THE MECHANISM OF RADIATION CARCINOGENESIS

(a) An Explanation of the Illusory Effect of Protraction of Radiation in Reducing Carcinogenesis for low LET Radiation.

(b) An Explanation of R.B.E. for Carcinogenesis.

(c) An Explanation of why Protracted High LET Radiation is as Effective (or more) as Acute Low LET Radiation in Carcinogenesis.

(d) The Unlikely Prospect that Protraction Will In Any Way Mitigate the Carcinogenic Effect of Radiation in Man.

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INTRODUCTION:

All responsible bodies concerned in setting standards for radiation of humans properly discount the possibility that fractionation of the radiation over time will mitigate carcinogenic effects of ionizing radiation[1]. Nevertheless, everyone, ourselves included, has always cherished the fond hope that perhaps fractionation of radiation might in some way mitigate the carcinogenic risk.

There are those who speak of "repair" - meaning that in some way, not known, cells will repair damage that is carcinogenic, provided enough time elapses between successive radiation insults. No logic ever was presented that was particularly satisfying for what the mechanism of such "repair" might be, but since "hope springs eternal", we, for a long time, participated in such hopes - especially since the outlook is so unfavorable without this hope.

However, our recent researches have led us to examine the experimental animal data which underly such hopes for fractionation protection, and as a result of careful analysis, we feel that all such hopes are essentially without foundation, and extremely unlikely ever to materialize.

Recently Dr. John Totter, specifically[2], and AEC-DBM in "Comments"[3] on our work have both indicated that we have largely ignored experimental animal data which suggest a lesser carcinogenic risk of fractionated radiation. While it should be emphasized that their comments should be totally irrelevant in the field of setting standards (witness ICRP approach), we do wish to comment on the totally erroneous AEC-DBM statements. We have certainly not "largely ignored" the experimental animal data. Indeed we have, for a long period, been studying such data and had planned to write in extenso why

we don't believe they provide any hope whatever for fractionation in the mitigation of radiation carcinogenesis. Certainly, as any responsible public health official knows, such experimental data should not be part of the proper conservatism expected in the consideration of standards. This is why we omitted such considerations in our IEEE Paper and in the Senate Subcommittee Hearings[4][5].

However, by now our researches are far enough along to allow us to make a presentation of why we consider the experimental data concerning fractionation protection to be an illusion, not a reality. Further, the presentation will allow us to present an integrated concept, including differences between protracted and acute low LET radiation, high LET versus low LET radiation, and the real nature of RBE (= relative biological effectiveness) for carcinogenesis.

The results lead us to be even more pessimistic concerning the expected number of additional cancers per year from FRC Guideline exposure than we previously were.

A PROPOSED MECHANISM FOR RADIATION CARCINOGENESIS

If the age-specific mortality rates in humans, for a particular cancer, are examined, it is noted that there is a rising age-specific mortality with age, and that for many cancers, there is a period of life where age-specific mortalities double over a five-year period. At some phases of life, and for certain cancers, the period may be less than five years or more than five years for this age-specific mortality doubling. For certain malignancies, e.g. leukemia, the age-specific mortality curve is complicated by an early peak, a decline with age, and then a steep rise.

While, for this analysis, we could have used any other period for the rate to double, we shall choose, as a reference, five years as the time to double the spontaneous incidence of a particular type of human cancer. No conclusions we draw will be materially altered if 6, 7, or 8 years were to be used as the doubling time. This concept of doubling time is hardly controversial, since it is just obvious from Vital Statistics[6].

Next, for a specific form of cancer that has been proved to be radiation-induced, there exists a dose of radiation that produces an excess of that cancer equal to its spontaneous rate of occurrence. This dose we have referred to as a doubling dose of radiation for that particular cancer. Furthermore, our analysis of data for specific cancers indicates that the doubling dose doesn't vary appreciably over a wide interval of total doses[7][8][9]. This is what we mean when we use "linear" theory. Indeed, everything we have to demonstrate below does not require absolute constancy of doubling dose over all dosage ranges.

Previously we suggested that this doubling dose is approximately 5 rads in-utero or in early infancy, and increases to $\sim$ 100 rads in adult life[5]. We had suggested that considerable evidence suggested the adult doubling dose might be much lower than 100 rads.

Most of our recent examinations of data suggest 50 rads to be closer than 100 rads for the doubling dose for human cancers in adult life. We shall use 50 rads as the doubling dose here. Other values could be chosen without alteration of the principles to be presented below - the essential point is that the doubling dose increases as we go from early infancy to adulthood.

(a) Translation of Doubling Dose to "Effective Aging"

If 5 years of adult life doubles the age-specific mortality for a particular cancer, and if, separately, 50 rads of ionizing radiation doubles

that mortality similarly, it has been widely suggested, especially by Jones[10], that the radiation dose can be translated into a specified number of years of "effective aging", at least for carcinogenesis.

We shall make this translation, and state, for adults at 30 years of age,

5 adult years is equivalent to 50 rads, or

1 rad = 0.1 adult year.

At the beginning of infancy, 5 rads appears to double the future incidence of cancer, so we can say 5 rads, in the milieu of the first year of life (or in-utero) is equivalent to 5 adult years of "effective aging" with respect to cancer production, or

in early infancy, 1 rad = 1.0 adult year.

In the intervening years, between 0 years of age and 30 years of age, the milieu changes so that 1 rad drops from 1.0 adult year finally to 0.1 adult year. We shall explore more than one shape of curve for this transition. The shape of this curve is not crucial for the general principles, although, as will become obvious, it is important for absolute values.

