**Prague – 4th Annual ARDENT Workshop Training Course**

**June 2015**

# Neutron Radiobiology

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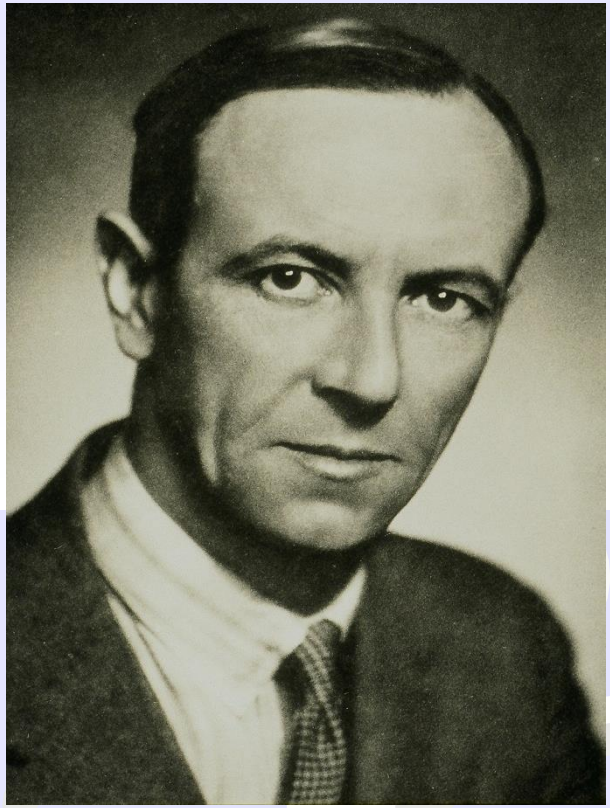
MRC Medical Research Council

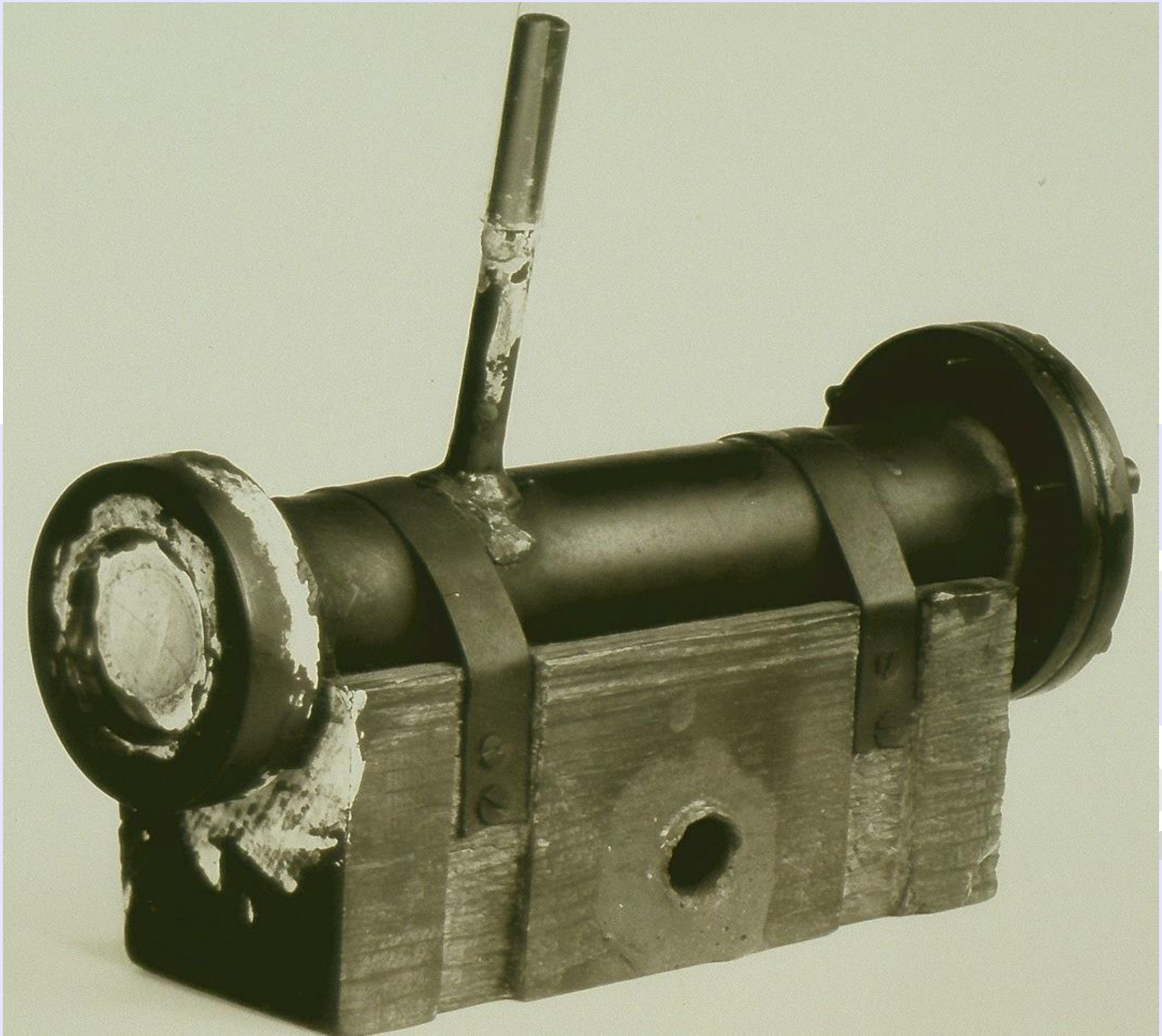
CANCER RESEARCH UK

UNIVERSITY OF OXFORD

**Ernest Rutherford & JJ Thomson, Trinity**



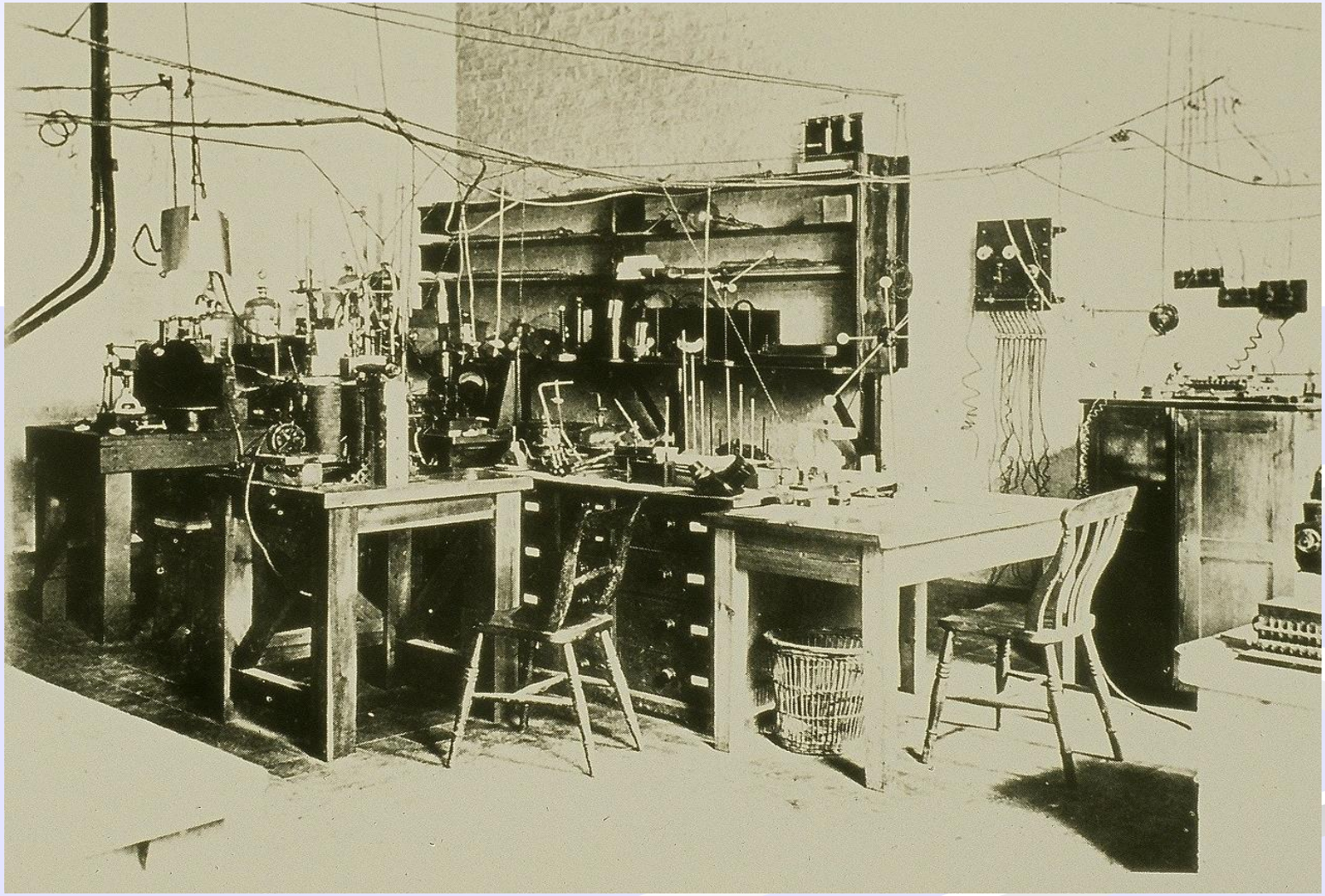
**James Chadwick, Caius**

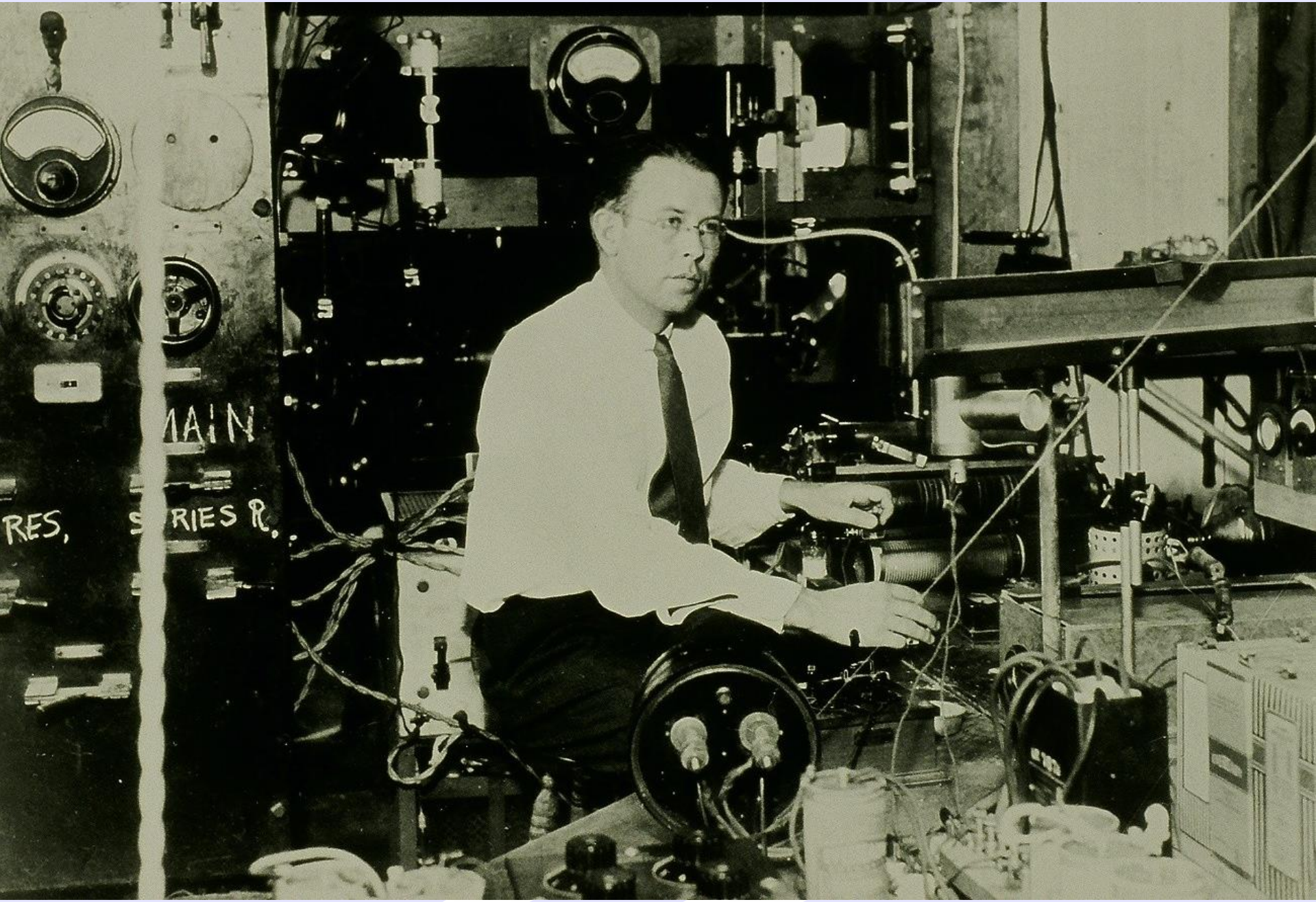


# Rutherford`s dream for higher energies

Royal Society, 1928 he said : *I have long hoped for a source of positive particles more energetic than those emitted from natural radioactive substances".*

# Rutherford's laboratory




MAIN
RES,
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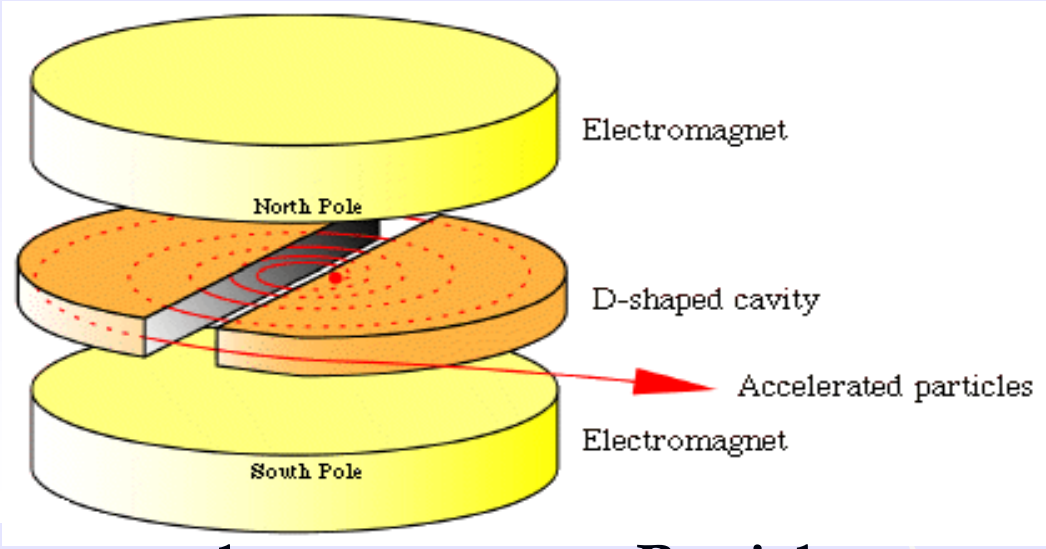
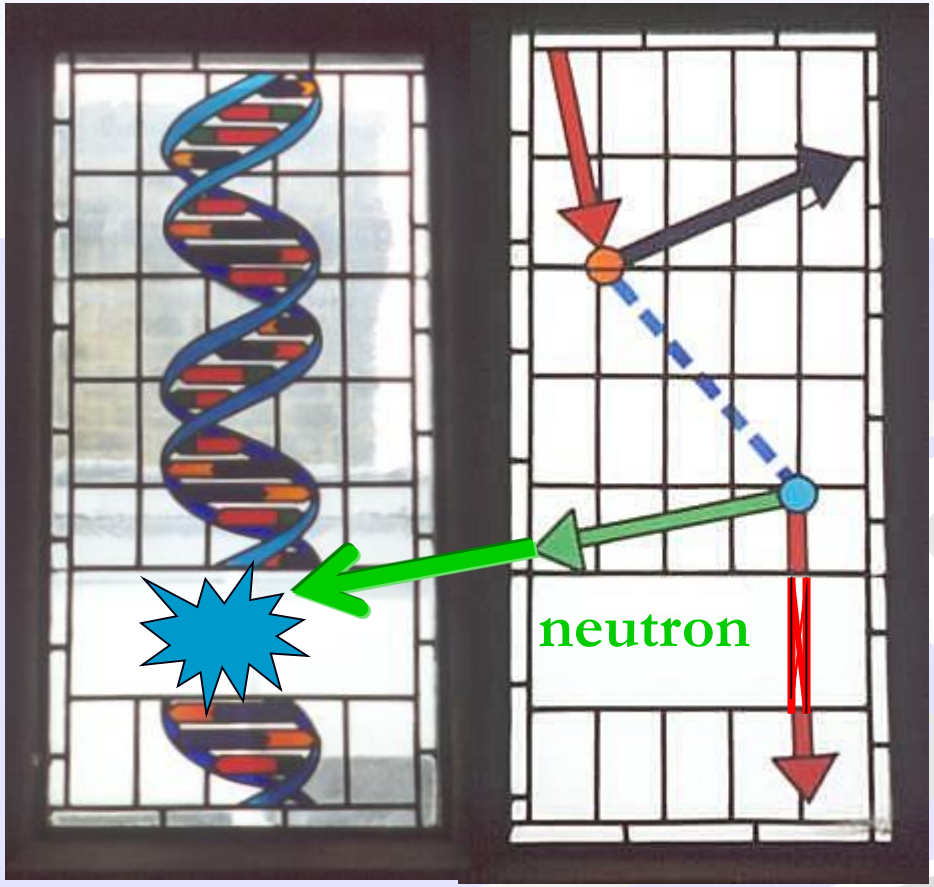
# The Cyclotron


- 2 D-shaped cavities between two electromagnets. Particle injected into one D shaped cavity of opposite voltage, & accelerates due to e/m field.
- Particle enters other D, polarity changes to maintain acceleration
- magnetic fields steers particles in ↑ spiral pathway, & extracted at maximum energy…isochronous synchrotrons have more complex shapes.
- For clinical use,.....metal degraders of different thicknesses inserted dynamically into beam to give desired range of energies for specified Bragg peak positions.

# Gonville and Caius College, Cambridge Hall: the Chadwick and Crick windows in Dining Hall



# All forms of Particle therapy have intrinsic uncertainties

Due to:

- Physics (dose) in different tissues
- Biology – how do different tissues and tumours respond to this treatment compared with x-rays?
- need BETTER UNDERSTANDING

LH Gray (PhD with Rutherford)

Louis Harold Gray

- studied neutron effects in biological systems.
- thought that neutrons were a tool for research, but NOT for cancer therapy
- defined "Relative Biological Effect" in early 'bean shoot' experiments
- Gray lost his post as Director of Radiotherapy Physics, Hammersmith Hospital
- The Gray Laboratory was created for him
- The SI unit of absorbed dose (Gy) is named after him (Bragg – Gray cavities).

