, and blood flow may have only minimal consequences on thermal dose determinations, once their effects on inactivation rates are quantified.

Tubiana[34] has stated emphatically that the goal of any cancer therapy is a maximum destruction of malignant cells with minimal or acceptable normal tissue damage; therefore, the ultimate doses for hyperthermic cancer treatment will be limited by normal tissue damage. Unlike tumors, normal tissue is more likely to show a predictable and generally applicable time-temperature relationship which will allow therapists to treat to an accurately predetermined maximum dose. This dose predictive capability is desperately needed since thermal damage frequently exhibits a threshold-like response where, once a certain dose of heat is given, only a slight increase in dose can cause a tremendous increase in tissue damage. In order for hyperthermia to achieve its true therapeutic potential, treatments must approach this threshold level as closely as possible. Improvements in heat delivery, temperature measurements, and thermal dose calculations during the actual treatment period are the only way this can be achieved.

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APPENDIX I

```
      PROGRAM TEQUIV
C
C          COPYRIGHT (C) 1983, S. SAPARETO
C          VERSION 2.01 LAST REVISION: 5/4/84
C
C          THIS PROGRAM IS DESIGNED TO TAKE SEQUENTIAL TEMPERATURE
C          VALUES AND CALCULATE THE ACCUMULATED EQUIVALENT TIME AND
C          DEGREE*MINUTES CONVERTED BACK TO TIME AT A REFERENCE
C          TEMPERATURE
C     VARIABLES:
          REAL TEMP(2000)                !TEMPERATURE DATA
          REAL TIME(2000)                !TIME DATA
          BYTE IDENT(80)                 !DATA FILE IDENTIFIER
          REAL TREF                      !REFERENCE TEMPERATURE
          REAL TBREAK                    !BREAK TEMPERATURE (PRESET TO 43.0)
          REAL TSTRT                     !STARTING TEMPERATURE FOR DEGREE-
                                          MINUTE CALCULATION
C
          LOGICAL NPRINT                 !LOGICAL VARIABLE FOR LISTING DATA
          REAL RESP                      !TEMPORARY RESPONSE VARIABLE
          REAL TSUM                      !EQUIVALENT TIME AT BREAK TEMPERATURE
C
          REAL T43                       !EQUIVALENT TIME AT REFERENCE
                                          TEMPERATURE
C
          REAL RABOVE                    !R VALUE ABOVE BREAK TEMPERATURE
                                          (PRESET TO 0.5)
C
          REAL RBELOW                    !R VALUE BELOW BREAK TEMPERATURE
                                          (PRESET TO 0.25)
C
          REAL TAVE                      !AVERAGE TEMPERATURE DURING DELTAT
          REAL SUMRF                     !EQUIVALENT TIME FUNCTION
          REAL DGMIN                     !DEGREE*MINUTES FUNCTION
          REAL TDM43                     !DGMIN CONVERTED TO TIME AT REFERENCE
                                          TEMPERATURE
C
          INTEGER IUNIT                  !TERMINAL INPUT
          INTEGER OUNIT                  !TERMINAL OUTPUT
          INTEGER LUNIT                  !LINE PRINTER (OPTIONAL)
```

```
C
      COMMON/PRESET/ TREF,TBREAK,RABOVE,RBELOW,TSTRT
C
C     TO MODIFY DEFAULT PARAMETERS CHANGE THESE DATA STATEMENTS
C     BEFORE COMPILING
      DATA NPRINT/.FALSE./
      DATA TREF,TBREAK/43.0,43.0/
      DATA RABOVE,RBELOW/0.5,0.25/
      DATA TSTRT/41.0/
      DATA IUNIT,OUNIT,LUNIT/5,7,7/
C     SET REFERENCE AND BREAK TEMPERATURES
      WRITE(OUNIT,1000)TREF