(b) Low LET Radiation (x-rays, γ-rays, βparticles) and the Illusory Protection Against Cancer by Protraction of Radiation

Upton is a leader in this general field of investigation. Recently, he pointed out the following: "In general, irradiation at a high dose rate is more effective than irradiation at a low dose rate, at least in the case of radiation of low linear energy transfer (LET), such as x-rays and gamma rays. When fractionated into several exposures of intermediate size and periodicity, however, a dose may be more tumorigenic than when given in a single brief exposure".[11]

DBM-AEC conveniently overlooks this last sentence when they herald the protection from fractionation. But to be as optimistic as possible, we will join DBM in overlooking that sentence, and focus on the "hopeful" side of the quotation - namely, that for low LET radiation a high dose rate is more carcinogenic than a low dose rate.

From what types of experiments does this hopeful note emerge? Upton has provided two representative experiments of the hopeful variety; (a) one for myeloid leukemia induction in RF male mice by Co^{60} gamma rays delivered chronically (0.0006 rads/min.) versus a single acute exposure of x-rays at 50-100 rads/minute delivered at 8-10 weeks of age; (b) a similar experiment for ovarian carcinogenesis on 10-week old RF female mice for γ rays at 7 rads per minute versus 5 rads per day.

Both experiments show that the final incidence of the particular leukemia, or ovarian cancer, is lower for the protracted radiation than for the acute radiation. Many people interpret such experiments to mean "repair" with respect to carcinogenesis is occurring in the protracted radiation. There is not the slightest scientific evidence for any such "repair", and indeed there is a more plausible explanation - an explanation that not only interprets these findings, but also predicts the difference between low LET and high LET radiation carcinogenesis. We shall provide this explanation below, but first we must examine the parameters of the experimental animal situation and translate them, as best as possible, to the relevant human situation. Let us consider the RF male mouse myeloid leukemia study.

Approximate Comparisons

	MOUSE (RF Male Mice)	MAN
Life Span:	~ 700 days	~ 70 years
Acute dosage delivered:	~ 60-70 days of life (1/10 life span)	~ 7-8 years of age (~ 1/10 life span)
Chronic Dosage:	0.0006 rads/min=0.86 rads/day	~ 0.86 rads for 1/10 year or
or	0.86 rads per 1/700 life span	~ 8-10 rads/year

Now, if we were to do a comparable experiment in humans, would a lesser carcinogenic effect be observed by protraction? Would this argue for repair? Let us see.

(c) An Explanation for the Apparent Effect of Protraction of Radiation in Reducing Carcinogenesis for Low LET Radiation

We shall use comparable parameters to those of Upton, and study in man:

(a) Response to 0-100 rads of Low LET radiation

(b) Acute dose to be delivered at 8 years of age

(c) Chronic dose to be delivered at doses of 10 rads per year or even at lower dose rates, starting at 8 years of age.

(d) Calculate the comparative expectancy of cancer later in life. (Similar in general to the Upton type of experiment).

WE SHALL USE OUR TRANSLATION OF RADS TO "EFFECTIVE AGING" IN ADULT YEARS AND BASIC PHYSICS.

Low LET Radiation interaction with matter

At 1 MEV or less x-rays and γ-rays deliver energy to tissue through their photo-electric or Compton conversion to electrons, so we can cover this group of radiations by consideration of β-particles.

1 rad=100 ergs/gram $= 6.25 \times 10^7$ MEV/gram.

For 1 MEV β-particles, this means 6.25×10^7 β-particles per gram.

The range in tissue for 1 MEV β-particles is ~ 4000 microns.

For a large cell (20 micron-diameter), a 1 MEV β-particle traverses 200 cells, on the average.

Therefore, 6.25×10^7 β-particles traverse 1.25×10^{10} cells.

For cells of ~ 20 microns, Volume $\simeq 4 \times 10^3 \mu^3$, so there are

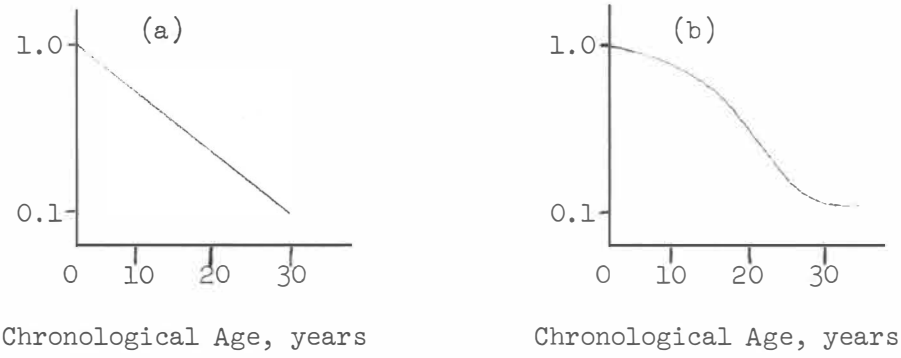
$\frac{10^{12}}{4 \times 10^3} = 2.5 \times 10^8$ cells per gram of tissue cells.

Obviously, this means each cell is traversed much more than once for delivery of 1 rad ($\frac{1.25 \times 10^{10}}{2.5 \times 10^8} \simeq 50$ times). So for βparticle irradiation, we can say that one rad will provide approximately uniform irradiation of the cells. (As we shall see later, this is not so for high LET radiation, such as α particles).

Now previously we set $\begin{cases} \text{at age 30 years} & 1 \text{ rad} = 0.1 \text{ year of aging} \\ \text{at birth} & 1 \text{ rad} = 1.0 \text{ year of aging} \end{cases}$

Change rate in the intervening period, we do not know, so we shall consider two possibilities, shown in the figure below.