**Neutron physics and their interaction with matter differ substantially to photons/x-rays.**

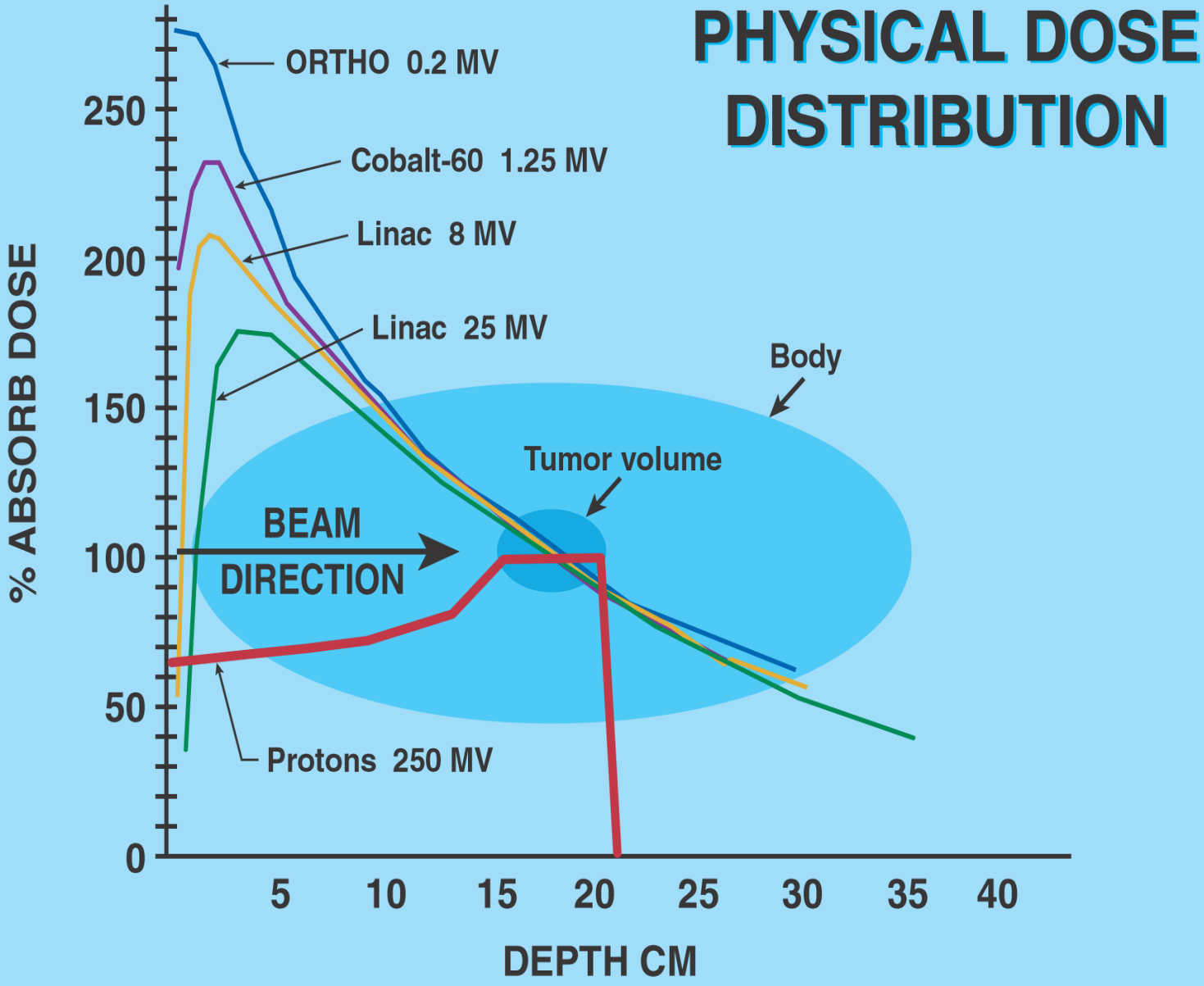
**Main ionisation is due to recoil protons, the lower the energy the greater their localisation and bioeffectiveness**

**Hydrogen capture is high, so Hydrogen rich tissues, such as lipids (fat), e.g. white matter of central nervous system, have greater KERMA and dose. White matter necrosis occurred with fast neutron therapy, also treatment fields showed subcutaneous fat atrophy.**

**Tissue composition important; C, N, O have different captures. Boron has high neutron capture, and can be used to replace carbon in biomolecules, especially in lower energy, epithermal energy range**

- Attenuation characteristics
- They are neutral particles and so do not have Bragg peaks
- They are attenuated pseudo exponentially with tissue depth, like X-rays, but depth-dose differ greatly with respect to Energy.
- Neutrons require far greater energy to reach the same depth as an X-ray, e.g.
- 64 MeV neutrons form a Be target are equivalent to 4 MeV X-rays.
- Early neutron generators had low Energies, 15-20 MeV and had similar depth dose characteristics to 200-300 keV X-rays.

# PHYSICAL DOSE DISTRIBUTION



# RBE - Relative biological effect

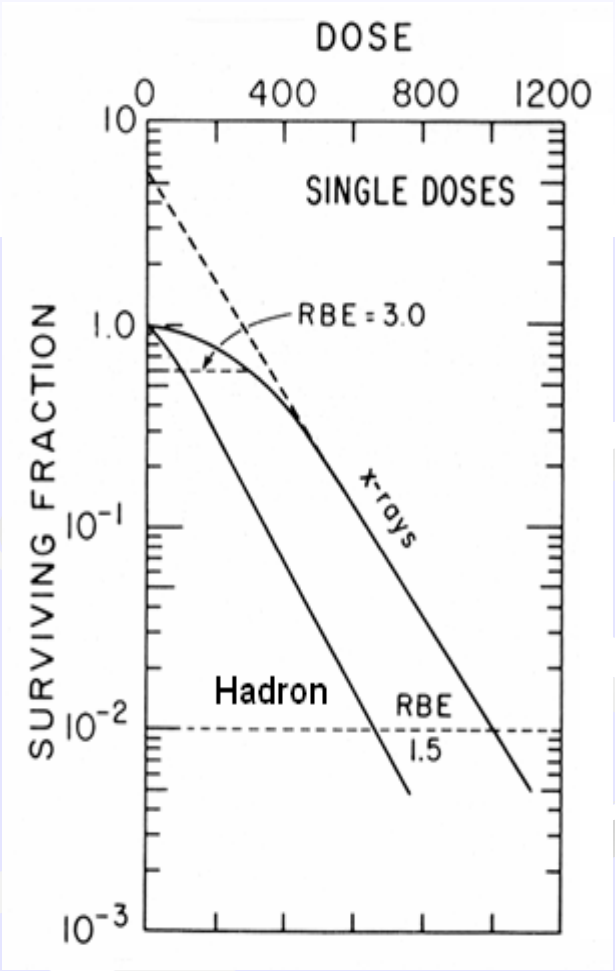
- Ratio of dose in low/high LET radiation for same bio-effect = $D_H/D_L$

$D_L$ is control Low LET radiation Co-60 or 6 MV X-rays [ NB formerly 150-250 KeV x-rays were used]

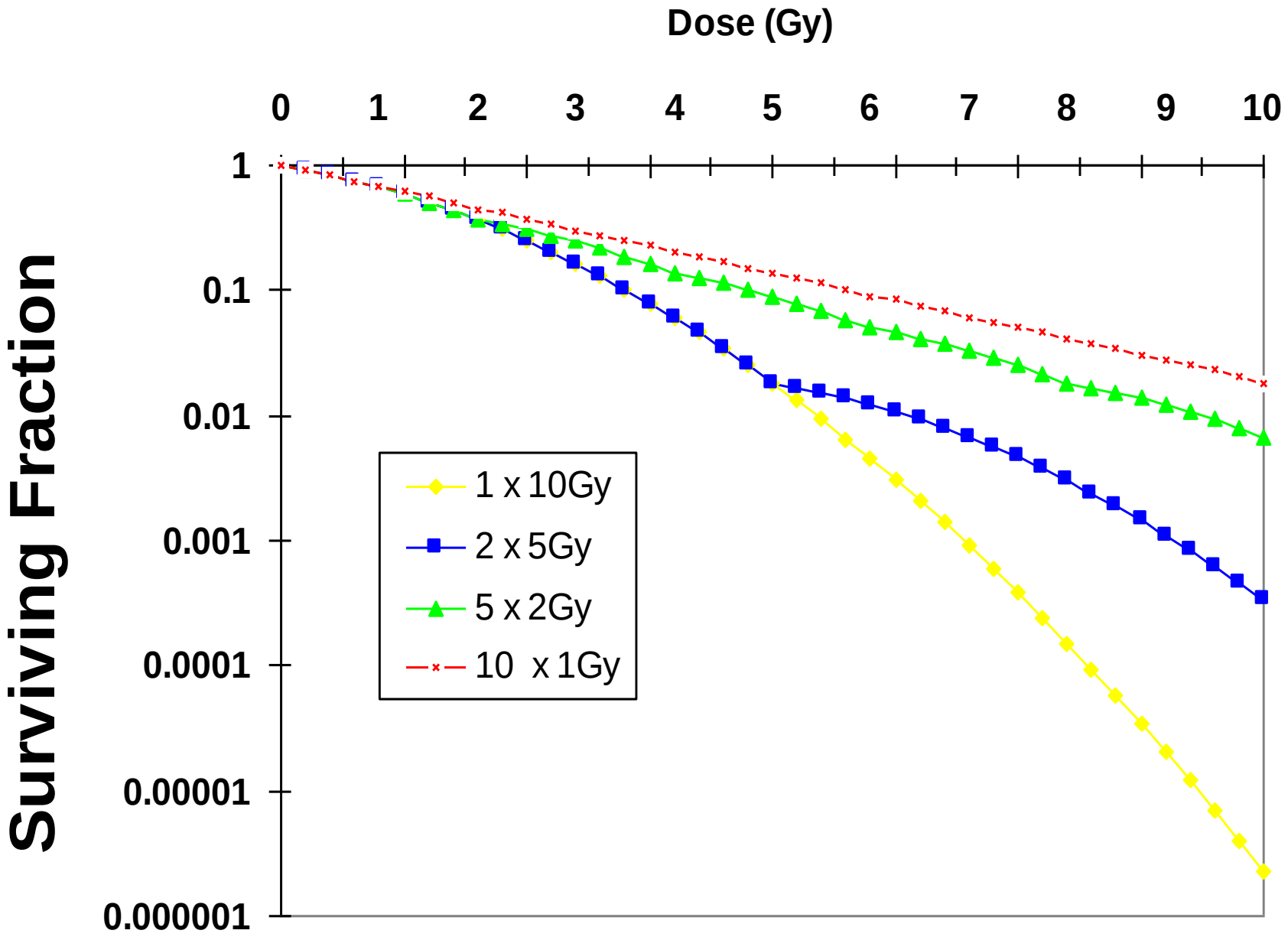
$D_H$ is the test high LET radiation

- RBE:

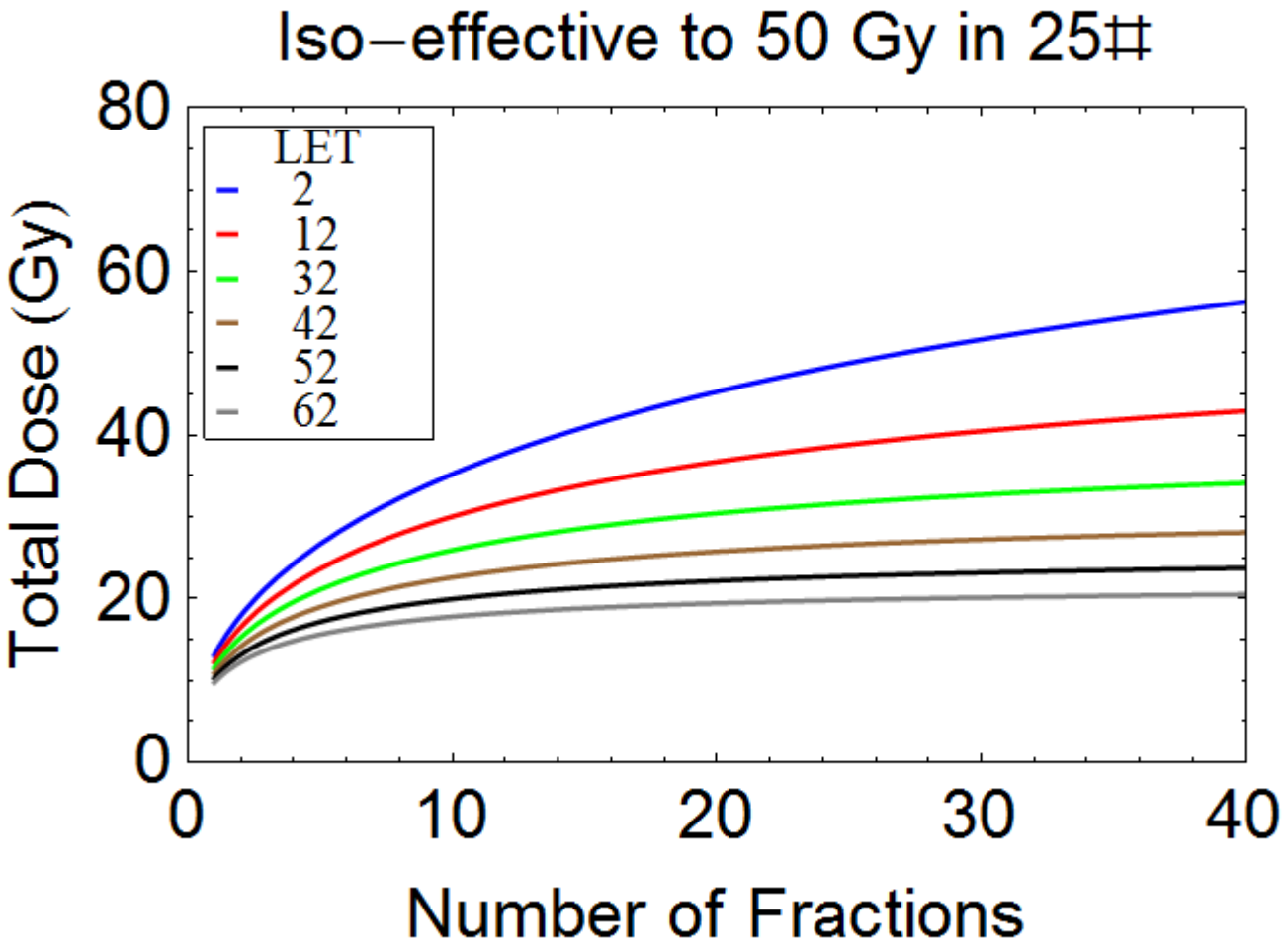
1. *varies with exposure dose (dose per fraction)*
2. *The photon component of RBE is more dependent on cell cycle proliferation and DNA damage repair capacity*
3. *varies with LET…..*

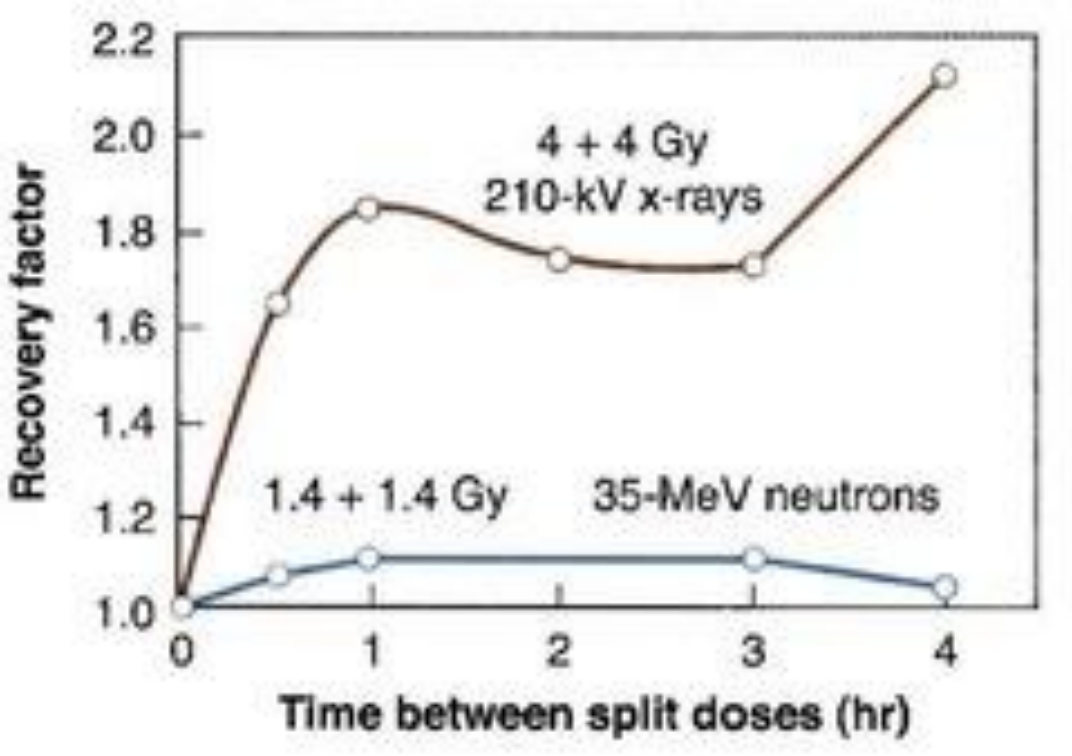


# *Effect of fractionation on critical normal tissue.*



**Unpublished Simulation for helium ions**






**Reduced proliferation and progression through cell cycle**

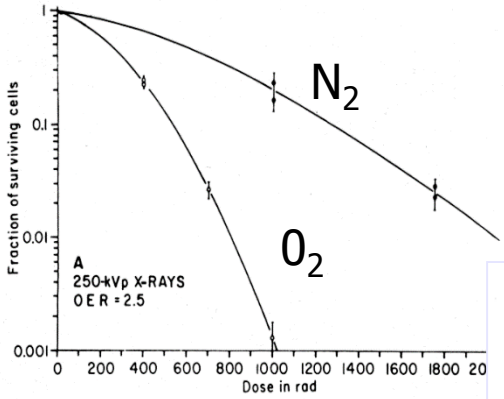
# To account for RBE in radiotherapy:

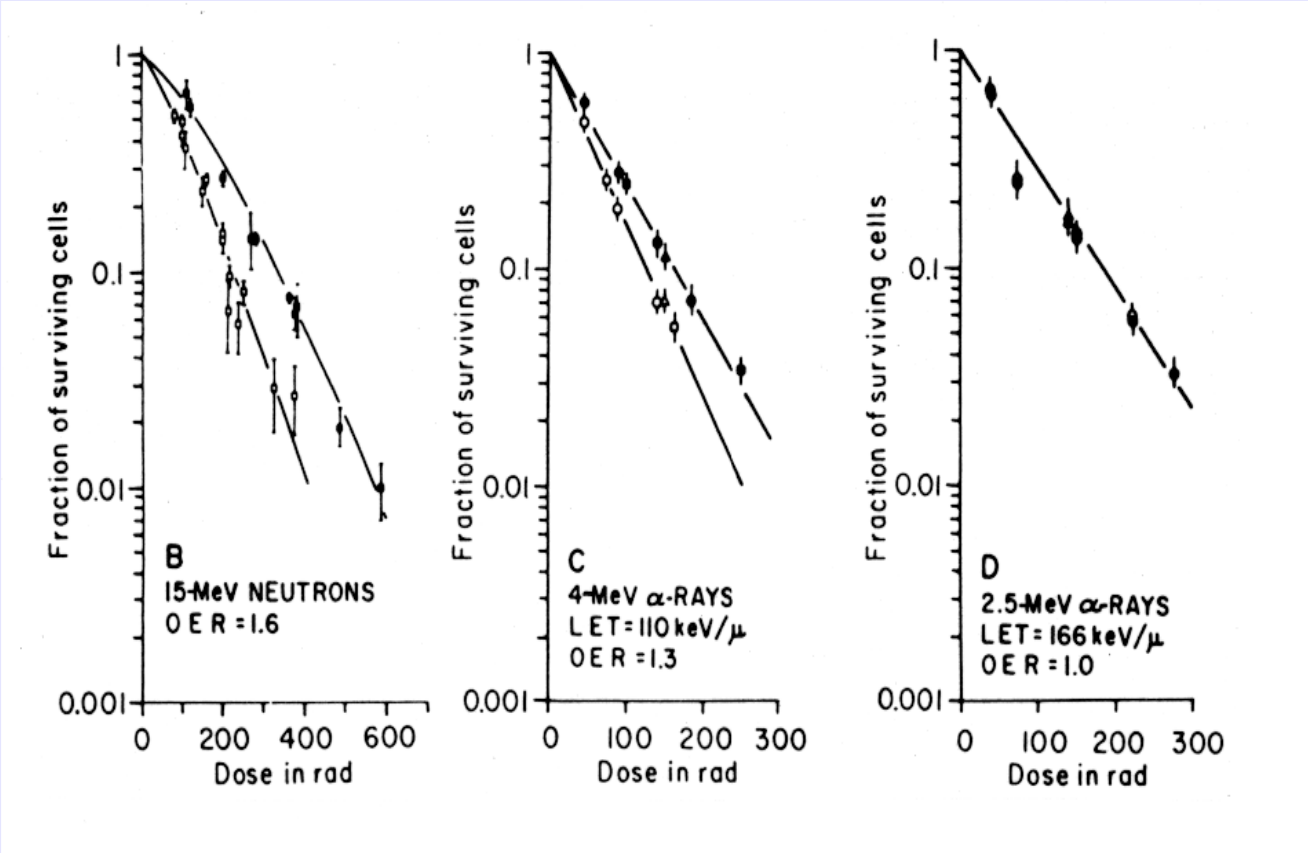
- The dose of high LET is divided by the RBE to give the actual dose given to the patient.
- But the prescribed dose remains the same and has been quoted – over the past 50 years as Cobalt-equivalent Gray, or Gy – RBE; or  equivalent Gy; or Gy-eq.
- RBE itself was often specified by a surviving fraction .e.g. $RBE_{0.1}$, or $RBE_{0.5}$

# Important Catch:
# RBE of x-ray and particle energy are inversely related - the lower the energy the higher the LET and RBE

# 15 Kev X-rays much higher RBE than 1 MeV x-rays.

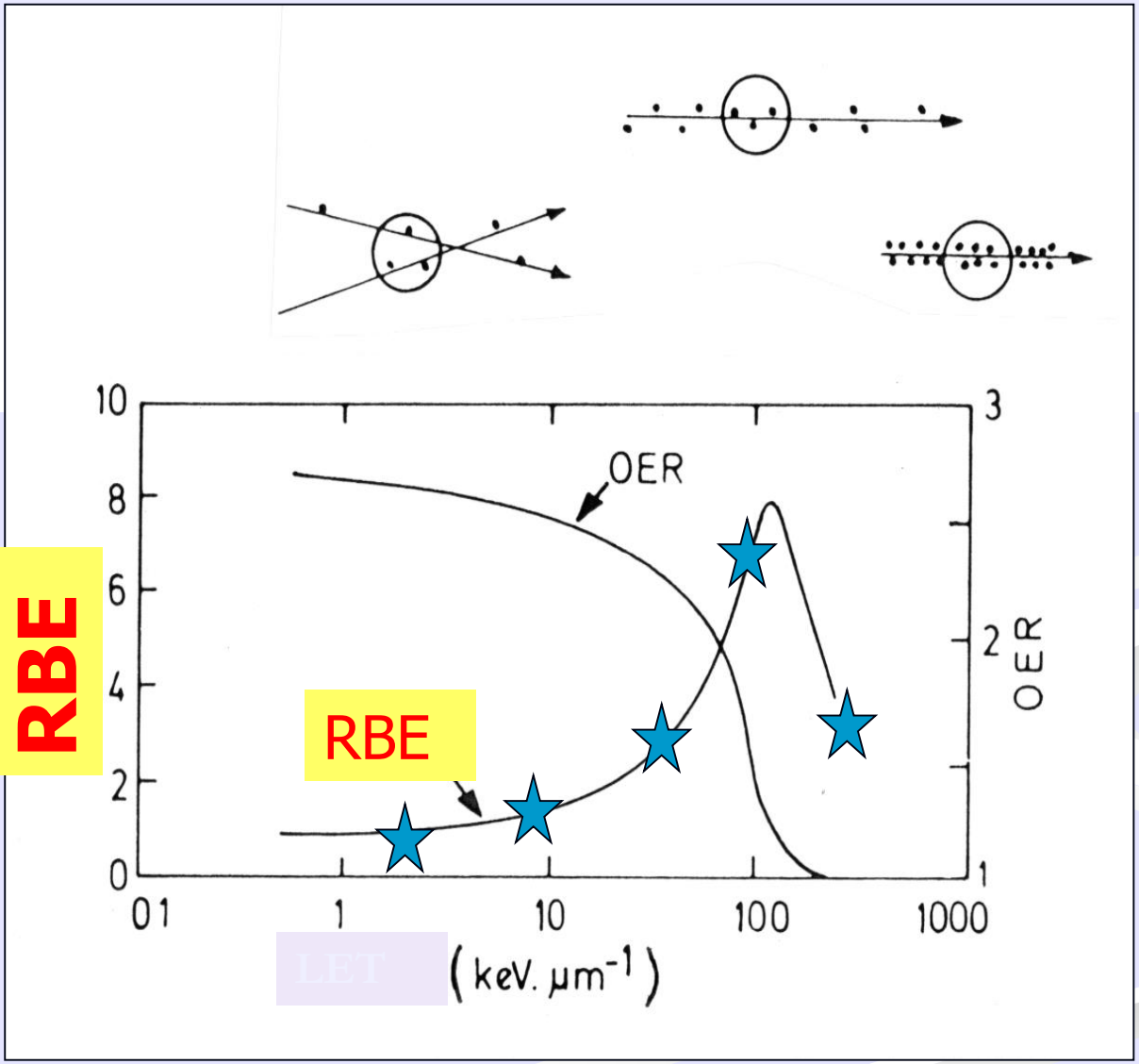
# High LET radiation and Hypoxia



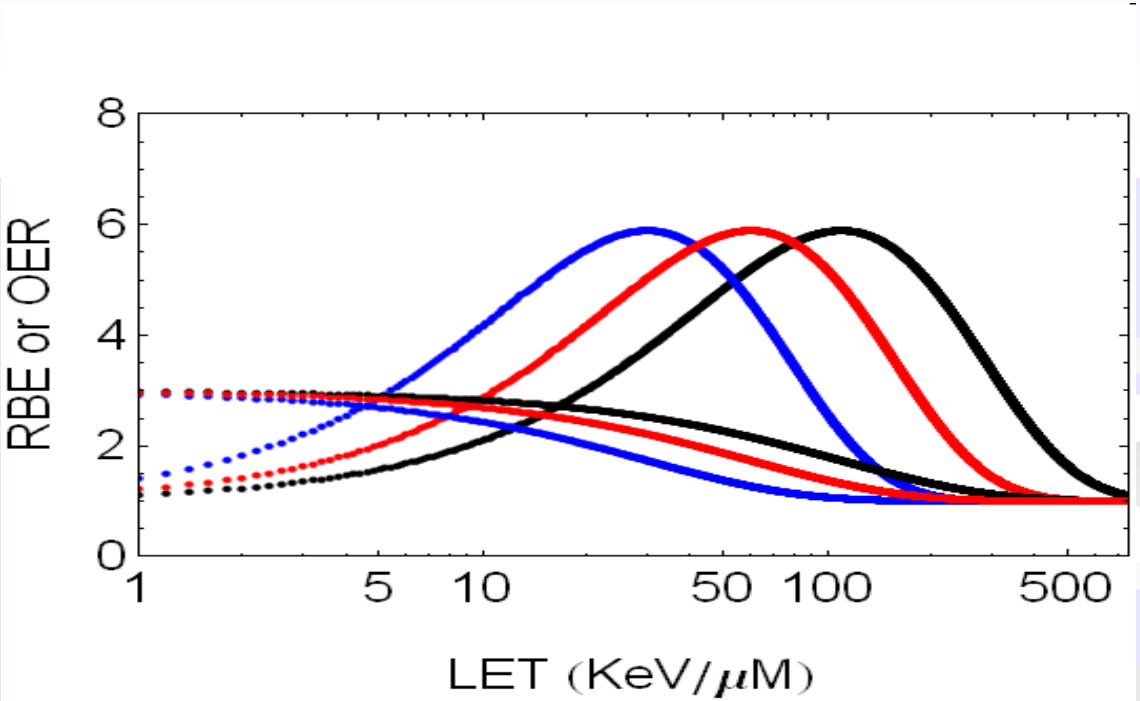

Human renal cells T1, ● hypoxia, ❍ normoxia;
from Broerse & Barendsen, IJRB, 13:559, 1967

# LET, RBE and OER are linked

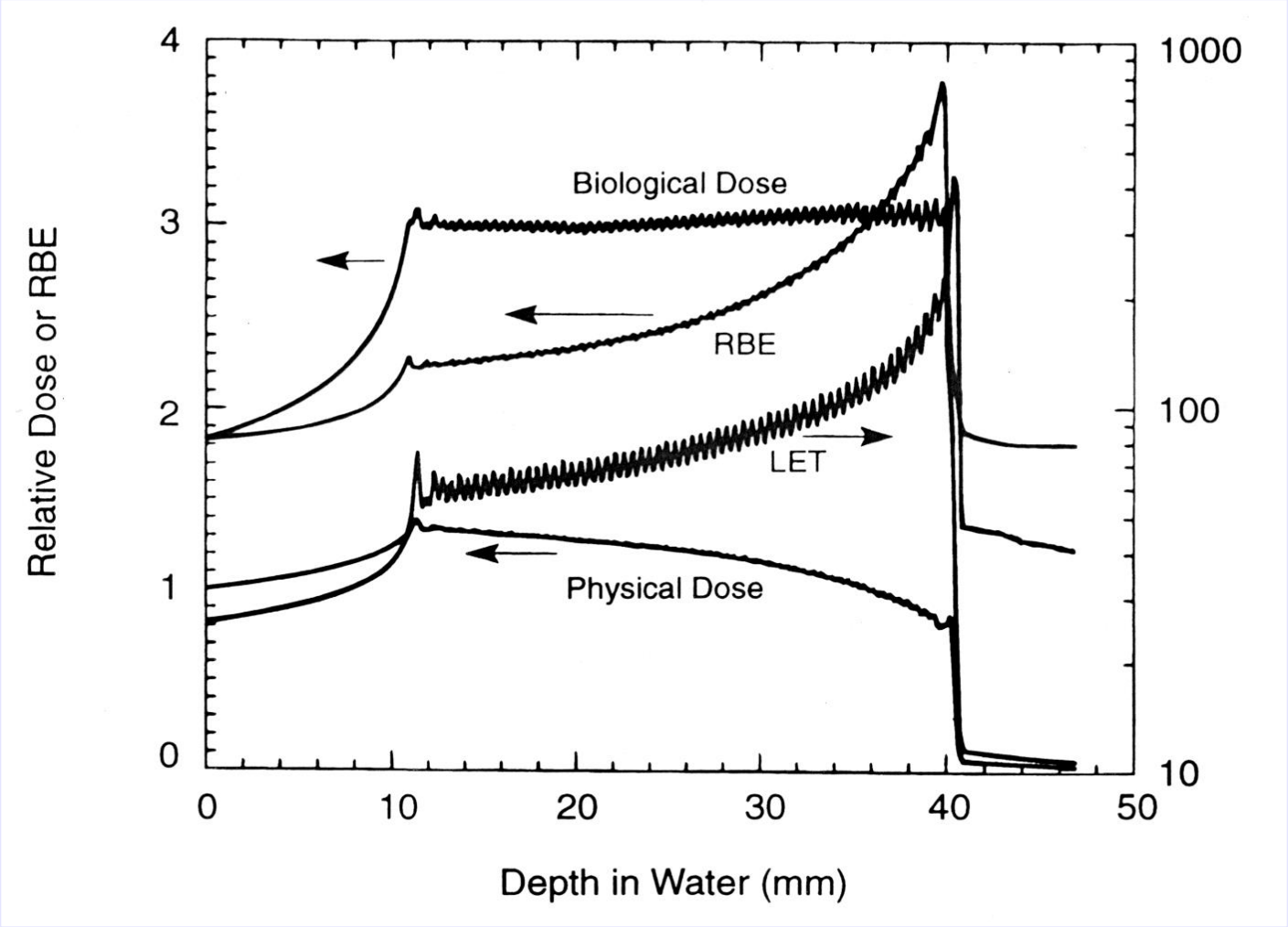



Tubiana, Dutreix & Wambersie, Hermann ed, 1986

# LET, RBE and OER……three ions, proton, helium and carbon



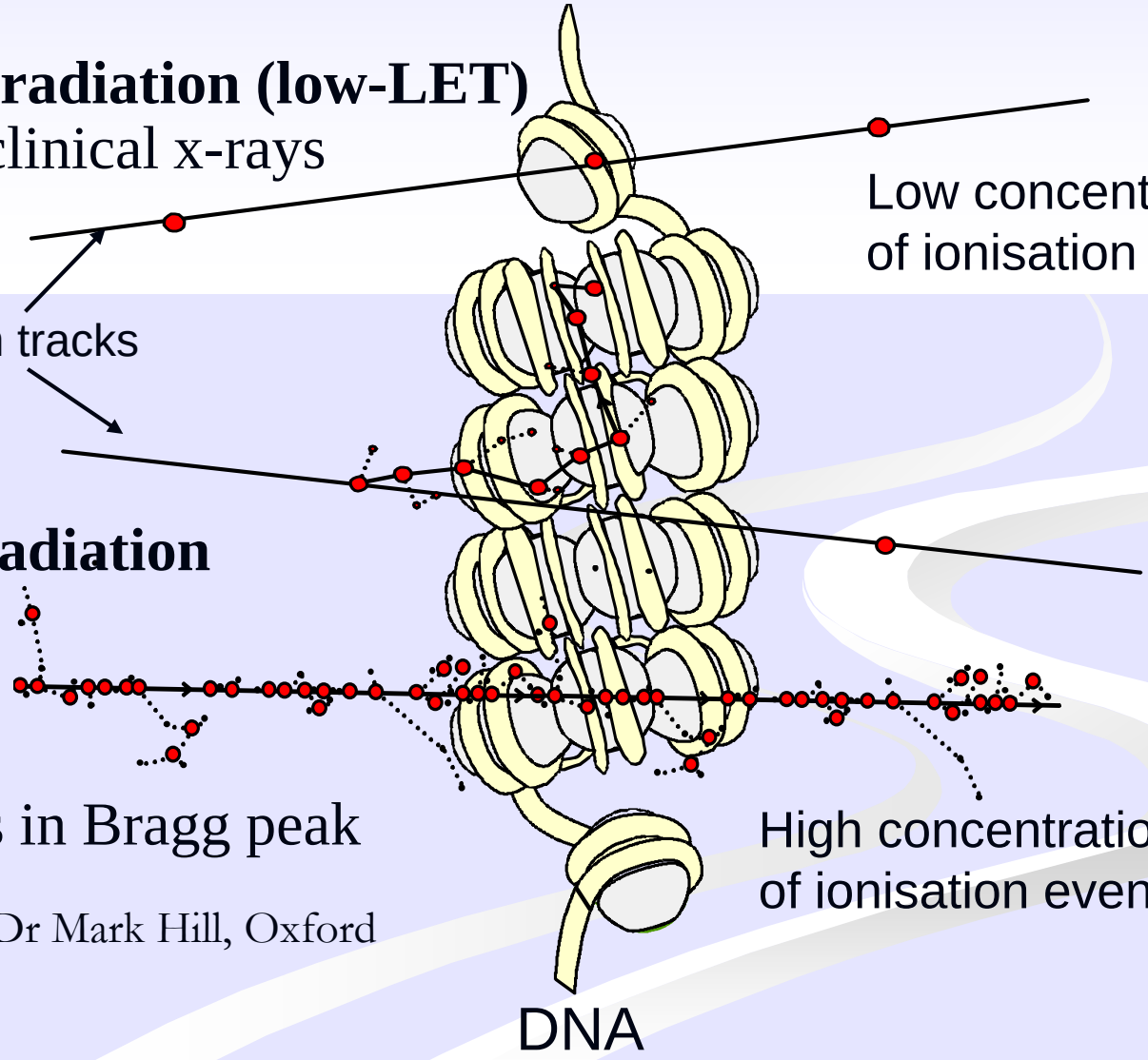
# Radiobiological complexity of ions SOBP




