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HOLT'S TREATMENT OF CANCER WITH RADIOTHERAPY AND UHF AN HYPOTHESIS (NUMBER 5)

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ABSTRACT

Radiotherapist Dr John Holt claimed that a pre-radiotherapy treatment with UHF 434 MHz greatly increased the sensitivity of cancer to the radiotherapy. He studied this effect. An analysis of his results and the literature indicate that the UHF probably stimulates an initial spindle checkpoint based halt to mitosis, by a process that involves the factors making-up the kinetochores of the metaphase chromosomes. One kinase, aurora B, is an important player for the spindle check, and seems sensitive to SIRT2 inhibition. This may explain the UHF effect prior to cancer radiotherapy.
Conclusion: The proposed activation of deacetylase Sirtuin2 by UHF may block the Spindle Checkpoint, increasing Radio-sensitivity.

Index terms: Cancer, Radiotherapy, UHF, Spindle, Checkpoint, Sirtuin2, Aurora B, Kinetochore.

INTRODUCTION

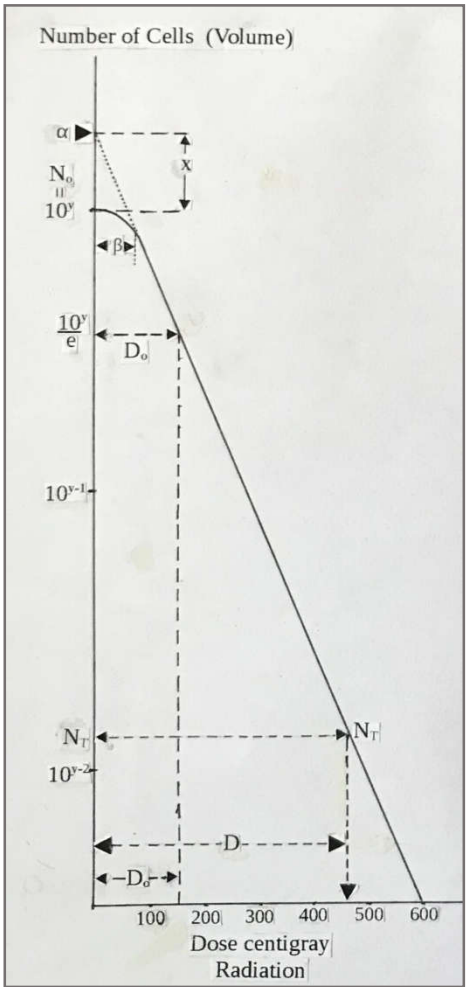
After preliminary assessments of the use of UHF clinically in the early 1970s, Dr John Holt showed an interest in exponential changes in biology (either positive or negative). Holt introduced mathematical equations into his clinical use and applications for his publications (Holt, 1977). There was reference to the study by Laird (1964). However, a graph forms the basis for the main equation (initially unattributed, but for which there were other associated references: (*Andrews, 1968; *van den Brenk, 1957, but these may be difficult to access.)

The basic graph (Figure 1) may be found in the teaching notes by van den Brenk, 1965. "It will be noted that this curve consists of two portions – an initial 'shoulder' (top left) over which increases of the dosage produces a lower rate of cell sterilization (killing) than the subsequent straight (exponential) portion. This type of curve is interpreted as meaning that the chromosomal lesion(s) induced by X-rays in a cell to cause cell sterilization is a 'multi-hit' effect and that more than one ionization must be produced within the target volume (of limited dimensions) to produce the lesion(s). If the degree of 'multi-hitness' were to increase, the width of the shoulder would also increase. If, on the other hand, a single ionization were sufficient to produce a target lesion, there would be no shoulder and the curve would be exponential throughout from zero dose onwards."

The equation as presented by Andrews (1978) is:

$S = 1-(1-e^{-kD})^n$

". . where S is the fractional survival of irradiated cells, e the natural logarithms, k is the negative slope, D is the dose and n suggests, metaphorically and not literally, the number of sensitive sites, or targets in a cell, each of which must be inactivated by a single interaction, hit or event before the cell is killed." "In the exponential portion of the curve the rate of cell killing is constant because in all cells n-1 targets have been activated, or hit, and only one target or sensitive site remains to be inactivated to cause cell death."