Figure 1



Tabular Values for 1 rad (Effective Years of Aging) Curve (a)	
Age (years)	Value per rad (years)
0	1.0
2	0.62
4	0.46
6	0.36
8	0.29
10	0.25
12	0.22
14	0.19
16	0.17
18	0.156
20	0.143
22	0.132
24	0.122
26	0.114
28	0.106
30	0.100
> 30	0.100

Tabular Values for 1 rad (Effective Years of Aging) Curve (b)	
Age (years)	Value per rad (years)
0	1.0
2	0.77
4	0.64
6	0.55
8	0.46
10	0.30
12	0.205
14	0.15
16	0.125
18	0.11
20	0.106
22	0.103
24	0.101
26	0.100
28	0.100
30	0.100
> 30	0.100

Now let us compare acute and chronic radiation with low LET radiation, using first Curve (A) and then Curve (B) for the variation in value per rad at the various chronological ages.

Curve (A) calculations

10 Rads Total Dose - Acute Delivery at 8 Years of Age

At age 8 years, 1 rad = 0.29 years of "Effective Aging"

Therefore, 10 rads = 2.9 years of "Effective Aging"

Chronic Delivery of 10 rads - at 1 rad per year for 10 years starting at age 8

1 rad in 8th year	Value per rad	=0.29	years "effective aging"
1 rad in 9th year	"	=0.27	" "
1 rad in 10th year	"	=0.25	" "
1 rad in 11th year	"	=0.23	" "
1 rad in 12th year	"	=0.22	" "
1 rad in 13th year	"	=0.21	" "
1 rad in 14th year	"	=0.19	" "

1 rad in 15th year	Value per rad=0.18 years	"effective aging"
1 rad in 16th year	" =0.17	" "
1 rad in 17th year	" =0.16	" "
Total 10 rads over 10yr period	=2.17 years of	"effective aging"

In an entirely analogous manner we can calculate the "effective years of aging" for 20 rads, acute and chronic, 30 rads, acute and chronic, etc. etc. out to any dose we choose. Presented in Table 1 are the results out to 100 rads.

TABLE 1 (Data from Figure 1a)

Accumulated Effective Years of Aging by Acute vs Protracted Radiation (low LET) Delivered at 8th Year (Human) Acute vs over a 10-year Interval

Total Dose Accumulated (low LET)	Acute Exposure (8th year)	Protracted (delivered between 8th-18th years)
	Cumulative Effective Years of Aging	
10 rads	2.9 years	2.17 years
20 rads	5.8 "	4.34 "
30 rads	8.7 "	6.51 "
40 rads	11.6 "	8.68 "
50 rads	14.5 "	10.85 "
60 rads	17.4 "	13.02 "
70 rads	20.3 "	15.19 "
80 rads	23.2 "	17.36 "
90 rads	26.1 "	19.53 "
100 rads	29.0 "	21.70 "

Now, in the usual type of experiment of this sort, one examines either the total accumulated cancers out to death, or the cancer occurrence rate at some later period in life. Both are valuable, but the major features of the story can be discerned by looking at age-specific mortality rate at, say, 40 years of age, chronological.

To determine the cancer mortality, we shall use the age-specific mortalities for all malignant neoplasms combined, derived from U. S. Vital Statistics for 1966 (USA)(Males)[6]. Any specific malignant neoplasm could

be studied, and indeed the results obtained will depend upon the age-specific mortality data for that neoplasm.

Reproduced in Table 2 are the Age-Specific mortalities for all malignant neoplasms by age.

TABLE 2

Age-Specific Mortalities, Males, All Malignant Neoplasms -

(Based upon USA - 1966 - Vital Statistics)

Chronological Age (Years)	Age-Specific Mortality (All Malignant Neoplasms) (Cases per 10^6 persons per year)
Under 1 year	52.4
1-4 years	88.2
5-9 "	78.1
10-14 "	68.2
15-19 "	91.6
20-24 "	113.8
25-29 "	141.3
30-34 "	215.0
35-39 "	368.0
40-44 "	691.4
45-49 "	1262.0
50-54 "	2382.5
55-59 "	3918.4
60-64 "	5980.6
65-69 "	8712.5
70-74 "	11365.8
75-79 "	13568.4
80-84 "	15723.7
85 and above	18123.2

Now we can tabulate, for chronological age 40 years, both the effective ages (chronologic + radiation aging calculated above) for the acute and chronic irradiation, and the mortalities from all malignant neoplasms (from Table 2) for both groups.

TABLE 3

CANCER MORTALITY IN RELATION TO ACUTE VS PROTRACTED RADIATION

(40 Years Chronological Age)

RADS	ACUTE RADIATION		PROTRACTED RADIATION	
	"Effective Age" (years)	Cancer Mortality (per 10^6/yr)	"Effective Age" (years)	Cancer Mortality (per 10^6/yr)
0	40.0	550	40.0	550
10	42.9	800	42.17	710
20	45.8	1130	44.34	970
30	48.7	1650	46.51	1200
40	51.6	2320	48.68	1650
50	54.5	3150	50.85	2140
60	57.4	4100	53.02	2700
70	60.3	5400	55.19	3250
80	63.2	6600	57.36	4060
90	66.1	8170	59.53	5050
100	69.0	9750	61.70	5750

Clearly, there are many more cancers in the acute irradiation group than the chronic irradiation group, but it all derives from the fact that the chronic irradiation was delivered at later and later periods of life when the effectiveness per rad is decreasing. So, instead of invoking mysterious, unknown "repair" mechanisms, we have an obvious explanation based upon known phenomena. Namely, irradiation early in life is much more serious in increasing cancer occurrence than irradiation later in life. These data are even more striking when presented as the excess, radiation-induced cancers in the next table.