T. Kanai et al, *Rad Res*, 147:78-85, 1997 (HIMAC, NIRS, Chiba, Japan)

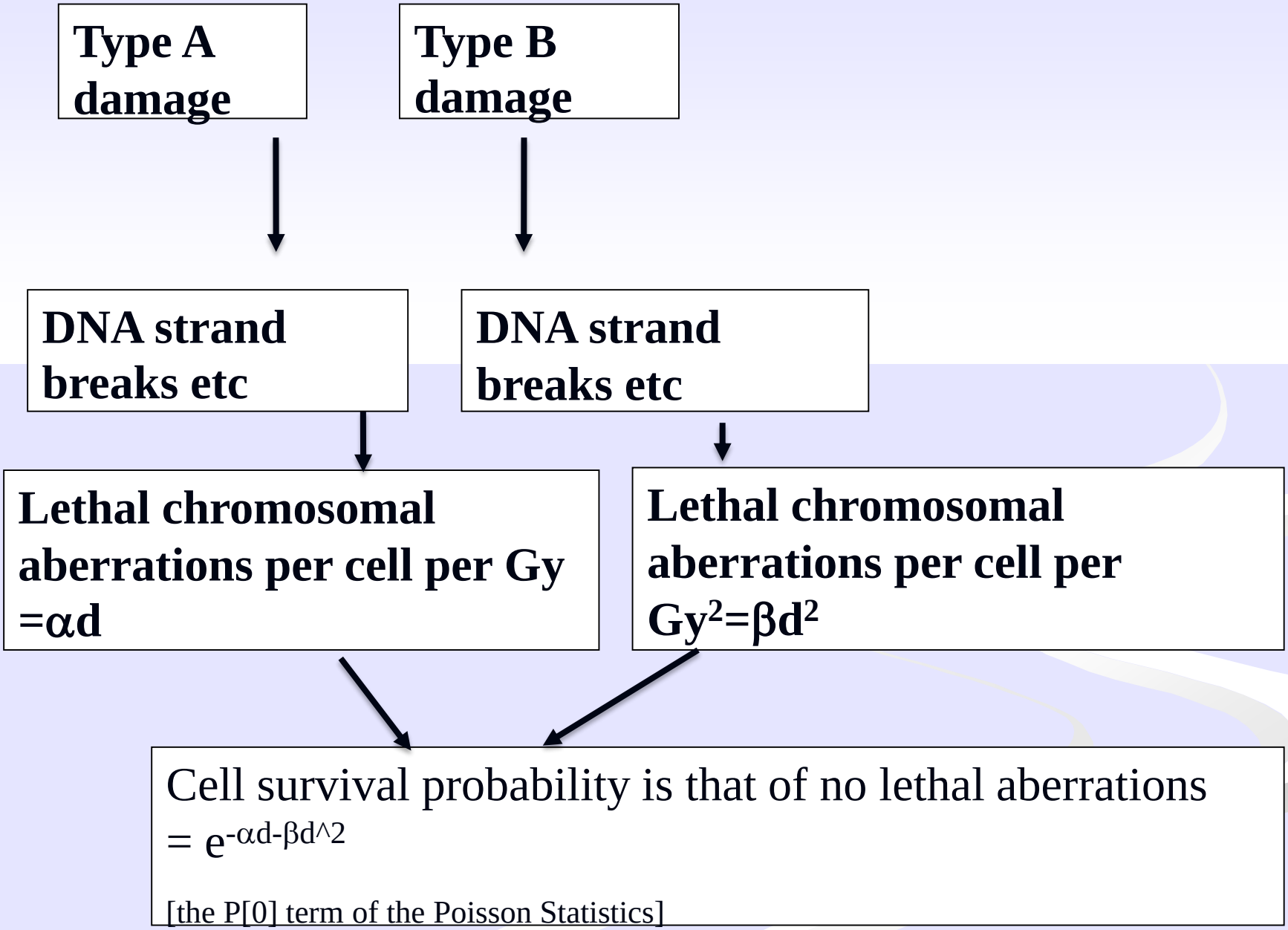
# Ionising Radiation a DNA
# LET=Linear energy transfer

**Sparsely ionising radiation (low-LET)**
e.g. conventional clinical x-rays




**Densely ionising radiation (high-LET)**
e.g. neutrons
α-particles
$C6^{+}$ ions, protons in Bragg peak

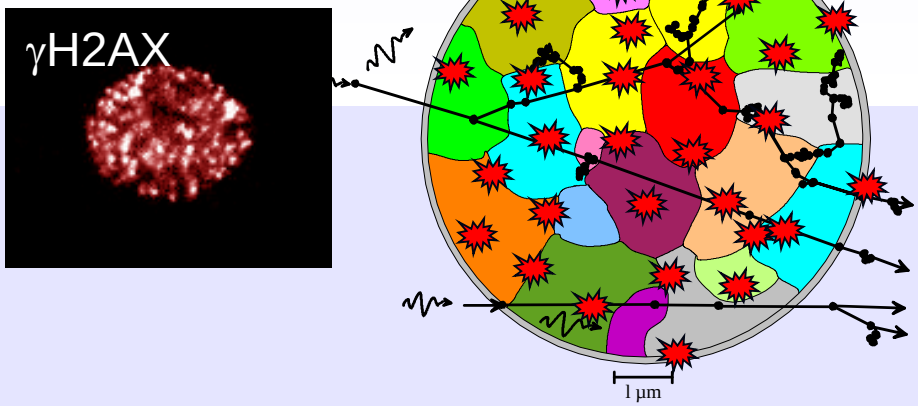
Modified, courtesy of Dr Mark Hill, Oxford


Type A damage
Type B damage
DNA strand breaks etc
DNA strand breaks etc
Lethal chromosomal aberrations per cell per Gy =αd
Lethal chromosomal aberrations per cell per Gy²=βd²
Cell survival probability is that of no lethal aberrations
= e^-αd-βd^2
[the P[0] term of the Poisson Statistics]

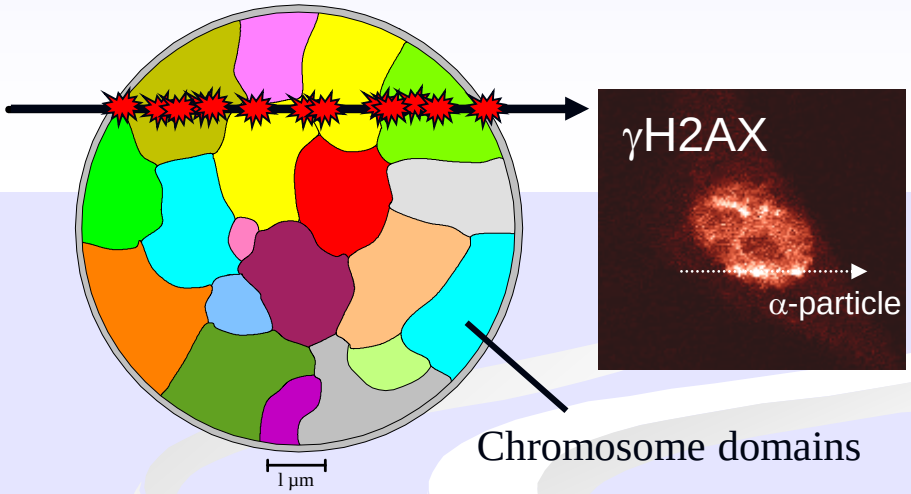
- The Single Strand (SS) and Double Strand breaks (DSB) reflect the dose given
- For example, 1 Gy yields 800 SSB, 40 DSB but only one lethal Chromosome break;
- Most if not all the SSB and DSB are repaired if in isolation ( sparsely distributed) in cell.
- γH2 AX staining is often used to show radiation damage within a cell – it is an index of radiation repair recruited in proportion to the damage; it clears with time, but at much lower rate for high LET damage.
- Since HIGH LET radiation causes greater killing at lower doses than for LOW LET, there is less ionisation, so less numbers of SSB and DSB, but more lethal and complex chromosome breaks,
- So, what is needed is a measure of DNA damage complexity in 3D as a density effect. It is well known that CLUSTERING of damage occurs with increasing LET and this is most efficient in terms of cell killing.

# Track structure on the nuclear/cellular scale

Low-LET (e.g. γ-rays)




High-LET (e.g. α-particles)




**1 Gy corresponds to:**

| Low-LET (e.g. γ-rays) | High-LET (e.g. α-particles) |
|---|---|
| ~1000 electron tracks | ~2 alpha tracks |
| ~20-40 DSB (*~20% complex*) | ~20-40 DSB (*~70% complex*) |
| Relatively homogeneous | Very non-homogeneous |

# RBE converts x-ray dose to particle dose

- Relative Biological Effect is used to divide the x-ray dose to give the equivalent particle dose
- Uncertainties in physical dose compounded with RBE uncertainty can lead to significant patient effects
- Dose –Effect relationship is non-linear & modified by shape of Dose Response curve

# RBE – components in a ratio

Changes with dose per fraction and cell cycling in repair proficient cells

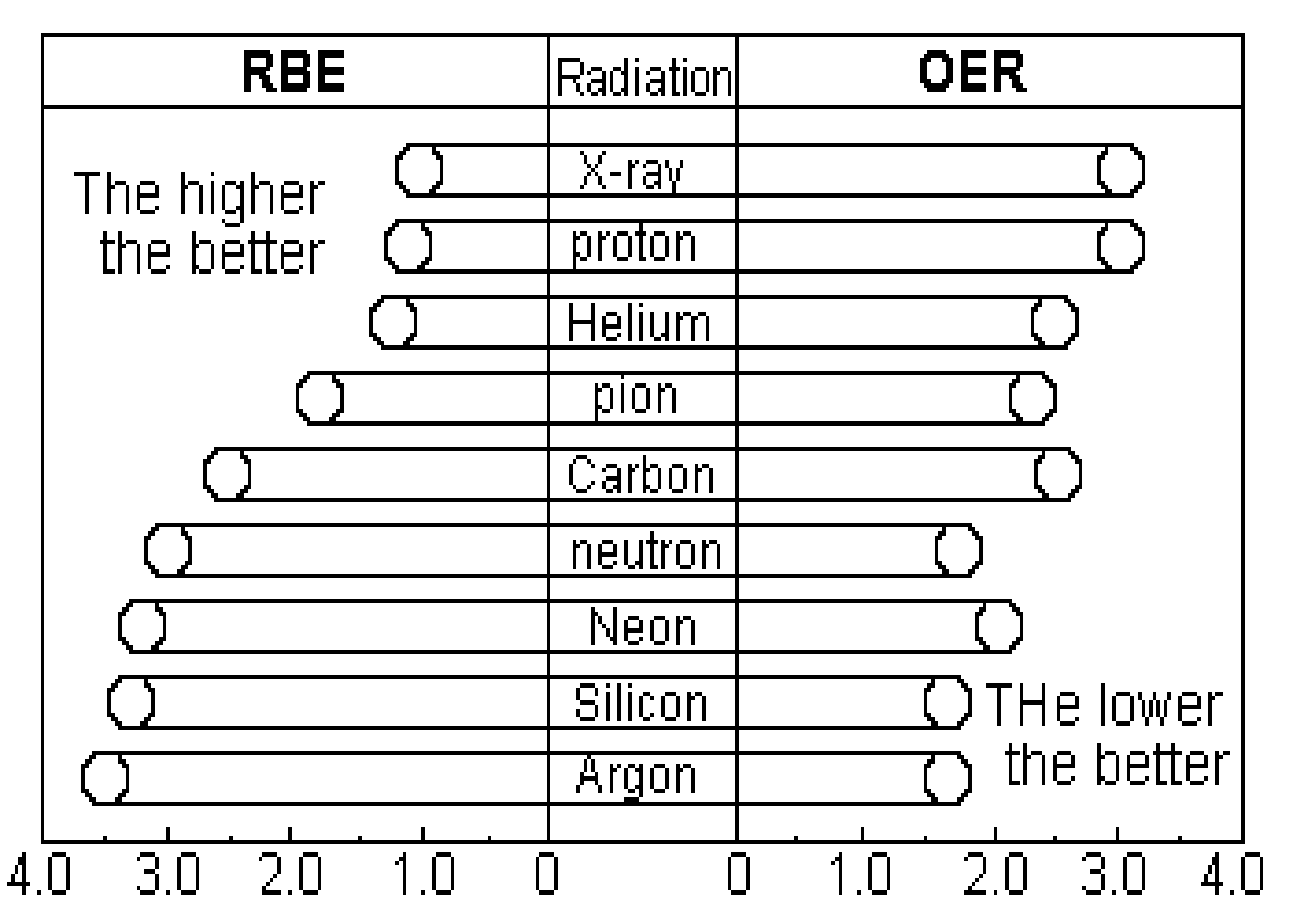
$$RBE = \frac{Dose_{[LowLET]}}{Dose_{[HighLET]}}$$

Little or no changes with dose per fraction and cell cycling in repair proficient cells

# RBE depends on ……..

- **Particle, Energy & Depth**
- Target **Volume**
- **Dose** per treatment ..RBE varies inversely with dose. A treatment plan contains many dose levels.
- **Facility: neutron & γ-ray contamination**
- **Cell & Tissue type : slow growing cells have highest RBEs.**
- **Use of single value RBE was mistake**

# RBE and OER for Protons…the old Berkeley data of E Blakely et al.



Br J Radiol. 1987 Jun;60(714):583-8.

**The effect of mixed fractionation with X rays and neutrons on tumour growth delay and skin reactions in mice.**

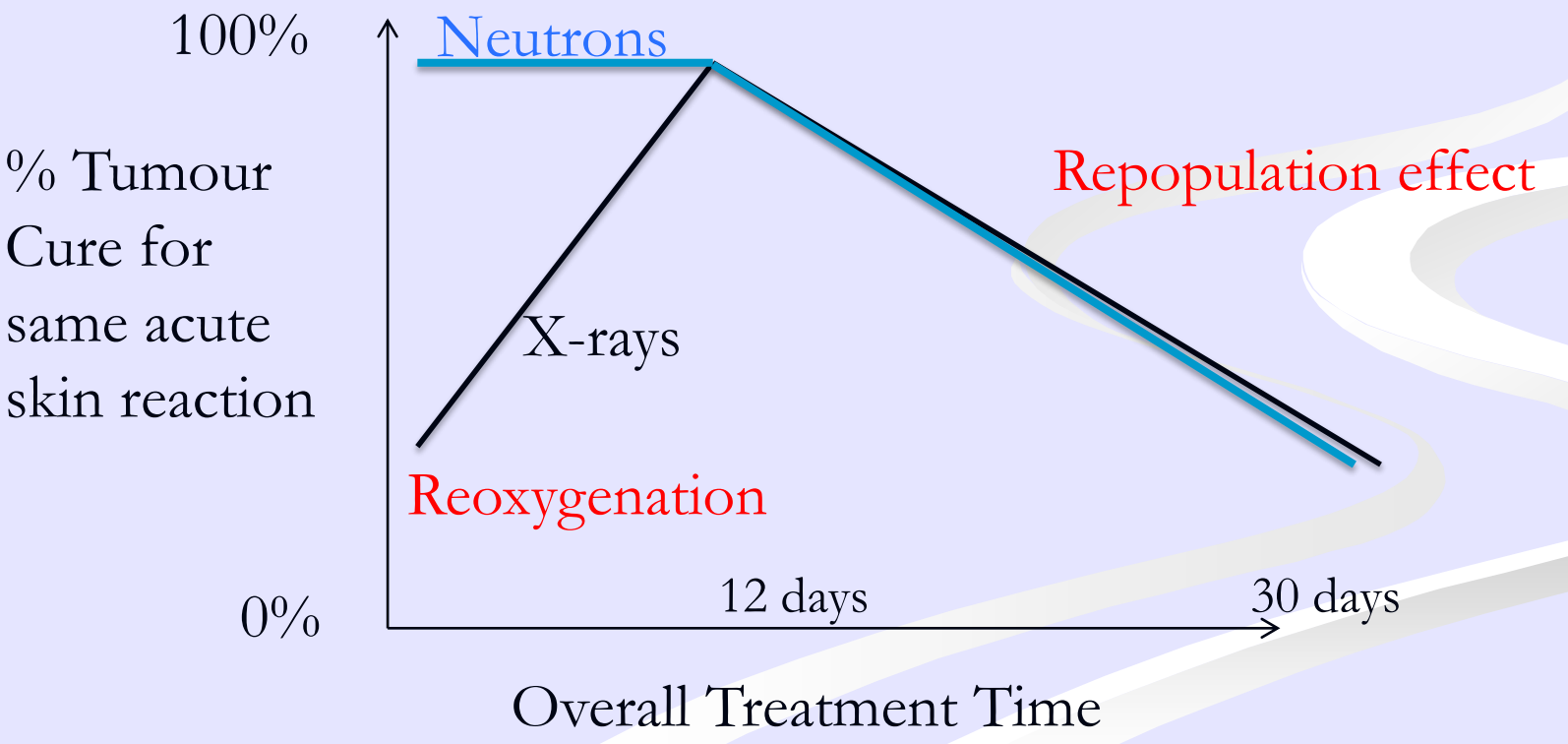
Carl UM, McNally NJ, Joiner MC.

- Effects of mixed fractionation schedules with X rays and neutrons on growth delay of a murine tumour and skin reactions. The schedules were five daily fractions of X rays, neutrons or mixtures (NNXXX, XXXNN or NXXXN).
- For clamped tumours (entirely hypoxic) or skin all three mixed schedules had the same effect.
- For unclamped tumours (hypoxic and oxic) giving the neutrons first (NNXXX) was more effective than the other two mixed schedules.