1000  FORMAT('$ENTER REFERENCE TEMPERATURE (DEFAULT=',F5.2,'): ')
      READ(IUNIT,1010)RESP
1010  FORMAT(F10.0)
      IF(RESP.NE.0)TREF=RESP
      WRITE(OUNIT,1020)TBREAK
1020  FORMAT('$ENTER BREAK TEMPERATURE (DEFAULT=',F5.2,'): ')
      READ(IUNIT,1010)RESP
      IF(RESP.NE.0)TBREAK=RESP
C     READ IN DATA
      CALL DATRD(TEMP,TIME,ILEN,IDENT)
C     CALCULATE DOSES
      T43=SUMRF(TEMP,TIME,ILEN)
      TDM43=DGMIN(TEMP,TIME,ILEN)/(TREF-TSTRT)
C     PRINT DATA FILE
      IF(.NOT.NPRINT)GO TO 200
      WRITE(LUNIT,1050)(TIME(I),TEMP(I),I=1,ILEN)
1050  FORMAT(5(1X,'(',F6.2,')',F5.2,' '))
C     OUTPUT RESULTS
200   WRITE(LUNIT,1060)IDENT,RABOVE,TBREAK,RBELOW,TBREAK
      ITREF=INT(TREF)
      WRITE(LUNIT,1070)TSTRT,ITREF,ITREF
      WRITE(LUNIT,1080)ILEN,TIME(ILEN),T43,TDM43
1060  FORMAT(/,1X,80A1,
     +       /,4X,'R=',F5.3,3X,'FOR TEMP>',F5.1,
     +       /,4X,'R=',F5.3,3X,'FOR TEMP<',F5.1,
     +       /,1X,70(1H-))
1070  FORMAT(1X,'|',6X,'DATA',4X,'|',4X,'TOTAL',4X,'|',6X,'t',10X,
     +       '|',2X,'t',4X,'(ABOVE ',F4.1,')  |',
     +       /,1X,'|',5X,'POINTS',3X,'|',4X,'TIME',5X,'|',7X,I2,8X,
     +       '|',3X,'dm',I2,13X,'|',
     +       /,1X,70(1H-))
1080  FORMAT(1X,'|',4X,I8,2X,'|',F8.2,' MIN |',F10.2,' MIN',3X,
     +       '|',F13.2,' MIN',3X,'|',
     +       /,1X,70(1H-))
      STOP
      END
C
      FUNCTION SUMRF(TEMP,TIME,ILEN)
C
C       THIS FUNCTION CALCULATES THE EQUIVALENT TIME AT THE CHOSEN
C       REFERENCE TEMPERATURES.
C
      REAL TEMP(2000)                    !TEMPERATURE ARRAY
      REAL TIME(2000)                    !CORRESPONDING TIME ARRAY
      REAL TREF                          !REFERENCE TEMPERATURE
```

```
      REAL TBREAK                          !BREAK TEMPERATURE
      REAL TSUM                            !EQUIVALENT TIME AT BREAK TEMPERATURE
C
      REAL RABOVE                          !R VALUE ABOVE BREAK TEMPERATURE
C                                          (PRESET TO 0.5)

      REAL RBELOW                          !R VALUE BELOW BREAK TEMPERATURE
C                                          (PRESET TO 0.25)

      REAL TAVE                            !AVERAGE TEMPERATURE DURING DELTAT
      REAL DELTAT                          !TIME INCREMENT BETWEEN TEMPERATURES
      INTEGER ILEN                         !TEMPERATURE AND TIME ARRAY LENGTH
C
      COMMON/PRESET/ TREF,TBREAK,RABOVE,RBELOW,TSTRT
C     CALCULATE EQUIVALENT TIME
      TSUM=0.0
      DO 100 J=1,ILEN-1
            R=RABOVE
            TAVE=ABS((TEMP(J)+TEMP(J+1))/2.0)
            DELTAT=ABS(TIME(J+1)-TIME(J))
            IF(TAVE.LE.TBREAK) R=RBELOW
            TSUM=TSUM+DELTAT*R**(TBREAK-TAVE)
100   CONTINUE
C     CONVERT EQUIVALENT TIME AT BREAK TEMPERATURE TO REFERENCE TEMPERATURE
      R=RABOVE
      IF(TREF.LT.TBREAK)R=RBELOW
      SUMRF=TSUM*R**(TREF-TBREAK)
      RETURN
      END
C
      FUNCTION DGMIN(TEMP,TIME,ILEN)
C
C       THIS FUNCTION CALCULATES THE DEGREE*MINUTES
C
      REAL TEMP(2000)                      !TEMPERATURE ARRAY
      REAL TIME(2000)                      !CORRESPONDING TIME ARRAY
      REAL TSTRT                           !STARTING TEMPERATURE FOR
                                           DEGREE-MINUTE CALCULATION
C
      REAL TAVE                            !AVERAGE TEMPERATURE DURING DELTAT
      REAL DELTAT                          !TIME INCREMENT BETWEEN TEMPERATURES
      REAL DGMIN                           !ACCUMULATED TEMP*TIME ABOVE TSTRT
      INTEGER ILEN                         !TEMPERATURE AND TIME ARRAY LENGTH
C
      COMMON/PRESET/ TREF,TBREAK,RABOVE,RBELOW,TSTRT
C     CALCULATE ACCUMULATED DEGREES*TIME ABOVE TSTRT