TABLE 4

RADIATION INDUCED (EXCESS) CANCERS FOR ACUTE vs PROTRACTED RADIATION
(At Chronological Age 40 years)

Dose (Rads)	ACUTE RADIATION Excess Cancers 10^6/yr.	CHRONIC RADIATION Excess Cancers 10^6/yr.	RATIO Acute/Chronic
0	0	0	----
10	250	160	1.56
20	580	420	1.38
30	1100	650	1.69
40	1770	1100	1.61
50	2600	1590	1.64
60	3550	2150	1.65
70	4850	2700	1.80
80	6050	3510	1.72
90	7620	4500	1.69
100	9200	5200	1.77

The factor of difference between acute and chronic exposure depends in part upon what age the mortalities are calculated for (40 years here), and the factor will be highly sensitive to the shape of the curve relating doubling dose at birth and at 30 years of age. These curves were demonstrated as Figure 1(a) and (b).

Let us now recalculate the story using Figure 1(b) for the value of 1 rad in "effective years of aging" from birth out to 30 years.

TABLE 5 (Data from Figure 1b)

Accumulated Effective Years of Aging by Acute vs Protracted Radiation (low LET)
Delivered at 8th Year (Human) Acute vs over a 10-year Interval

Total Dose Accumulated (low LET)	Acute Exposure (8th year)	Protracted (delivered between 8th-18th years)
	Cumulative Effective Years of Aging	
0	0 years	0 years
10	4.6 "	2.32 "
20	9.2 "	4.64 "
30	13.8 "	6.96 "
40	18.4 "	9.28 "
50	23.0 "	11.60 "
60	27.6 "	13.92 "
70	32.2 "	16.24 "
80	36.8 "	18.56 "
90	41.4 "	20.88 "
100	46.0 "	23.20 "

Now we can calculate the effective ages and the corresponding "all malignant neoplasm" mortalities as before. These are presented in Table 6.

TABLE 6

CANCER MORTALITY IN RELATION TO ACUTE VS PROTRACTED RADIATION

(40 Years Chronological Age)

RADS	ACUTE RADIATION		PROTRACTED RADIATION	
	"Effective Age" (years)	Cancer Mortality (per 10^6/yr)	"Effective Age" (years)	Cancer Mortality (per 10^6/yr)
0	40.0	550	40.0	550
10	44.6	1000	42.32	720
20	49.2	1760	44.64	1000
30	53.8	2950	46.96	1250
40	58.4	4550	49.28	1780
50	63.0	6500	51.60	2320
60	67.6	9000	53.92	2980
70	72.2	11450	56.24	3720
80	76.8	13470	58.56	4600
90	81.4	~ 15700	60.88	5350
100	86.0	~ 16000-17000	63.20	6600

It can be noted here, for 50 rads, the ratio $\left(\frac{\text{acute,excess}}{\text{chronic,excess}}\right) = \frac{5950}{1770} = 3.36$ in contrast with 1.64 for the data derived from Figure 1a. Thus, <u>how</u> the doubling dose curve goes up from birth to 30 years is highly determinative of the <u>illusory</u> protection afforded by protraction.

We would like to compare our human curve more closely with Upton's mouse curve, but to do so requires knowledge of the precise nature of the doubling dose variation with age, and also would require the age-specific incidence of myeloid leukemia at specified periods in life for the mouse, which is not provided[11]. The general features are clearly similar in making it <u>appear</u> that protraction lessens carcinogenesis. In Upton's data, which are excellent, the delivery of 300 rads protracted, at 0.86 rads per day means 300/0.86 = 349 days after initiation of experiment at 60 days of life to deliver the dose to the mouse. Since this is ~ $\frac{1}{2}$ the life span of the mouse, the correspondence in humans would require spreading the dose

out to 35 years or later. If we did this, we would be delivering most of the dose in the lower sensitivity adult period compared with the very sensitive childhood period. The calculation would be straightforward, and would lead to an enormous difference between acute and protracted radiation. Upton also found that as he moved up beyond 300 rads (> some 20 doubling doses) the leukemia incidence began to decline. We suspect this means the cells were effectively so aged they could no longer respond with leukemogenesis. Human evidence indicates that malignancy curves slow their rise at very advanced ages. Upton proved (see p.27) decreased sensitivity to radiation leukemogenesis beyond 70 days in mice.

In summary, this analysis of low LET radiation indicates that protracted radiation does precisely what it is expected to do when account is taken of the radiation being delivered later in life, when the doubling dose is higher than in childhood. Acute radiation also does what is expected - when all of it is delivered in early childhood, the carcinogenesis is severe, just as is predicted.

It may be pointed out that in almost all the literature, experiments showing the illusory protection by fractionation, the acute irradiation is performed early in life and the protracted irradiation is started at the same point, but continued into a much later part of the life span. One wonders why the experimenters, in the name of thoroughness, do not always do the additional acute exposure at the end of the protraction period as well as at the beginning. We suspect a psychologic factor may operate here. In any event, this issue is of the greatest relevance in our considerations. Let us calculate the expected results. The data for 100 rads total exposure of low LET radiation can be utilized to test this crucial issue. In Table 3 a comparison is made:

100 rads delivered acutely in the 8th year of life
100 rads delivered, protracted, at 10 rads per year
from the 8th through the 17th year of life, inclusive.