# NEUTRONS best with few fractions in short times

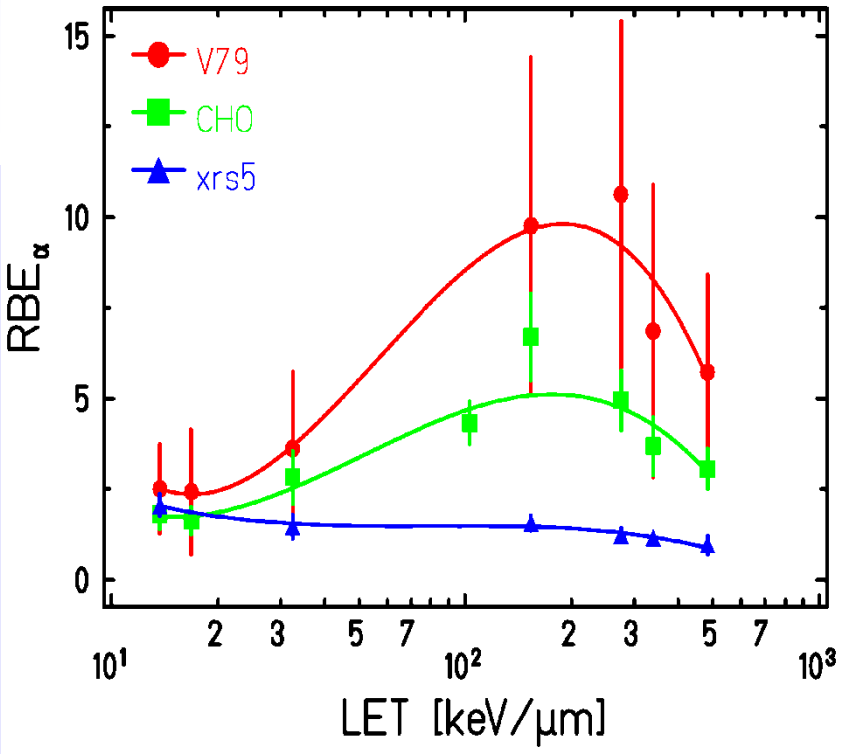
**Optimum fractionation of the C3H mouse mammary carcinoma using X-rays, the hypoxic-cell radiosensitizer Ro-07-0582, or fast neutrons**

J.F. Fowler, P.W. Sheldon, Juliana Denekamp,
& S.B. Field, Int J Radiat Oncol Biol and Physics, 1, 579–592

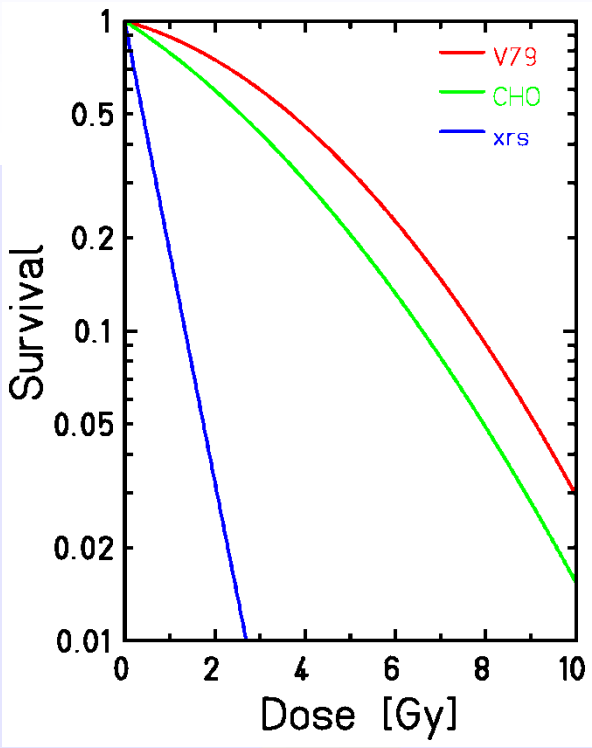


# RBE depends on Cell Type and its α/β ratio which reflects repair capacity

Carbon ions

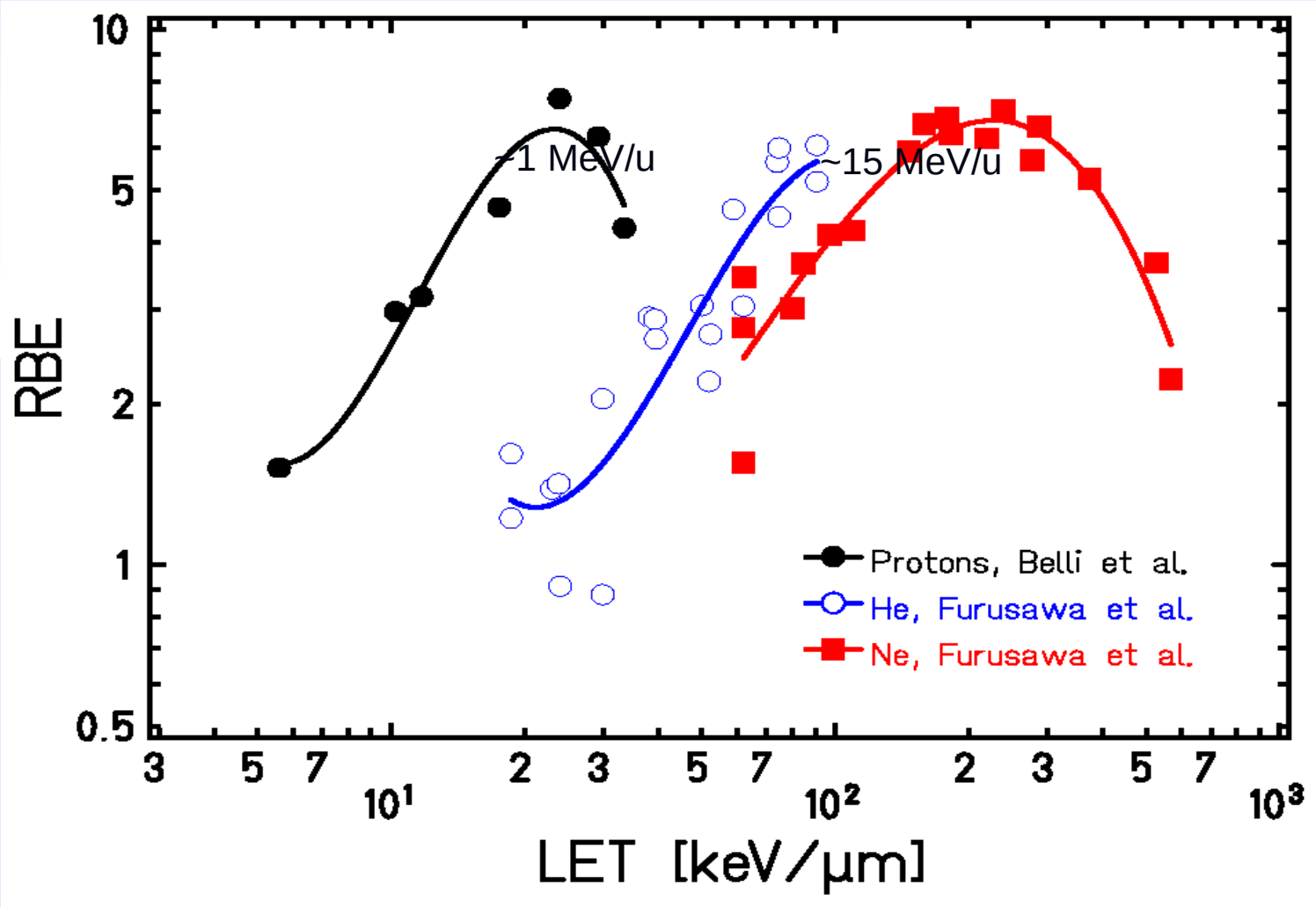



X-rays




Radioresistant cells with greatest curvature (higher DNA repair capacity) show higher RBEs (GSI, **Weyreuther** et al)

# RBE depends on A and Z




- RBE maximum is shifted to higher LET for heavier particles
- The shift corresponds to a shift to higher energies

# Biological Effective Dose
# - how do we get there?
# By definition of the "Log cell kill"=E

$$SF = e^{-\alpha d - \beta d^2},$$

$$SF^N = e^{-N(\alpha d + \beta d^2)},$$

$$-\ln(SF^N) = E = N(\alpha d + \beta d^2)$$

# BED - The Concept

- **Represents total dose if given in smallest fraction size**

$$E = n(\alpha d + \beta d^2)$$

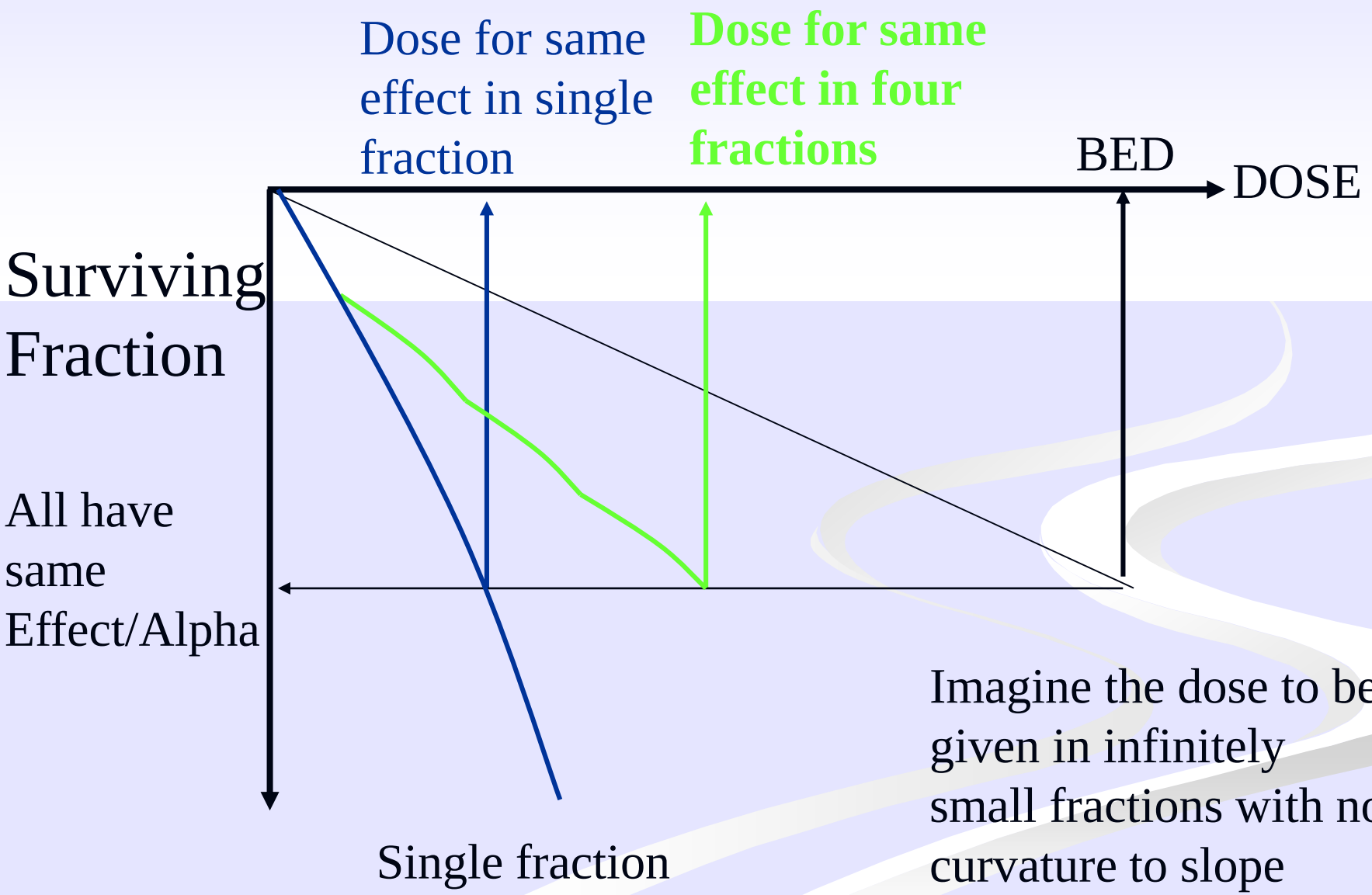
$$d \to 0, nd\alpha >> nd^2\beta$$

$$E \to nd\alpha$$

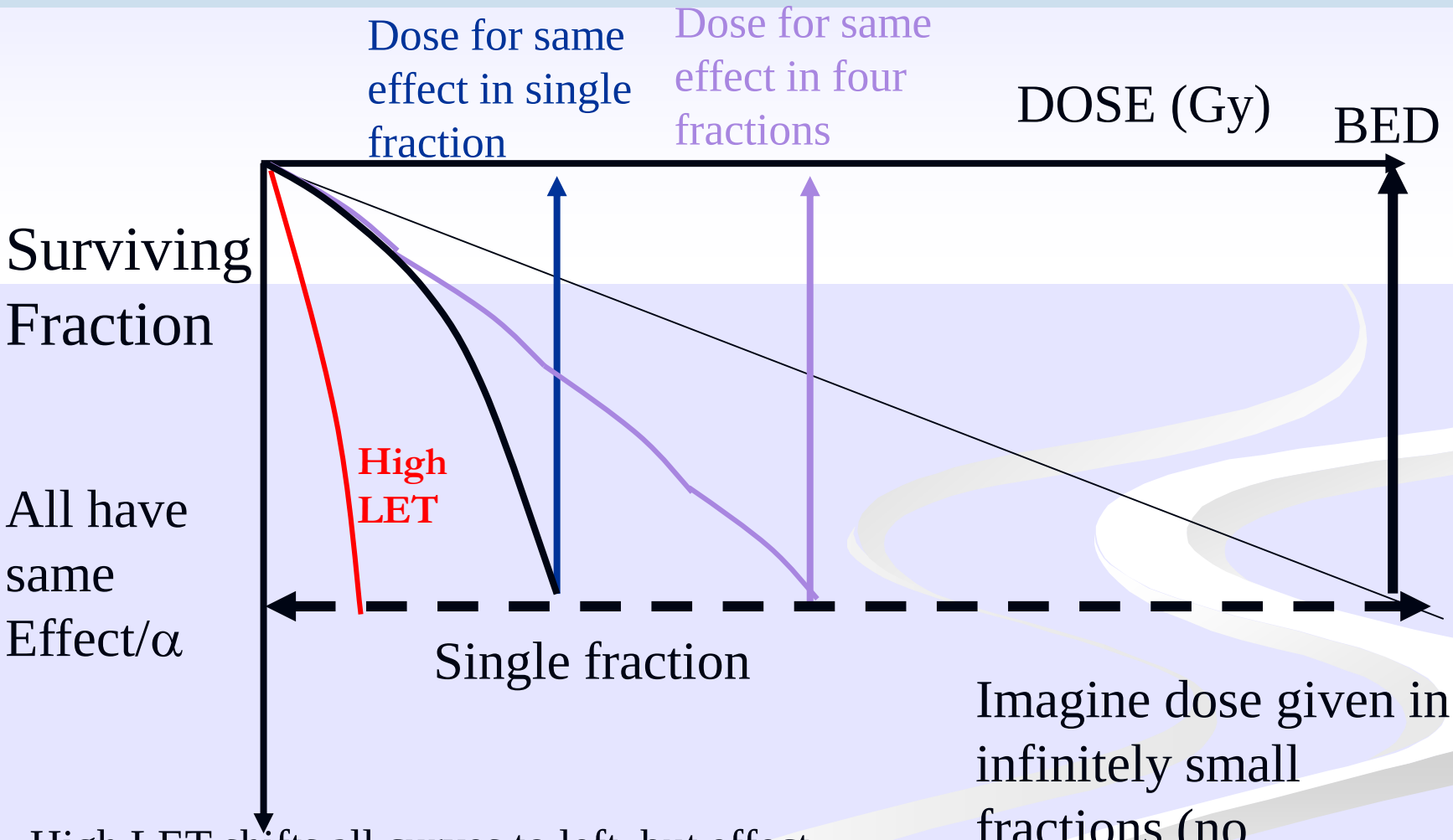
$$\frac{E}{\alpha} \to nd$$

$$BED = \frac{\mathrm{E}}{\alpha} = nd\left[1 + \frac{d}{\alpha / \beta}\right]$$

# How can we picture BED ?



# How can we picture cell survival for high low and high LET radiations?



$$N_1.d_1(1+d_1/(\alpha/\beta)) = N_2.d_2(1+d_2/(\alpha/\beta))$$

IMPLICATIONS

- Can compare any two variants of dose and number of fractions that give same effect
- Used in assessing bio-effectiveness of different fractionation schedules
- Variants for dose rate, RBE, oxygen effect etc available.

**Increase in α is greater than in β with LET**
**RBEmax>RBEmin;**
**Since RBEmax dominates cell killing at low dose, so the RBE is always larger at low rather than at higher doses.**
**Typical values RBEmax=5-7; RBEmin=1.2 -1.6**

# Useful equations for high LET radiations

$$E = \alpha_H d_H + \beta_H d_H^{\,2} = \alpha_L d_L + \beta_L d_L^{\,2}$$

RBE is defined as $\mathbf{d_L/d_H}$

$$d_H \to 0, RBE_{MAX} = \frac{\alpha_H}{\alpha_L}$$

= the RBE at low dose

$$d_H \to \infty, RBE_{MIN} = \sqrt{\frac{\beta_H}{\beta_L}}$$

= the RBE at high dose

The RBE between RBEmax and RBEmin is given by solving the first equation for $d_L$, and then divide by $d_H$, so that

$$RBE = \frac{-k + \sqrt{k^2 + 4d_H k RBE_{\max} + 4d_H^{\,2} RBE_{\min}}}{2d_H}$$

Where *k* is the low LET $\alpha/\beta$ ratio

Jones, Carabe and Dale BJR 2006 – adapted for treatment interruption calculations

# High LET Biological Effective Doses for iso-effective fractionation schedules

$$E = N(\alpha_H d_H + \beta_H d_H{}^2)$$

$$BED = \frac{E}{\alpha_L} = n\left(\frac{\alpha_H d_H}{\alpha_L} + \frac{\beta_H d_H{}^2}{\alpha_L}\right)$$

$$RBE_{MAX} = \frac{\alpha_H}{\alpha_L};$$

$$RBE_{MIN} = \sqrt{\frac{\beta_H}{\beta_L}},$$

$$\therefore RBE_{MIN}{}^2.\beta_L = \beta_H$$

*Thence*

$$BED = nd_H\left(RBE\max + \frac{RBE\min^2}{(\alpha/\beta)_L}\right)$$

$$BED = nd_H\left(RBE\max + \frac{RBE\min^2}{(\alpha/\beta)_L}\right) - K_H(T - T_K)$$

- **the low LET $\alpha/\beta$ ratio is used**
- **RBEs act as multipliers**
- **RBE values will be between RBEmax and RBEmin depending on the precise dose per fraction**
- **$K_H$ is daily high LET dose required to compensate for repopulation $\cong K_L/RBE_{max}$ low doses**
- **If a Japanese accelerator breaks down, a British equation can compensate for the delay in completion**