The graphs/equations were introduced to his practice utilizing target theory . . . "known as the 'multitarget, single hit' type.' . . ."used by Holt and remained essentially unchanged for the rest of his Medical practice duration.

Quoted by Holt (drawn from Andrews) :

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$N_r = N_t[1-(1-e^{-D/D_0})^x]^y$

Where:

N_T = tumour cell numbers remaining after treatment

D = radiation dose [centigray (cGy)] per treatment (day)

D_o = is the radiation dose required to obtain $N_T = N_{T/e}$

y = number of radiation doses (days) of D cGy

x = constant for each cancer

For the graph (Figure 1):

α represents the hypothetical number of cells (volume) at the start of radiotherapy;

n_0 represents the number of viable cells (volume) present at the start
x represents the hypothetical cell number lost, presumably by successful lethal "hits."

Examination of Figure 1 shows that an increasing value of x will have the exponential-phase line more to the right and the β dose increase and related to an higher D_o dose, with an associated increased resistance of the cancer.

Figure 1 How Holt collected clinical data for the equations has been described (Holt, 1983). "Estimation of tumour volumes before treatment was by calliper measurement, aided by computerized x-ray scans or tomography or other device if it was indicated, and used for substitutes for n_0 in the equations. The post-treatment volumes were estimated in one of two ways. Where the measurable masses remained, they were reassessed by similar techniques. If complete resolution occurred, the patients were followed-up for as long as possible before the residual volume n_1 was estimated. All patients who developed a clinically detectable recurrence in the treated area were then assumed to have at least 1 ml of cancer present (or more if it was measured at a greater volume). Assuming a doubling time of 30 days, the volume of cancer which probably existed at the cessation of therapy was calculated and used as 'n_1'. If the site was recurrence-free at 12 months, it was assumed the 'n_1' was less than 10-4 ml, and this number was used in the equation." Not a short-term project. He collected a sizeable amount of clinical data.

His main interest at this stage was the radio-sensitivity (D_0), and he presented two tables detailing results from many patients, so illustrating the radio-sensitivities of 27 patients and the values of D_0 values, here condensed. (Sadly, he did not seem to reveal the values of x that he would have measured.)

Table 1 Adapted from Holt (1983)

Prior RT Dose (cGy)	D_0 (cGy)	Recent RT, Dose, (cGy)	Recent D_0 (cGy)
Mean = 5880	368	Mean = 981	20.4
SD = 2220	225	SD = 375	8.95
Number = 27		Number = 27	

RT=Radiotherapy, cGy=centiGray, SD=standard deviation

Holt's estimates for x

Cancer/tissue	Number of x units/cell (estimated)
Squamous cell carcinoma – skin (body)	x= 2-4, rarely >7
Squamous cell carcinoma (Head/neck)	x= 4 → ?, rarely <4
Cervix uteri	x → 15, occasionally 15-20
Limb (anoxic)	x ~ 15 or more
Hyperbaric oxygen "HBO_2"	x= 3-7 &HBO_2 → <2
Heating → 41.8 °C	x→ >2
UHF before Radiotherapy	x→ 1

In a later publication (Holt,1995) he gave attention to the (per patient) constant x ("n" by Andrews, 1978). He hypothesized and believed that the x units in the formula represented intracellular energy-creating units, being "hit" or damaged by the X-rays, (which he had labelled ERex &/or Rexp &/or Re from time to time; Re-redox cycles). He proposed (Holt, 2000a) that:

"The number of ERex in a cancer cell varies from 2 to at least 25, perhaps 40 or more (*van den Brenk, 1959). A cancer cell only requires two (or rarely 3) 'active' [Re-redox cycles] to keep it alive. All others are 'inactive.' Each cell has 1-2 'active' x units. Cancer cells could have more units, but only 1-2 would be 'active.'" "x is the number of targets per cell which must be destroyed to kill that cell." Whilst these concepts stimulated his enquiries and research, his interpretation and belief in the roles of the x units may not be considered viable today. *Quoted by Holt 2000a

Holt believed that the average number of x units per cell in a tumour was related positively to the degree of radio-resistance shown by the tumour.