      DGMIN=0.0
      DO 100 J=1,ILEN-1
            TAVE=ABS((TEMP(J)+TEMP(J+1))/2.0)
            DELTAT=ABS(TIME(J+1)-TIME(J))
            IF(TAVE.GT.TSTRT)DGMIN=DGMIN+DELTAT*(TAVE-TSTRT)
100   CONTINUE
      RETURN
      END
C
      SUBROUTINE DATRD(TEMP,TIME,ILEN,IDENT)
```

```
C
C     THIS SUBROUTINE COLLECTS TEMPERATURE DATA FROM THE TERMINAL
C           VARIABLES:
           REAL TEMP(2000)                    !TEMPERATURE VALUES
           REAL TIME(2000)                    !TIME VALUES
           BYTE IDENT(80)                     !FILE IDENTIFIER
           INTEGER ILEN                       !LENGTH OF TEMP ARRAY
           INTEGER IUNIT                      !TERMINAL INPUT
           INTEGER OUNIT                      !TERMINAL OUTPUT
C
C            WRITTEN BY S.SAPARETO     3/15/83
C            LAST REVISION:     3/15/83
C
           DATA IUNIT,OUNIT/5,7/
C     READ THE FIRST LINE IDENTIFYING THE FILE
           WRITE(OUNIT,1000)
1000       FORMAT(' ENTER IDENTIFIER (ONE LINE): ')
           READ(IUNIT,1010)IDENT
1010       FORMAT(80A1)
C     READ THE TIME AND TEMPERATURE VALUES
           WRITE(OUNIT,1020)
1020       FORMAT(' ENTER TIME(MIN),TEMPERATURE VALUES, <RET>:',
     +             /,'     (<RET> TO END DATA)')
           ILEN=0
           DO 100 I=1,2000
                READ(IUNIT,1030,END=200)TIME(I),TEMP(I)
                IF(TIME(I).EQ.0. .AND. TEMP(I).EQ.0.)GO TO 200
100        CONTINUE
1030       FORMAT(2F10.0)
200        ILEN=I-1
           RETURN
           END
C
           SUBROUTINE DATRD(TEMP,TIME,ILEN,IDENT)
C
C     THIS SUBROUTINE READS A TEMPERATURE DATA FILE OF THE FOLLOWING
C     FORM:
C               LINE 1:
C                    COLUMNS    1-9: IDENTIFIER (9A1)
C                    COLUMNS  10-13: TIME INCREMENT (I4) (SECONDS)
C                    COLUMNS  14-80: ADDITIONAL COMMENTS
C               LINE 2-END:
C                    TEMPERATURE VALUES SEPARATED BY A SPACE OR COMMA
C
C            VARIABLES:
           REAL TEMP(2000)                    !TEMPERATURE VALUES
           REAL TIME(2000)                    !TIME VALUES
           REAL DELTAT                        !TIME INCREMENT BETWEEN TEMPERATURE
C                                             VALUES

           BYTE FILNAM(14)                    !DATA FILE NAME
           BYTE IDENT(80)                     !FILE IDENTIFIER
           INTEGER ILEN                       !LENGTH OF TEMP ARRAY
           INTEGER IUNIT                      !TERMINAL INPUT
           INTEGER OUNIT                      !TERMINAL OUTPUT
```

```
C
C           WRITTEN BY S.SAPARETO     9/2/81
C           LAST REVISION:  2/14/83
C
      DATA IUNIT,OUNIT/5,7/
      WRITE(OUNIT,1000)
1000  FORMAT('$ENTER FILE: ')
      READ (IUNIT,1010) FILNAM
1010  FORMAT(14A1)
C     OPEN THE DATA FILE
      OPEN(UNIT=4,NAME=FILNAM,TYPE='OLD')
C     READ THE FIRST LINE IDENTIFYING THE FILE
      READ(4,1020)IDENT
1020  FORMAT(80A1)
      DELTAT=0.
C     DETERMINE THE TIME INCREMENT BETWEEN POINTS FROM POSITIONS 10-13
C     OF IDENT
      DECODE(80,1030,IDENT)IDELT
1030  FORMAT(9X,I4)
      DELTAT=FLOAT(IDELT)/60.
      WRITE(OUNIT,1040)DELTAT*60.
1040  FORMAT('$ENTER TIME INCREMENT (SECONDS)(DEFAULT=',F5.0,'): ')
      READ(IUNIT,1050)RESP
1050  FORMAT(F10.0)
      IF(RESP.GT.0.)DELTAT=RESP/60.
C     READ THE TEMPERATURE VALUES FROM THE FILE
100   READ(4,*,END=200) (TEMP(I),I=1,2000)
200   ILEN=I-1
C     CALCULATE THE TIME VALUES
      DO 300 I=1,ILEN
            TIME(I)=DELTAT*FLOAT(I-1)
300   CONTINUE
      CLOSE(UNIT=4)
      RETURN
      END
```