We must now add the calculation for 100 rads delivered acutely at the end of the protraction period, namely at 17th year of life.

From Figure 1a, we have 1 rad = 0.158 years of aging.
Therefore, 100 rads = 15.8 years of aging.

Now we can calculate the expected cancer mortalities for all three groups at a chronological age of 40 years.

Radiation Group	Effective Age	Cancers per 10^6/year
100 rads delivered acutely (8th year of life)	69.0	9750
100 rads delivered at 10 rads per year protracted (8th-17th year of life)	61.7	5750
100 rads delivered acutely (17th year of life)	55.8	3540
Spontaneous	40.0	550

Note: The protracted radiation produces a much higher cancer mortality (5200 excess cases per 10^6/year) than the same total dose delivered acutely in the 17th year (2990 excess cases per 10^6/year)! If most experimenters had delivered their acute radiation dose at the end of the protraction period rather than at the beginning, the literature would by now be filled with a different illusion - namely, that protracted radiation is more carcinogenic than acute radiation.

The view that is correct, in all probability, is that fractionation has nothing at all to do with the carcinogenic effect, if due account is taken of the sensitivity of the cells to radiation varying with age of the

experimental animal or human. Again, this simply points out the great hazard of irradiation early in life.

Thus, all the "protection" afforded by protraction in such experiments is illusory. There is not one shred of evidence requiring "repair" mechanisms to be operative to explain the observations. And as we shall see below, the consideration of high LET radiation makes these comments even more relevant.

HIGH LET RADIATION

The Explanation of why even Protracted High LET Radiation is as Effective (or more) as Acute Low LET Radiation.

High LET Radiation Interaction with Matter

Many mysterious explanations have been suggested for the inordinately high effectiveness of high LET radiation, such as greater density of ionization along the track being more damaging, or less likely to be "repaired". We shall require none of these mysterious explanations and base our analysis only upon:

(a) Linear hypothesis, indicating risk per rad is the same for high LET radiation as for low LET radiation

plus (b) The physics of the interaction of high LET radiation with matter.

For illustrative purposes, we shall use 5 MEV Alpha Particles. (One could study fast neutrons, protons or deuterons just as well).

Let us consider two sizes of cells, 10 microns in diameter, and 20 microns in diameter. This pretty well covers the general classes of mammalian cells. And as we shall see, the cell diameter is critical with respect to the effect of high LET radiation.

10 micron diameter cells interacting with 5 MEV α particles

As before, 1 rad = 6.25×10^7 MEV/gram

For 5 MEV α particles, this means $\frac{6.25 \times 10^7}{5} = 1.27 \times 10^8$ α particles/gram

For 10 micron diameter, cell volume = $4/3\pi(5)^3 = 523.7\mu^3$.

$\therefore$ Cells per gram tissue = $\frac{10^{12}}{523.7} = 1.910 \times 10^9$ cells.

Range, in tissue, of 5 MEV α particles = 45 microns[12].

Therefore, average alpha particle traverses $\frac{45}{10} = 4.5$ cells.

For 1.25×10^7 α particles per gram corresponding to 1 rad,

then, $1.25 \times 10^7 \times 4.5 = 5.62 \times 10^7$ cells traversed.

But 1 gram of cells = 1.91×10^9 cells.

Therefore, 1 rad can provide α particles traversing only

$$\frac{5.625 \times 10^7}{1.910 \times 10^9} = 0.02943, \text{ fraction of cells.}$$

Note: The delivery of 1 rad of 5 MEV alpha particles leaves 97.06% of the cells receiving no radiation. Thus, this represents highly uneven irradiation, and this is of the utmost importance in explaining the effects observed.

Furthermore, we must now give consideration to the Bragg curve for specific ionization along the 5 MEV alpha particle track. From Lapp and Andrews[12], we can say, approximately, that for 5 MEV alpha particles, the ionization per unit path is 2x as high in the last half of the range as in the first half. Therefore, even for those cells that are traversed, one-half of them get twice the dosage of the other half.

For 1 rad, we saw above that 0.02943 is the fraction of 10 micron cells traversed.

Thus $(\frac{1}{2})(0.02943) = 0.014715$ is the fraction receiving twice the dose received by the other 0.014715 fraction.

Let x = the dose in rads received by the cells in the first half of the range for total delivery of 1 rad of 5 MEV α particles.

Then 2x = the dose in rads received by the cells in the second half of the range.

The vast bulk of cells (fraction = 0.9706) receive no dose.

Now calculate x, for the delivery of 1 rad overall.

$(0.014715)(2x) + (0.014715)(x) + (0.97057)(0) = 1.0$

$(0.044145)(x) = 1.0$

$$x = \frac{1}{0.044145} = 22.65 \text{ rads}$$

$2x = 45.30$ rads.

Therefore, the delivery of 1 rad of 5 MEV α particles gives rise to a population of cells which to a very close 1st approximation is as follows:

0.014715 of the cells receive 45.30 rads as dose

0.014715 of the cells receive 22.65 rads as dose

0.97057 of the cells receive No irradiation

Now, for the successive delivery of 1 rad followed by another and another, we must apply this same distribution to the members of each of these 3 populations. We shall go through this for a total dose of 2 rads and of 3 rads to illustrate the principles. For more extensive dosage, either some equations will be utilized or a computer iteration performed. For now, the study of 1 rad, 2 rads, 3 rads will suffice, including a study of carcinogenesis by acute low LET radiation versus high LET radiation.