Whilst he presented x briefly (Holt, 1995) it is not until 2001 that a more complete study of x and amended formula, to include Z, the temperature factor, 1 at 38°C, rising to 2.0 at 41.8°C; the other factors being- the N_g cells that survive from the initial N_0 subjected to D centiGy X-ray over y daily doses. D_0 and x are constants for each particular cancer; N_0 = initial tumour size, N_g = residual tumour after daily doses of D centiGy, D_0 is the radio sensitivity value in centiGy and x is the number of targets per cell which must be killed for the cell to die. A is the growth rate and T the time between N_0 and N_g.

There is the strange similarity regarding the calculated numbers of x units in normal and cancer patients and the numbers of centrioles reported in normal and malignant cells. The latter could be markers for (example) centrosome formations, with their associated enzymes attachments (e.g. the anaphase-promoting complex/cyclosome [APC/C]).

Spindle Checkpoint

By examination of the graph, the Xray dose(time) represented by β, is the dose (time) during which there is no, or minimal, cell death. The most likely cause for this is a checkpoint halt to mitosis, allowing time for the DNA repair processes to operate (reducing Xray sensitivity) for which the spindle checkpoint seems most likely. Any fault or mismatch in the linking of the spindle microtubules and the appropriate kinetochores on chromosome(s), results in the checkpoint being activated, and further progress in the mitosis halted for a time, thereby giving an opportunity for corrective reparation actions to be undertaken.

Work on this by Mikhailov *et al.,* 2002 indicated that "significant damage" (from pulsed Ultra Violet [UV] light) "substantially delays exit from mitosis . . . in human cells this delay occurs during metaphase." The suggested explanation is "extensive chromosomal damage . . . produces one or more 'wounded' kinetochores; these then have a difficult time maintaining a proper (stable) attachment to the spindle." Typical delays *in vitro* were 5 hr (usual control ~ 1 hr). (*In vivo* delays would likely be longer.)

The assumption here is that the ionizing X-ray dosing is at least as damaging to the chromosomes as UV light, making the activation of

the spindle checkpoint likely and producing the shoulder in the graph of figure 1.

UHF SENSITIZER

Holt's claim that UHF sensitized cancer to Xray treatment seemed supported by his calculations of D_0 (see above). But the reason remained an enigma, generating skepticism.

In a previous essay, an hypothesis was presented that the UHF administered by Holt before radiotherapy could start a chain reaction:

UHF➔NQO1/NAD(P)H➔NAD+↑➔ SIRT2↑➔Aurora B kinase↓ ➔ metaphase malfunction↓➔ Checkpoint halt

Checkpoint Operation & Vulnerability

Participants in the checkpoint operation may be divided into 2 main groups :

- **Messengers**: Mad1, Mad2, BubR1 etc.

This group is stimulated by the failure of one or more microtubules to attach to an appropriate kinetochore and drives the checkpoint machinery to halt mitosis at metaphase.

Whilst lack of Mad2 &/or BubR1 speeds-up mitosis (Meraldi *et al..* 2004) mechanisms to block the messengers, once activated, are not obvious.

- **Helpers**: Kinetochore site preparation, (pre-microtubule-kinetochore attachment);

Spindly, Dynein-1, RZZ, POLO, Aurora A, Aurora B, NDC80, etc. Barbosa, *et al.,* (2020) reports that the kinase Aurora B seems to play a key role in modulating the kinetochore-microtubule attachments through phosphorylation of several kinetochore proteins. Interference at this level seems a more promising vulnerability.

Checkpoint inhibition: Increased expression of SIRT2 (as believed to occur following Holt's UHF 434 treatments; Traill, 2022) may reduce the activity the levels of the kinases Aurora A and B in HeLa cells (Kim 2011). Such effects in cancers may impede the initiation of the Spindle Checkpoint response and provide an explanation that may support Holt; that the UHF boosted the cancer sensitivity to radiotherapy. This response would be mitosis related, less like the earlier hypothesis relating a checkpoint halt induced by radiation damage on intranuclear structures, especially the nucleoli (Traill 2023). The relative importance of each needs to be determined.

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