Low LET $$BED = N\ d(1 + \frac{d}{\frac{\alpha}{\beta}})$$

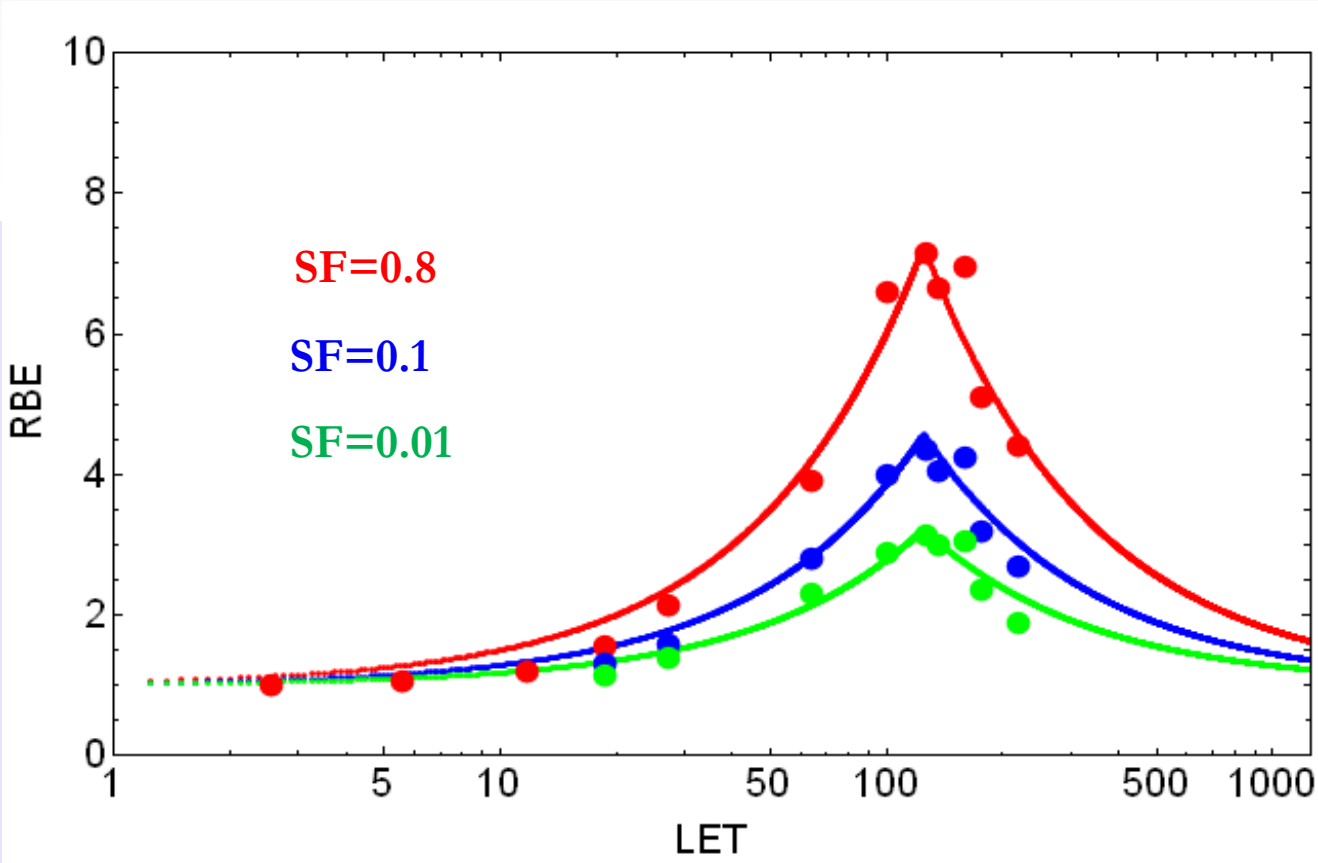
High LET $$BED = N\ d(RBEmax + RBEmin^2.\frac{d}{\frac{\alpha}{\beta}})$$

For same tissue type (i.e. same $\alpha/\beta$)
High LET BED>Low LET BED

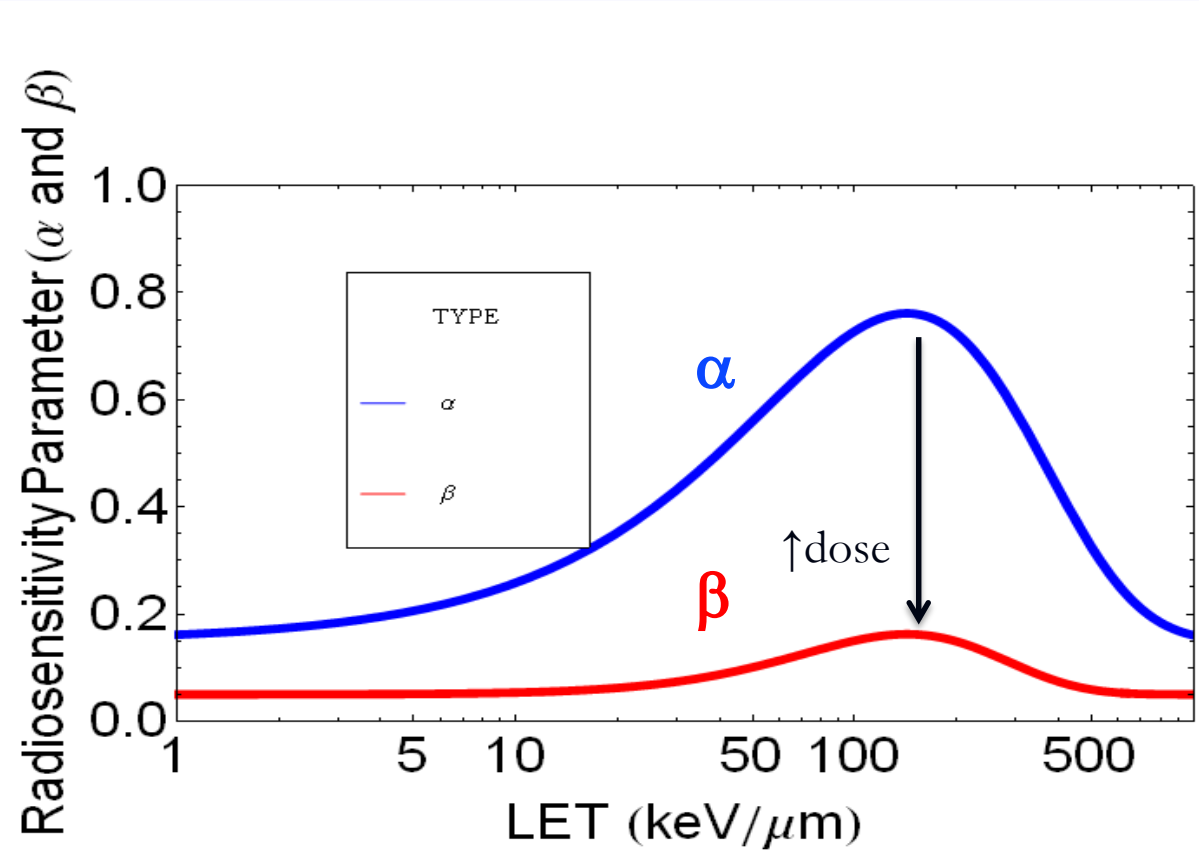
Differences become larger when $\alpha/\beta$ is small
Small $\alpha/\beta$ (2-3 Gy) in slow proliferation states/stable tissues and tumours. Larger $\alpha/\beta$ in rapidly proliferating tissues and tumours.

# Data of Barendsen (1968), monoenergetic alpha particles and deuterons only for three levels of dose [cell surviving fraction]

Oxford Model



# Assume same turnover point for increment in α and β with LET , in order to preserve symmetry of relationship when dose changes.




With increasing dose a greater proportion of damage is due to β curve (where damage proportional to dose squared)

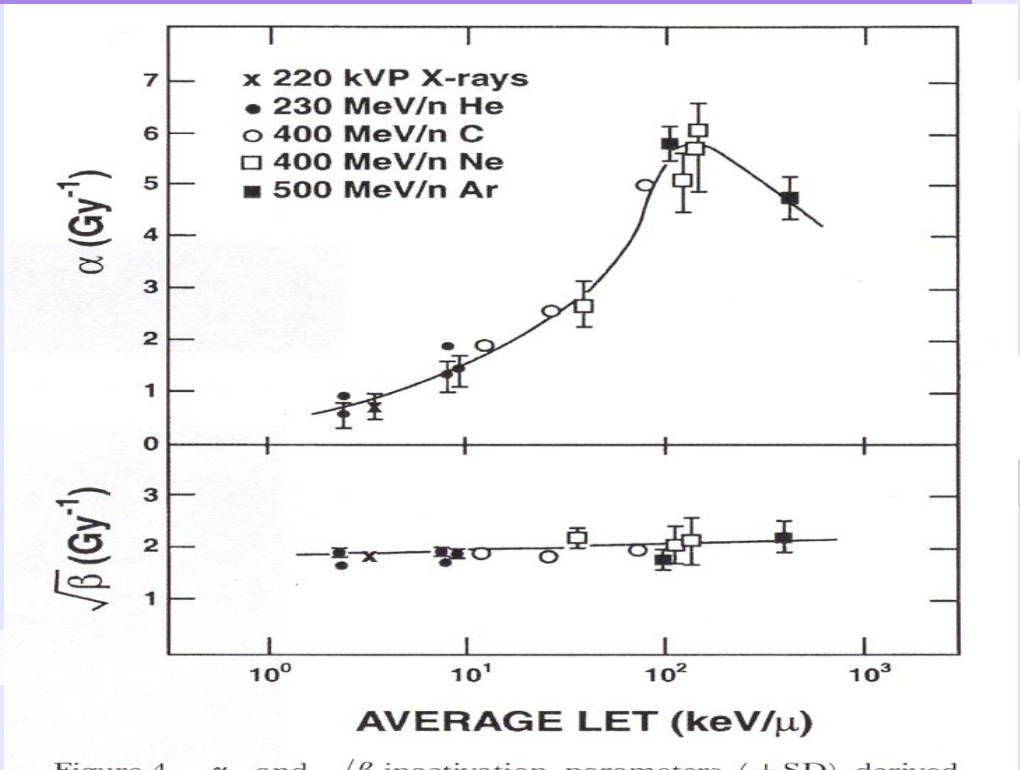
# Does β parameter change with increasing LET ?

Since ratio $\sqrt{\beta_H}:\sqrt{\beta_L}$ is the $RBE_{MIN}$ - at very high dose – then this ratio needs to be known if >1

More research necessary to confirm if $RBE_{MIN}>1$ at range of high LET beam energies.

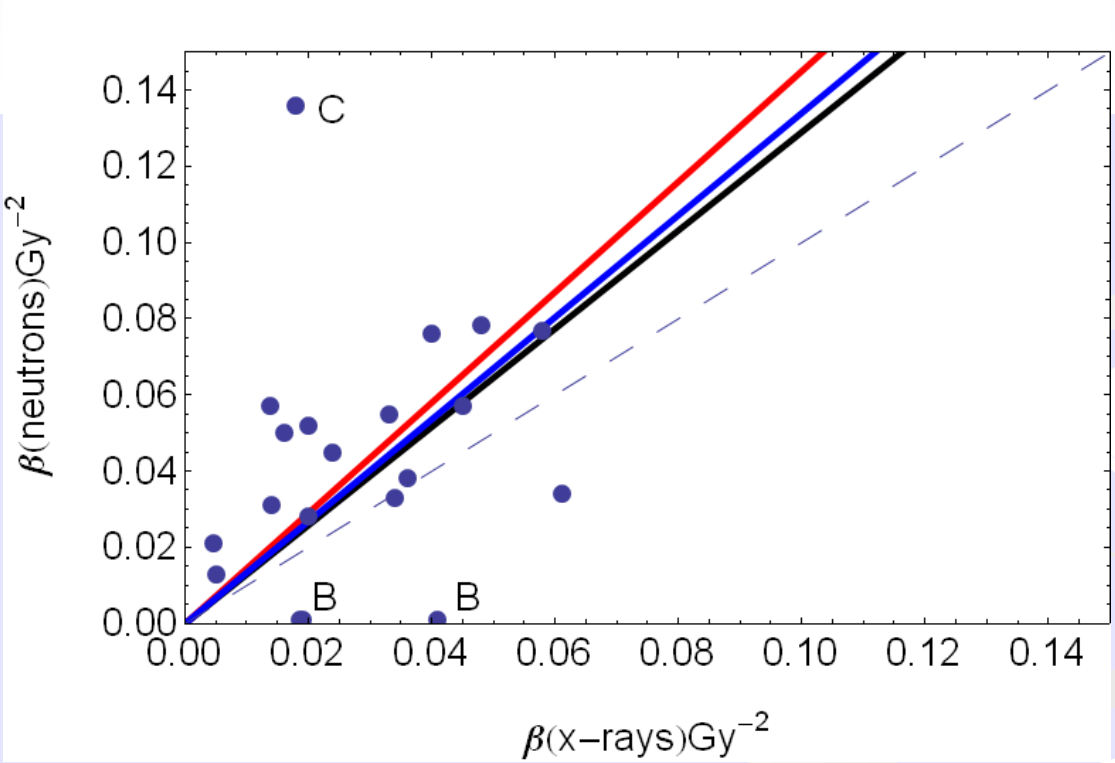
For each beam, each cell/tissue type would need to have this ratio estimated.

Chapman (IJRB 2003) measured $\sqrt{\beta}$, a larger number than β, and found no significant difference with increasing LET in CH V-79 in plateau phase.



Beta increases with LET [in the case of fast neutrons] in 23 human tumour cell lines. BUT the increase is small compared to ALPHA

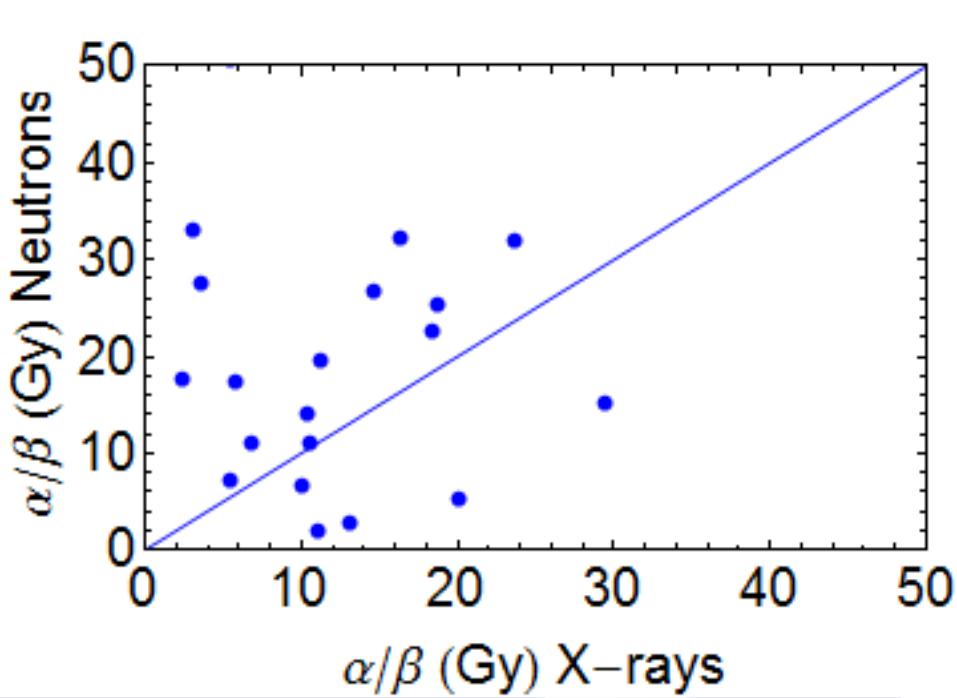
Jones B, 2009 Brit J Radiology



**Britten and Warenius et al , Clatterbridge UK**

**α increases by 3.17**

**√β increases by 1.59**



# Fast neutrons

- Looked attractive in laboratory setting
- Cells killed more efficiently RBE of 2-4 in different cell types
- Reduced oxygen dependency : OER around ~1.6
- Three cyclotrons built in UK

1. Hammersmith 2. Edinburgh 3. Clatterbridge

# Hammersmith

- Low energy…depth dose like 200Kev X-rays; only superficial tumours treated. Fixed horizontal beam.
- Attempt at control trial included patients treated at different hospitals and to a variety of doses for X-rays.
- Fractionation:1.5 Gy three times per week.
- Side effects ? Under-reported….severe side effects patients operated at other hospitals, did not return etc etc.

# Edinburgh

- Used gantry but beam equivalent to 250 KeV x-rays
- Randomisation between megavoltage x-rays and neutrons…all patients in same hospital. Dose per fraction lower 0.9 Gy neutrons, five times per week.
- Deep tumours treated (e.g. bladder) using multiple fields > 4 for neutrons, </=4 for x-rays.
- Dissappointing results …no improvement; high incidence of severe normal tissues reactions.

# Clatterbridge [near Liverpool]

- Used much higher energy neutrons (64MeV) equivalent in % depth dose to 4 MeV x-rays, so same number of fields used; fractionation was same as hammersmith; overall RBE of 3;
- Fractionation:1.6 Gy three times per week.
- Results: no advantage in tumour control; side effects slightly increased; high metastatic rate; trial closed.
- Centre converted to eye proton therapy

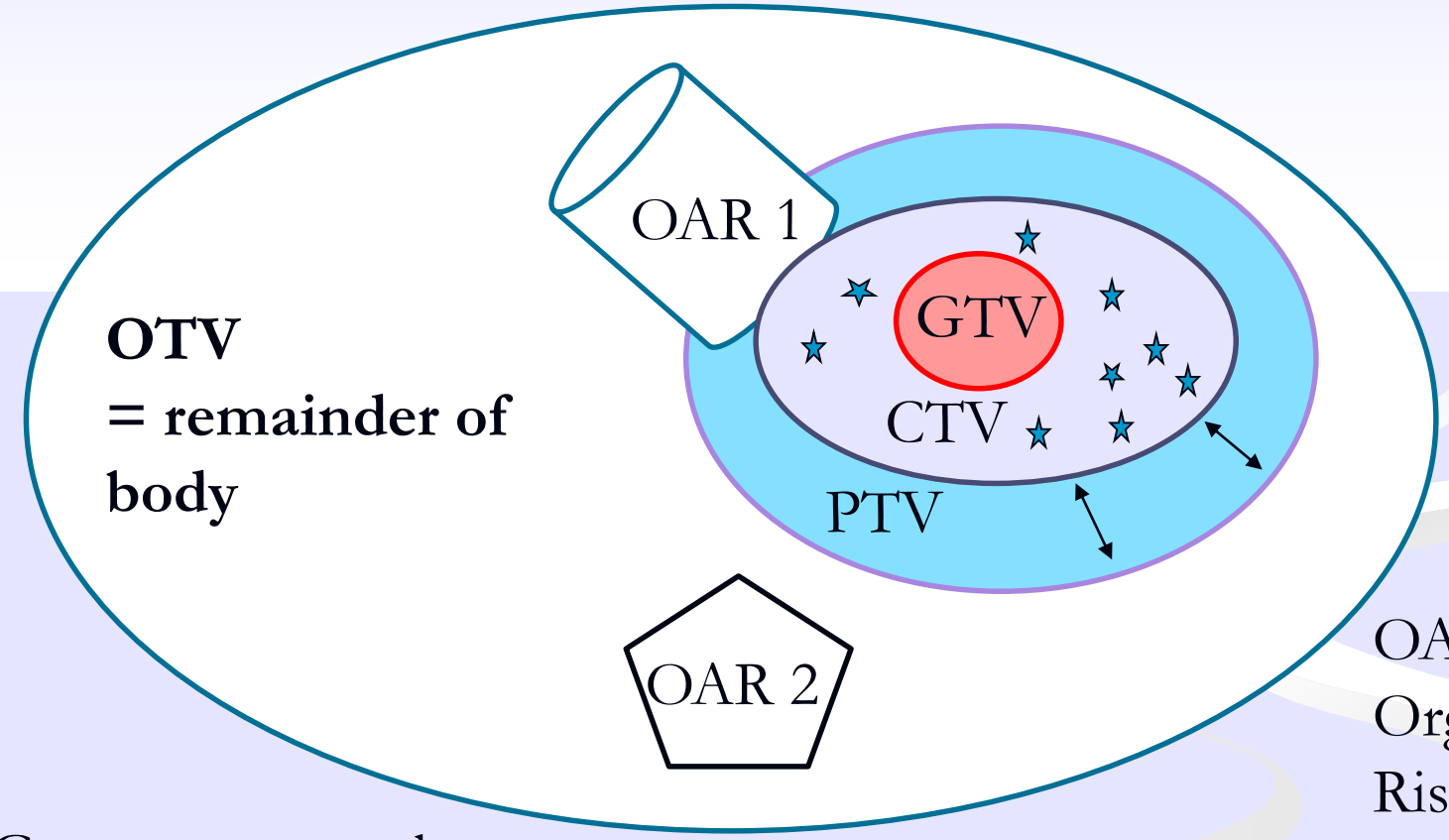
# Clinical fast neutrons

**Duncan W, 1994. An evaluation of the results of neutron therapy trials. Acta Oncol. 33, 299-306.**

**Errington RD, Ashby D, Gore SM et al, 1991. High energy neutron treatment for pelvic cancers: study stopped because of increased mortality. British Medical Journal, 302, 1045–1051.**