So, for 1 rad total we have the distribution above. Now let us add the 2nd rad to each population:

The 0.014715 fraction of cells having received 45.30 rads

$(0.014715)(0.014715) = 0.0002165$ receive 45.30 rads more

$(0.014715)(0.014715) = 0.0002165$ receive 22.65 rads more

$(0.014715)(0.97057) = 0.0142819$ receive no additional radiation

Now go on to the fraction of cells that had received 22.65 rads at the first rad overall

The 0.014715 fraction of cells having already received 22.65 rads

(0.014715)(0.014715) = 0.0002165 of cells receive 45.30 rads more

(0.014715)(0.014715) = 0.0002165 of cells receive 22.65 rads more

(0.014715)(0.97057) = 0.0142819 of cells receive no additional radiation

Lastly, the

0.97057 fraction of cells having received 0 rads during lst rad overall

(0.97057)(0.014715) = 0.0142819 of cells receive 45.30 rads more

(0.97057)(0.014715) = 0.0142819 of cells receive 22.65 rads more

(0.97057)(0.97057) = 0.9420060 of cells receive no additional radiation

Now let us total these up, after 2 rads overall

0.0002165 + 0 = 0.0002165 of cells have received 90.60 rads

0.0002165 + 0.0002165 = 0.0004330 of cells have received 67.95 rads

0.0142819 + 0.0002165 + 0.0142819 = 0.0287803 of cells have received 45.30 rads

0.0142819 + 0.0142819 = 0.0285638 of cells have received 22.65 rads

0.942006 = 0 = 0.9420060 of cells have received no radiation

Total = 1.000,000

2 rads overall

Fraction of Cells	Dose
0.0002165	90.60 rads
0.0004330	67.95 rads
0.0287803	45.30 rads
0.0285638	22.65 rads
0.9420060	0 rads

Now we can consider each of these sub-populations when the 3rd rad is added.

The 90.60 rad group

(0.0002165)(0.014715) = 0.00000319 receive additional 45.30 rads

(0.0002165)(0.014715) = 0.00000319 receive additional 22.65 rads

(0.0002165)(0.97057) = 0.00021013 receive no additional radiation

The 67.95 rad category

(0.0004330)(0.014715) = 0.000006372 receive additional 45.30 rads
(0.0004330)(0.014715) = 0.000006372 receive additional 22.65 rads
(0.0004330)(0.97057) = 0.000420257 receive no additional radiation

The 45.30 rad category

(0.0287803)(0.014715) = 0.0004235 receive additional 45.30 rads
(0.0287803)(0.014715) = 0.0004235 receive additional 22.65 rads
(0.0287803)(0.97057) = 0.0279333 receive no additional radiation

The 22.65 rad category

(0.0285638)(0.014715) = 0.0004203 receive additional 45.30 rads
(0.0285638)(0.014715) = 0.0004203 receive additional 22.65 rads
(0.0285638)(0.97057) = 0.0277232 receive no additional radiation

The 0 rad category

(0.9420060)(0.014715) = 0.0138616 receive additional 45.30 rads
(0.9420060)(0.014715) = 0.0138616 receive additional 22.65 rads
(0.9420060)(0.97057) = 0.9142828 receive no additional radiation

Now, after 3 rads, we have a population distribution of the following doses, which we must calculate by combining groups above:

135.90 rad category
113.25 " "
90.60 " "
67.95 " "
45.30 " "
22.65 " "
0 " "

The 135.90 Category

0.00000319 fraction of cells

The 113.25 Category

0.00000319 + 0.00000637 = 0.00000956 fraction of cells

The 90.60 Category

0.00021013 + 0.00000637 + 0.00042350 = 0.00064000 fraction of cells

The 67.95 Category

0.00042030 + 0.0004235 + 0.0004203 = 0.0012641 fraction of cells

The 45.30 Category

0.0279333 + 0.0004203 + 0.0138616 = 0.0422152 fraction of cells

The 22.65 Category

0.0277232 + 0.0138616 = 0.0415848 fraction of cells

The 0 Category

0.9142828 + 0 = 0.9142828 fraction of cells

So, we have

3 rads overall

Fraction of Cells	Dose (rads)
0.00000319	135.90
0.00000956	113.25
0.00064000	90.60
0.00126410	67.95
0.04221520	45.30
0.04158480	22.65
0.91428280	0

Now we can go on to consider cancer production for high LET and low LET radiation.

Cancer Calculations: (α particles vs low LET acute)

1 rad total: Let us consider a child in the 8th year of life

Let us deliver 1 rad of low LET acutely

Let us deliver 1 rad of 5 MEV alpha particles

Let us use Figure 1a, which sets 1 rad = 0.29 effective yrs.of aging

Now compare low LET with high LET 5 MEV α particles

For 1 rad low LET the effective aging = 0.29 years.

For 1 rad of 5 MEV alpha particles we have a population distribution

0.014715 of cells received 45.30 rads. $\therefore$ (45.30)(0.29)=13.14 years of aging
0.014715 of cells received 22.65 rads. $\therefore$ (22.65)(0.29)= 6.57 years of aging
0.97057 of cells received 0 rads. $\therefore$ (0)(0.29)= 0 years of aging

Consider cancer mortality at age 40, chronological

	Effective Age	Fraction of Cells	Cancer Rate/ 10^6/yr.	No. of Cancers (Fraction x Rate)
5 MEV α particles-1 rad	53.14	0.014715	2740	40.32
	46.57	0.014715	1220	17.95
	40.00	0.97057	550	533.81
			Total	592.08
Low LET Radiation-1 rad acute	40.29	1.0000	570	570
Spontaneous	40	1.0000	570	550

Therefore, low LET radiation produces 20 excess cancers

high LET radiation produces 42.08 excess cancers

RBE = $\frac{42.08}{20}$ = 2.10 times as high for high LET radiation.

Now go on to 2 rads total dose

For 2 rads low LET, the effective aging = 0.58 years.

For 2 rads of 5 MEV α particles we have a population distribution:

0.0002165 of cells received 90.60 rads. $\therefore$ (90.60)(0.29)=26.27 years of aging
0.0004330 of cells received 67.95 rads. $\therefore$ (67.95)(0.29)=19.71 years of aging
0.0287803 of cells received 45.30 rads. $\therefore$ (45.30)(0.29)=13.14 years of aging
0.0285638 of cells received 22.65 rads. $\therefore$ (22.65)(0.29)= 6.57 years of aging
0.942006 of cells received 0 rads. $\therefore$ (0)(0.29)= 0 years of aging

So, at chronological age 40 years

	Effective Age	Fraction of Cells	Cancer Rate/ 10^6/yr.	No. of Cancers (Fraction x Rate)
5 MEV α particles 2 rads	66.27	0.0002165	8300	1.80
	59.71	0.0004330	5180	2.24
	53.14	0.0287803	2740	78.86
	46.57	0.0285638	1220	34.85
	40.00	0.942006	550	518.10
			Total	635.85
Low LET - 2 rads-acute	40.58	1.0000	591	591
Spontaneous	40	1.0000	550	550

Therefore, for 2 rads:

low LET radiation produces 41 excess cancers

high LET radiation produces 85.85 excess cancers

RBE = $\frac{85.85}{41}$ = 2.09 times as high for high LET

Now go on to 3 rads total dose

For 3 rads of low LET radiation, the effective aging = 0.87 years.

For 3 rads of high LET α particles we have a population distribution:

0.00000319 received 135.90 rads. ∴ (135.90)(0.29)=39.41 years of aging
0.00000956 received 113.25 rads. ∴ (113.25)(0.29)=32.84 years of aging
0.0006400 received 90.60 rads. ∴ (90.60)(0.29)=26.27 years of aging
0.00126410 received 67.95 rads. ∴ (67.95)(0.29)=19.71 years of aging
0.04221520 received 45.30 rads. ∴ (45.30)(0.29)=13.14 years of aging
0.04158480 received 22.65 rads. ∴ (22.65)(0.29)= 6.57 years of aging
0.91428280 received 0 rads. ∴ (0)(0.29)= 0 years of aging

So, chronological age = 40 years

	Effective Age	Fraction of Cells	Cancer Rate/ 10^6/yr.		No.of Cancers (Fraction x Rate)
5 MEV αparticles 3 rads	79.41	0.00000319	14600		0.05
	72.84	0.00000956	11750		0.11
	66.27	0.0006400	8270		5.29
	59.71	0.00126410	5180		6.55
	53.14	0.04221520	2730		115.25
	46.57	0.04158480	1210		50.32
	40.00	0.91428280	550		502.86
				Total	680.43
Low LET 3 rads, acute	40.87	1.0000	611		611
Spontaneous	40.00	1.0000	550		550

Therefore, for 3 rads:

low LET radiation produces 61 excess cancers

high LET radiation produces 127.28 excess cancers

RBE = $\frac{130.43}{61}$ = 2.14 times as high for high LET radiation.

Special Points of Note Concerning High LET Radiation-Carcinogenesis

1. We have made no requirement that the high LET be acute or fractionated. If delivered in the same year of life, it wouldn't matter. This probably accounts for those experiments indicating no effect of fractionation for α particles.

2. The RBE in all 3 cases (1, 2, 3 rads) came out $\sim$ 2.1 for α particles. However, these were all delivered in the 8th year of life. If we had spread the α particle radiation from 8th year through 18th year, we would be operating in a region where 1 rad is worth progressively less in terms of years of effective aging. The RBE of this type of "fractionation" (over 10 years) versus 8th year of age delivery of acute low LET radiation might come down to 1.0 or thereabouts. Starting at 2.10, we could afford several years of fractionation and still have the fractionated high LET radiation be as effective as, or more effective than acute low LET radiation for carcinogenesis.

3. Cell Size is extremely important in determining RBE.
All the calculations above are for cells of 10 microns diameter. If we go to 20 microns diameter,

The number of cells traversed per α particle is $\frac{1}{2}$ as many.

The number of cells per gram of tissue is 1/8 as many.

(Linear versus cube variation)

Therefore, the fraction of all cells traversed will rise, and hence the uneven distribution of radiation will be lessened. Since the greater efficacy of high LET radiation hinges on this uneven distribution of dose, the RBE would decrease for a tissue where the cells are larger compared with one where they are smaller. This is now demonstrated below.

High LET Radiation in Cells with 20 microns diameter

For 20 microns diameter, cell volume = $4/3\ \Pi(10^3) = 4179\mu^3$.

Therefore, 1 gram of tissue has $\frac{10^{12}}{4.179 \times 10^3} = 2.39 \times 10^8$ cells.

But 1 rad of 5 MEV α particles represents 1.25×10^7 $\frac{\alpha \text{ particles}}{\text{gram}}$

Each α particle traverses $\frac{45}{20} = 2.25$ cells.

Therefore, 1 rad of α particles provides traverse through

$$(1.25)(2.25) \times 10^7 = 2.81 \times 10^7 \text{ cells.}$$

Finally, fraction of cells traversed = $\frac{2.81 \times 10^7}{2.39 \times 10^8} = 0.1176$

Fraction of cells not traversed = 0.8824.