**Debate about trials extends to protons and ions….see amongst others Glimelius B, Montelius A, 2007. Proton beam therapy – do we need the randomised trials and can we do them? Radiother Oncol. 83:105-9.**

# ICRU target volume definitions + Outside Target Volume OTV



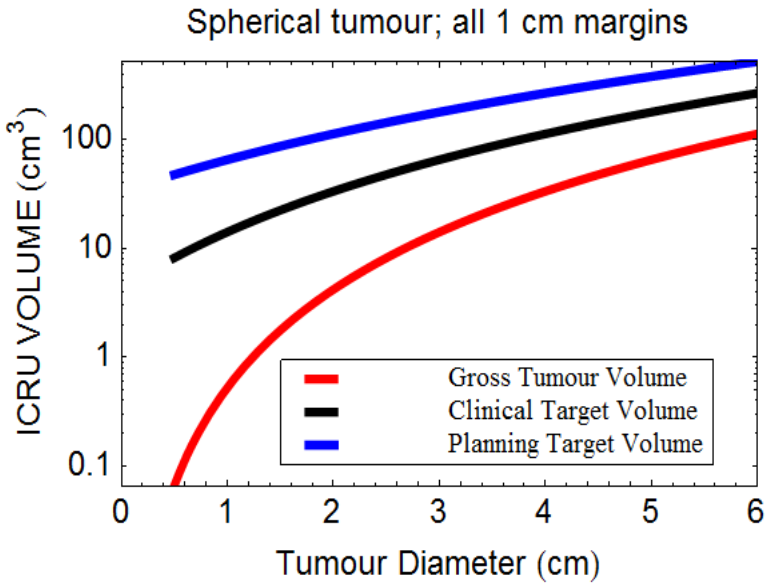

GTV Gross tumour volume

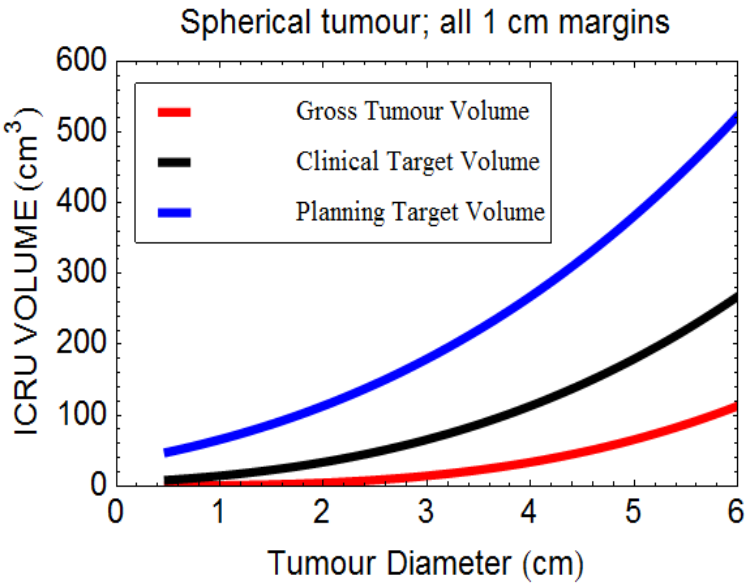
CTV Clinical target volume contains normal tissue

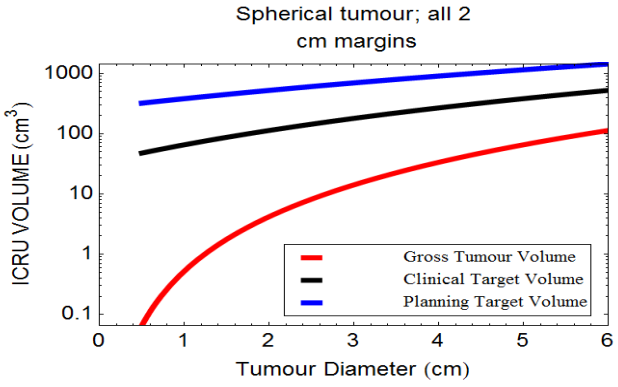
PTV Planning target volume contains normal tissue

OAR = Organs at Risk – within CTV, PTV and OTV

# Normal tissue volumes which have to be treated



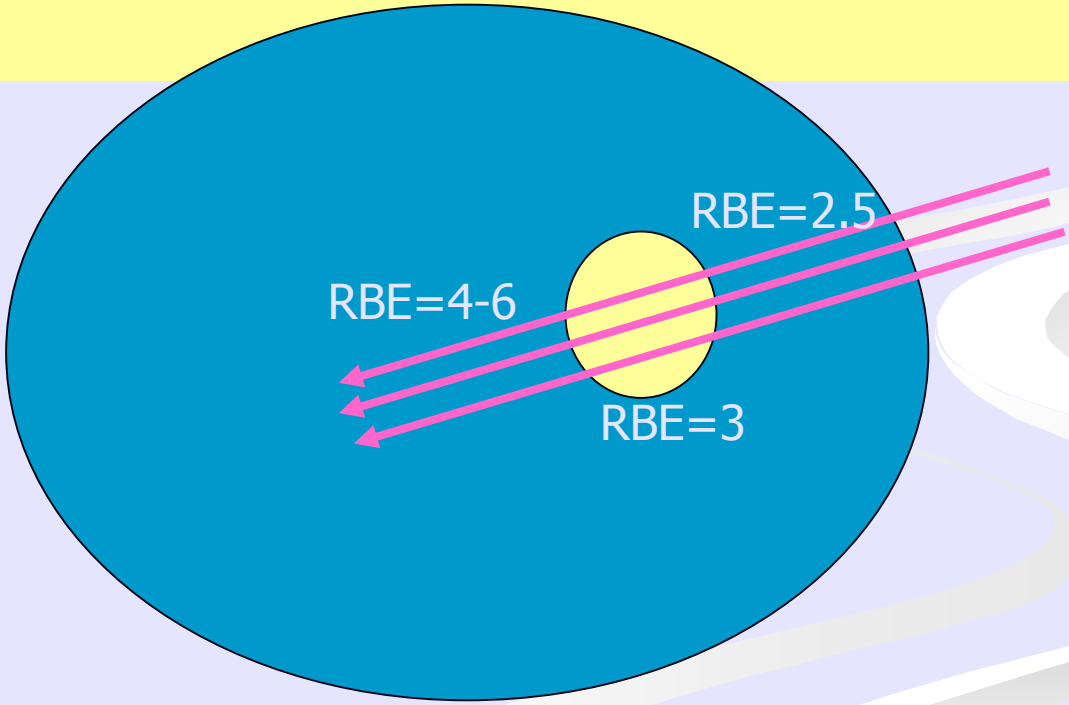



| Dose Status | TCP [Z1+Z2] | Z2 side effects | Z3 side effects |
|---|---|---|---|
| **Z1↑,Z2↑, Z3↓** | better | worse* | better |
| | | | |
| **Z1↑,Z2=, Z3↓** | better | equal** | better |
| **Z1=,Z2=, Z3↓** | equal** | equal ** | better |
| **Z1=,Z2↓, Z3↓** | worse | better | better |

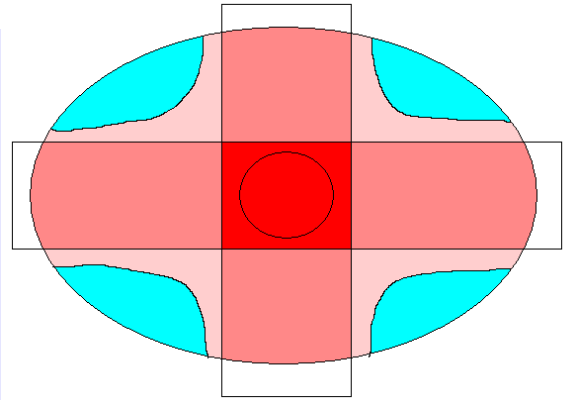
| Dose Status | Tumour Control (in Z1 and Z2) | Z2 side effects | Z3 side effects |
|---|---|---|---|
| Z1↑, Z2↑, Z3↓ | • much better if $RBE_C > RBE_{Rx}$<br>better or equal or worse (depending on dose ↑) if $RBE_C \leq RBE_{Rx}$ | better only if $RBE_{NT} < RBE_{Rx}$ and depending on dose ↑<br>Worse if $RBE_{NT} \geq RBE_{Rx}$ | Better if dose reduction sufficient to overcome any disadvantage in RBE |
| Z1↑, Z2=, Z3↓ | • better if $RBE_C > RBE_{Rx}$<br>• better, equal or worse depending on dose ↑ in Z1, equality of α/β or extent of $RBE_C < RBE_{Rx}$ | Better if $RBE_{NT} < RBE_{Rx}$<br>Equal if $RBE_{NT} = RBE_{Rx}$<br>Worse if $RBE_{NT} > RBE_{Rx}$ | Better if dose reduction sufficient to overcome any disadvantage in RBE |
| Z1=, Z2=, Z3↓ | • Better – only if $RBE_C > RBE_{Rx}$<br>• Same if $RBE_C = RBE_{Rx}$<br>• worse depending on extent of $RBE_C < RBE_{Rx}$ | Better if $RBE_{NT} < RBE_{Rx}$<br>equal - only if $RBE_{NT} = RBE_{Rx}$<br>Worse if $RBE_{NT} > RBE_{Rx}$ | Better if dose reduction sufficient to overcome any disadvantage in RBE |
| Z1=, Z2↓, Z3↓ | Worse, unless if $RBE_C > RBE_{Rx}$ | Better if $RBE_{NT} \leq RBE_{Rx}$<br>Could be equal if $RBE_{NT} > RBE_{Rx}$ depending on dose↓ | Better if dose reduction sufficient to overcome any disadvantage in RBE |

# Neutron Therapy –

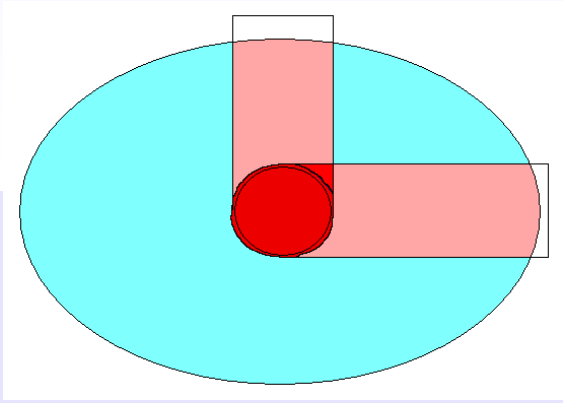
**Dose fall off with depth past tumour with increase in RBE. Prescription of radiation used RBE of 3 at tumour depth and assumed this to be the case at all other points within a patient. Results not surprising in retrospect.**

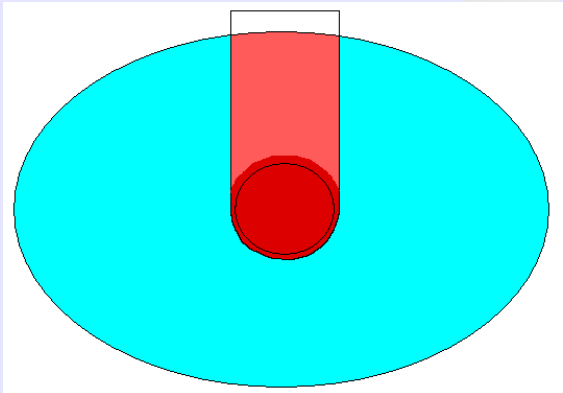


# Photons X



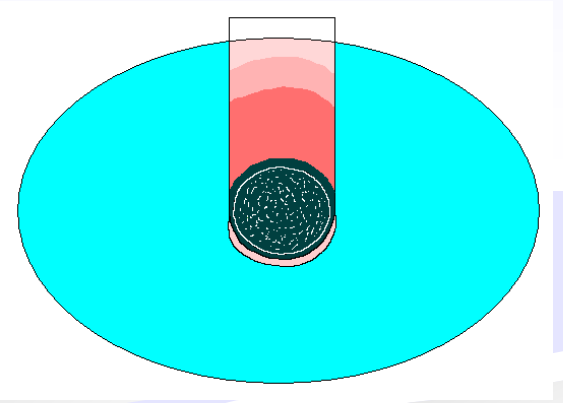
# Protons



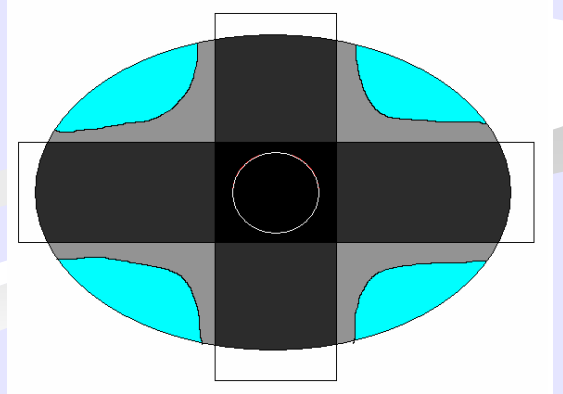


# Carbone

**EBR >> 1**



# Neutrons



**Efficacité biologique relative EBR ≈ 1**

# Neutron skin RBE
# Hopewell et al 1988 (Brit J Radiology)

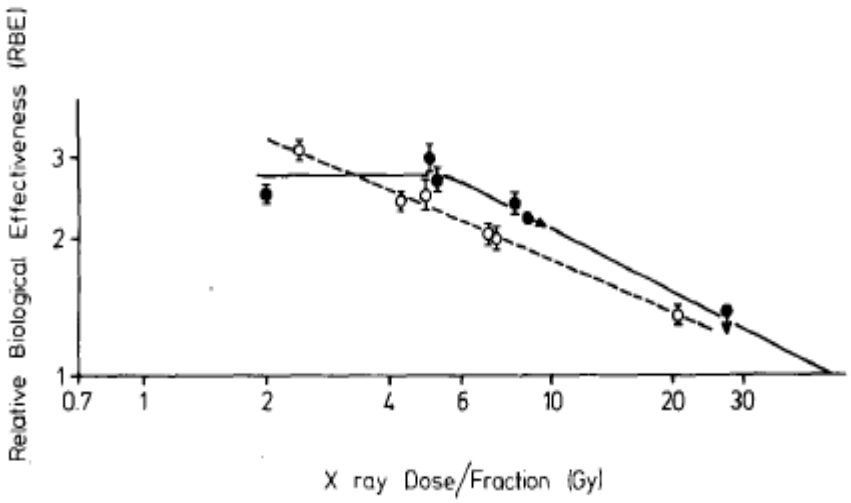



**Figure 6.** Log–log plot of the RBE (±SE) value for early moist desquamation (●) and late dermal necrosis (○) in pig skin as a function of the X-ray dose per fraction.

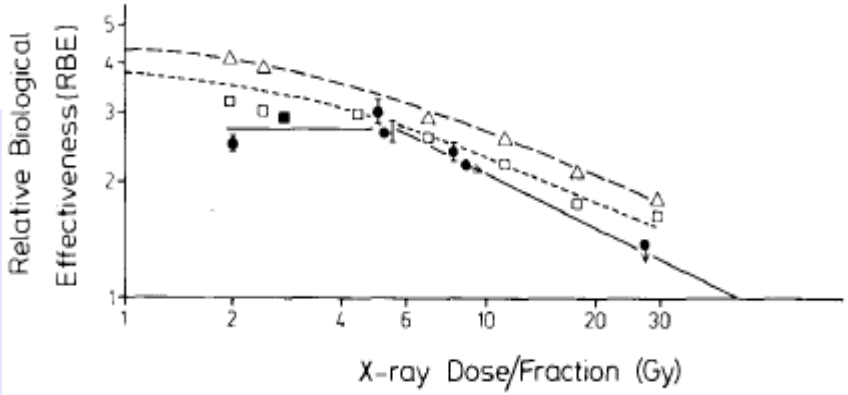
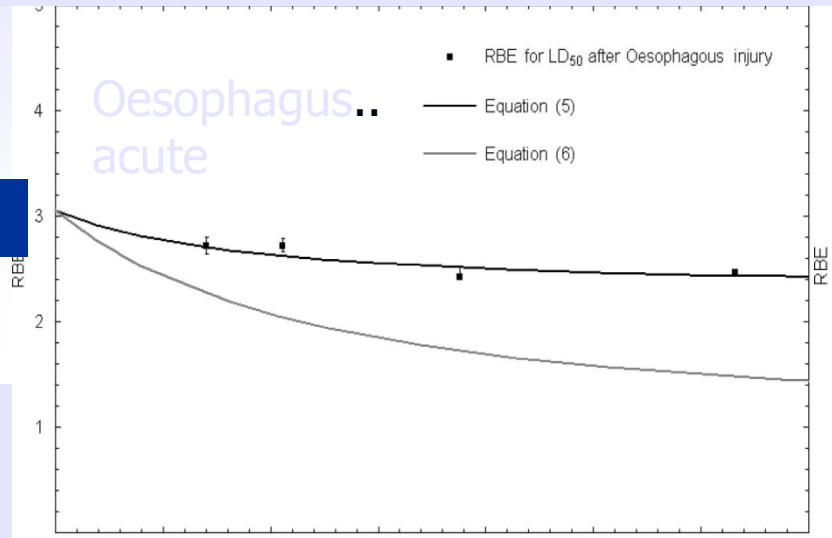
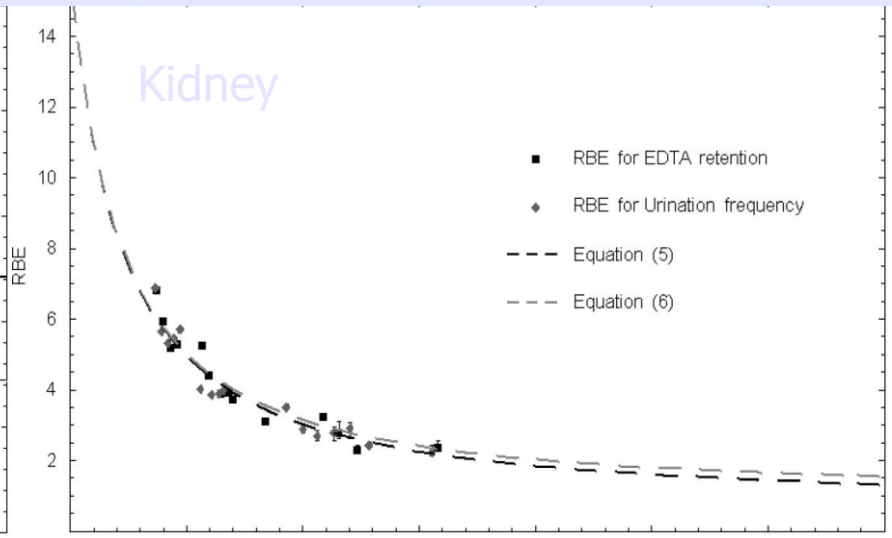