What is the rad dosage to the cells traversed? Again, using the Bragg ionization for 5 MEV α particles, we can note that, of the cells traversed, $\frac{1}{2}$ receive 2x the dose received by the other half. Proceeding as with cells of 10 microns diameter, let x = dose in rads received by the cells in the first half of the range

$\frac{1}{2} \times 0.1176 = 0.0588$ fraction of cells in first half of range
$\frac{1}{2} \times 0.1176 = 0.0588$ fraction of cells in second half of range.

Therefore,

$$0.0588(x) + 0.0588(2x) = 1.0$$

$$0.1764x = 1.0$$

$$x = 5.67 \text{ rads}$$

$$2x = 11.34 \text{ rads}$$

Thus, our distribution of cells after 1 rad delivery (for 20 micron cells) is as follows:

Fraction of Cells	Dose (rads)	Effective Aging(yrs)
0.0588	11.34	(11.34)(0.29)=3.29
0.0588	5.67	(5.67)(0.29) =1.64
0.8824	0	(0)(0.29) = 0

Now we can go on to calculate cancer mortality at chronological age 40 years for this distribution of cells and a total dose of 1 rad.

	(20-micron cell diameter)			
	Effective Age	Fraction of Cells	Cancer Rate/ 10^6/yr.	No.of Cancers (Fraction x Rate)
5 MEV α particles 1 rad	43.29	0.0588	830	48.80
	41.64	0.0588	650	38.22
	40.00	0.8824	550	485.32
			Total	572.34
Low LET Radiation-1 rad	40.29	1.000	570	570.00
Spontaneous	40.00	1.000	550	550.00

Therefore, 1 rad High LET Radiation produces 22.34 excess cancers

1 rad Low LET Radiation produces 20.0 excess cancers

$$\text{RBE} = \frac{22.34}{20.0} = 1.12 \text{ times as high for high LET radiation.}$$

Contrasting this RBE = 1.12 for cells of 20-micron diameter with the RBE = 2.10 for cells of 10-micron diameter, the enormous influence of cell size becomes apparent. In the literature there is much puzzlement about the variation in RBE from experiment to experiment, often on different tissues or different animals. Unless cell sizes are known and accounted for, such variation in RBE is not surprising.

4. RBE will be energy dependent for the high LET radiation. For α particles of greater energy than 5 MEV, the fraction of cells receiving the full Bragg specific ionization effect will lessen. Hence, the uneven distribution of dose will be less than here calculated and the RBE will decline.

5. The RBE will, for any realistic cell size or energy of α particle, remain higher than unity, when the high LET radiation is distributed over time in the same manner as the acute low LET radiation.

6. None of these effects have anything to do with hypothetical "repair" mechanisms. They result only from unevenness of dose distribution for high LET radiation.

7. The RBE will depend upon the shape of the spontaneous curve of cancer mortality versus age. It can, therefore, be different for different cancers and even at different ages for the same cancer.

THE ANSWER TO DR. STORER'S REQUEST FOR A FACTOR OF 5 REDUCTION IN CARCINOGENESIS FOR FRACTIONATED LOW LET RADIATION VERSUS ACUTE LOW LET RADIATION

Storer has suggested that a five-fold "brownie point" allowance be made in our estimates of cancer mortality from radiation because low LET radiation fractionated is supposed to be less carcinogenic than acute low LET radiation[13]. We hope the analysis of this report will demonstrate to Storer why we deny him his five-fold factor. He has apparently been misled by the very point this analysis is all about -- namely, that the fractionation "protection" is an illusion, reflecting only the fractionated radiation occurring later in life. The fractionated radiation distributed over a larger part of the life span produces as much carcinogenesis as is expected for the doubling doses at the various points in the life span. There is no reason whatever to bring in hypothetical "repair" since the observations are explainable without it.

The calculations presented here are for human protracted radiation between the 8th and 17th year of life, chosen to be comparable with the experiment of Upton on irradiation of RF male mice at 56 to 70 days of age. For our human analogy to accord with Upton's experiments it would be necessary to know that the effectiveness of radiation in the Upton experiment decreases, in terms of leukemogenesis per rad beyond 70 days of age of mouse. And indeed Upton did conclusively prove just that in a separate publication, with a

demonstration that a marked decrease in leukemogenesis per rad occurs for radiation at 180 days of age versus irradiation with the same dose (300 rads x-irradiation) at 70 days[14]. Thus, the analogy between our human calculation and Upton's mouse data is reasonable.

CONCLUSION

The Unlikely Prospect that Protraction Will in any way Mitigate the Carcinogenic Effect of Radiation in Man

The experimental observations of "apparent" fractionation protection have here been explained away as an illusion, based upon delivering part of the fractionated radiation at a later time of life, when the radiation sensitivity is lower! No suggestion of "repair" is required or credible. What these studies do teach us is that the younger the individual, especially early childhood, the worse is the carcinogenic hazard per rad of radiation. It is bad to deliver radiation to individuals at 30 years of age, when the doubling dose is in the neighborhood of 50 rads; it is far worse to deliver it in infancy or childhood when the doubling dose is closer to 5 or 10 rads.

In our estimates of cancer production from population irradiation at FRC Guidelines we were conservative, using 100 rads as doubling dose and allowing no credit for the more serious effect per rad at earlier ages. Now, we realize the adult doubling dose may be closer to 50 rads, and further we should definitely credit the radiation as more carcinogenic for the early years of life. Both of these effects will materially increase our estimate above the 16,000 cancer cases previously predicted. And from what we now analyze concerning the illusion of protection by fractionation, one of the last hopes for mitigation of effect has all but evaporated.

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