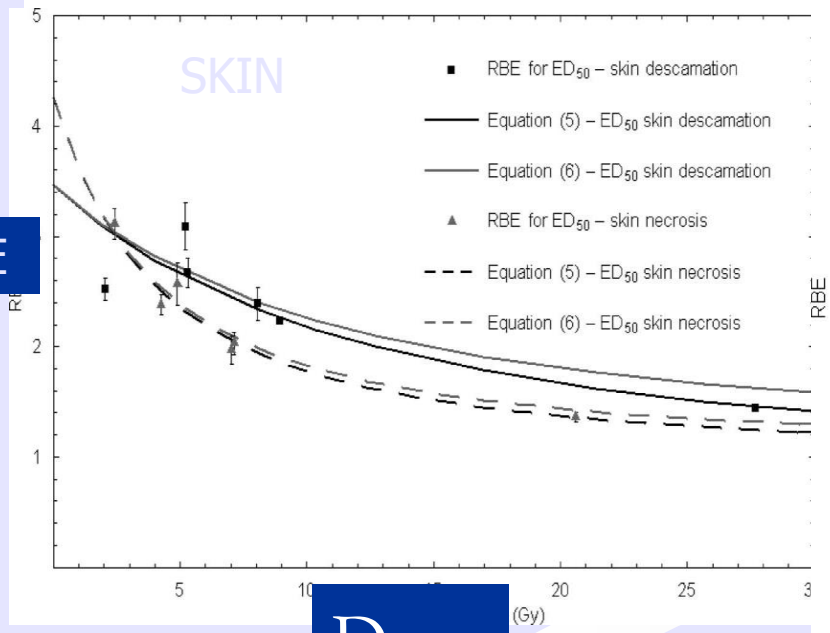

**Figure 7.** Log–log plot of the RBE for early moist desquamation in the skin of pigs (■, ●) or mice (△, □) against the X-ray dose per fraction. The results obtained using neutrons generated by 42 $MeV_{d\rightarrow Be}$ (●), 62 $MeV_{p\rightarrow Be}$ (□), 16 $MeV_{d\rightarrow Be}$ (△) and 66 $MeV_{p\rightarrow Be}$ (■) are compared. For the studies with mice (Joiner & Field, 1988) only the data points for doses $\geqslant 2$ Gy per fraction are plotted. The curves fitted to these results are those based on the predictions of the linear-quadratic model (for further explanation see text).

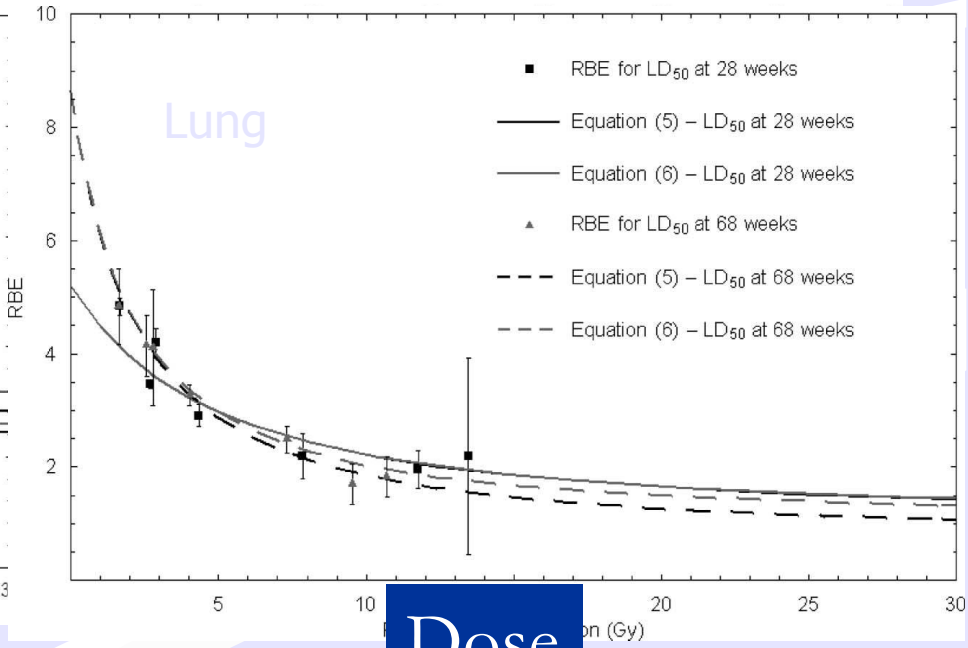
# Examples of Hammersmith & Clatterbridge animal neutron experiments – Carabe-Fernandez et al IJRB 2007




RBE




RBE

Dose

Dose

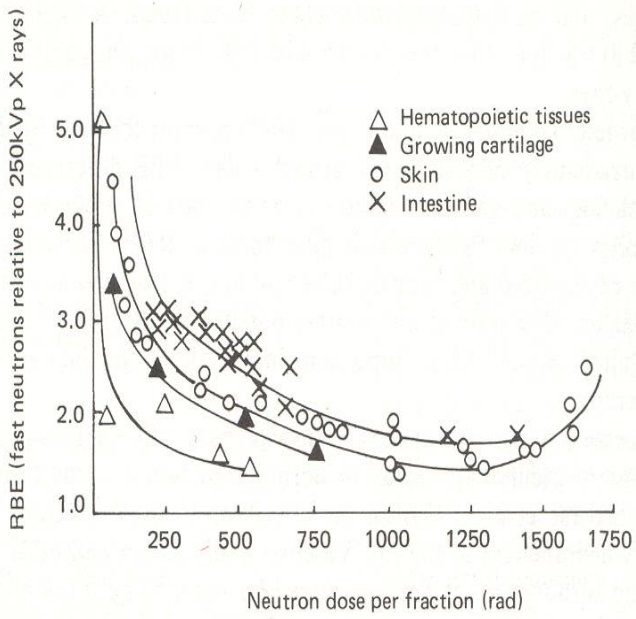



Figure 15.22. RBE for fast neutrons relative to 250-kV X-rays as a function of neutron dose for certain normal mammalian tissues, as indicated. Hornsey, 1970.

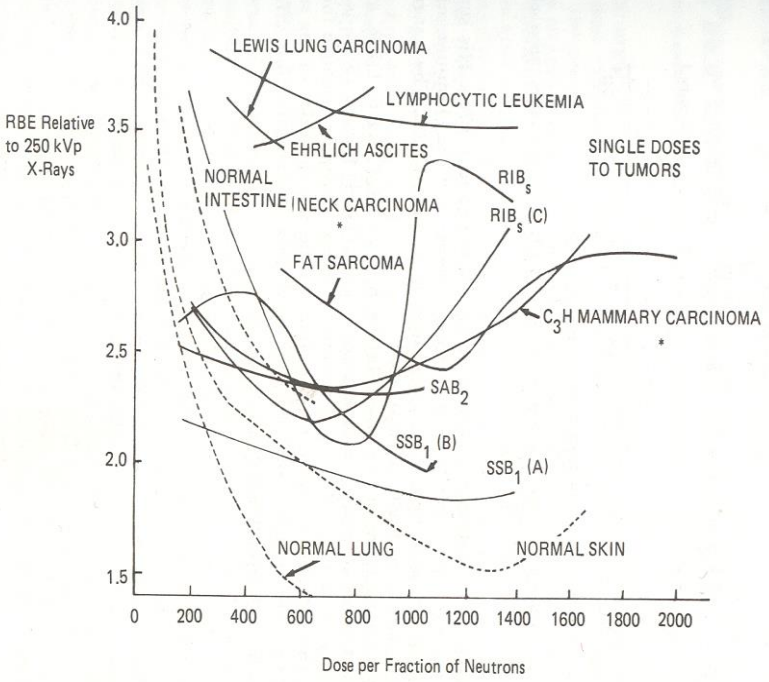



Figure 15.23. RBE for single doses to various tumors as a function of the dose per fraction of neutrons. Data from various sources. Field, 1976.

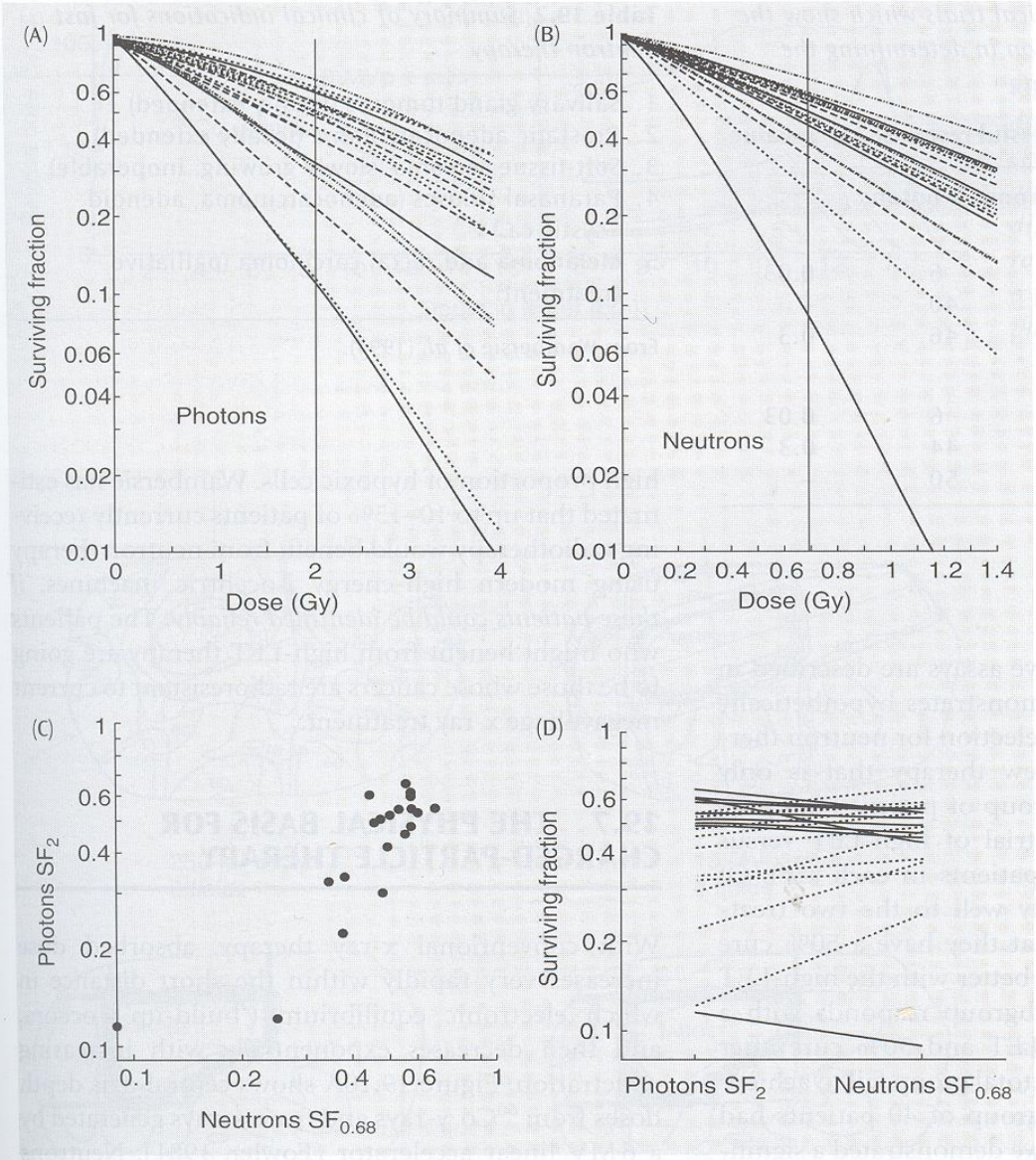



**Figure 19.9** *Response of 20 human tumour cell lines to (A) 4 MVp photons, or (B) p(62.5)-Be neutrons. The vertical lines show the photon (2 Gy) and neutron (0.68 Gy) doses that give the same median cell survival; the average RBE is therefore 2/0.68 = 2.94. Panel C shows that the range of cell survival at the reference neutron dose of 0.68 Gy is less than the range of photon $SF_2$ values. In 9/20 of the cell lines neutrons gave lower cell survival than photons at these doses (panel D).*

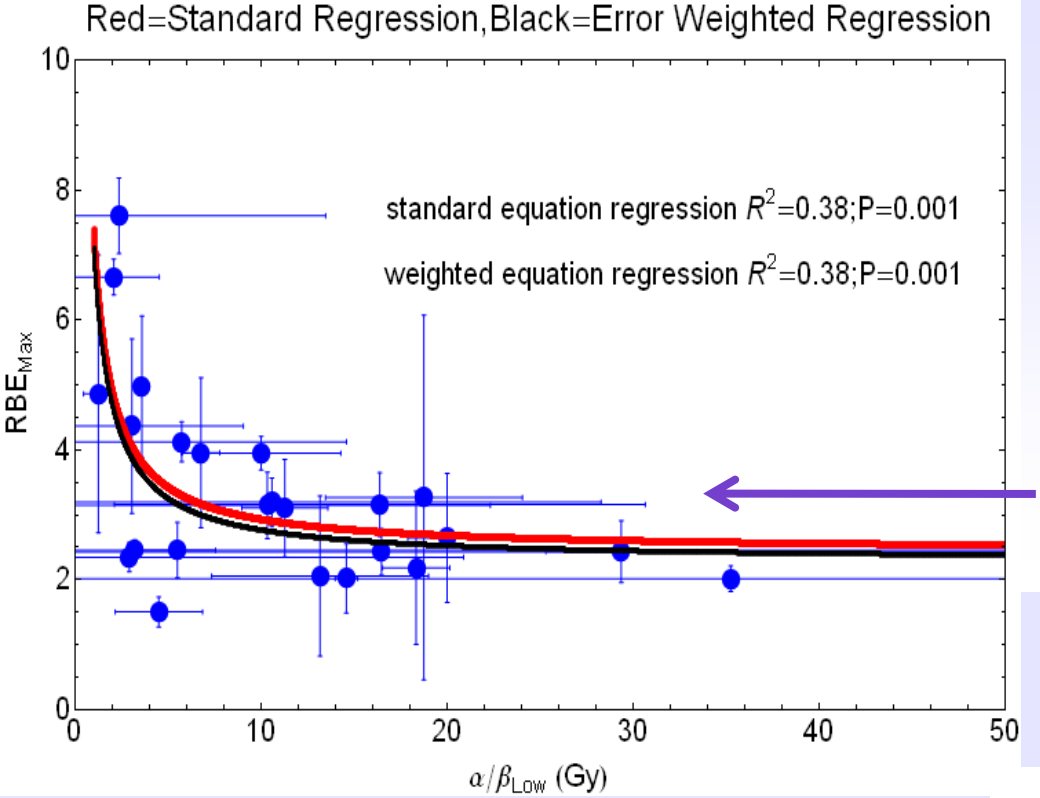
**From previous definitions of $RBE_{max}$ and $RBE_{min}$**

$$RBE_{\max} = \frac{\alpha_H}{\beta_H} \cdot \frac{RBE_{\min}^{\,2}}{\left(\frac{\alpha_L}{\beta_L}\right)} = \frac{Q}{\left(\frac{\alpha_L}{\beta_L}\right)}$$

$$RBE_{\min} = \sqrt{\frac{\alpha_L}{\beta_L} \cdot \frac{RBE_{\max}}{\frac{\alpha_H}{\beta_H}}} = S\sqrt{\frac{\alpha_L}{\beta_L}}$$

Impose lower limit boundary conditions C and K on each RBE (which are RBE change due to beam physics alone)→

$$RBE_{\max} = C + \frac{A}{\left(\frac{\alpha_L}{\beta_L}\right)} \qquad RBE_{\min} = K + B\sqrt{\frac{\alpha_L}{\beta_L}}$$



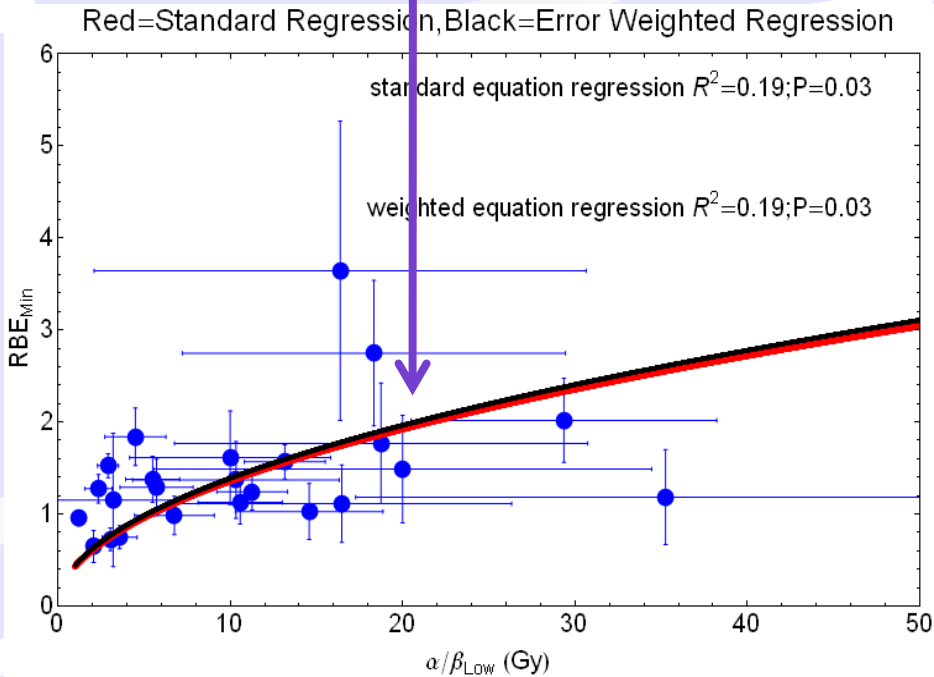

**L=Low LET, H=High LET**

$$RBE_{MAX} = \alpha_H/\alpha_L$$

$$RBE_{MIN} = \sqrt{(\beta_H/\beta_L)}$$

$$\mathbf{RBE_{MAX} = A+B/(\alpha/\beta)_L}$$

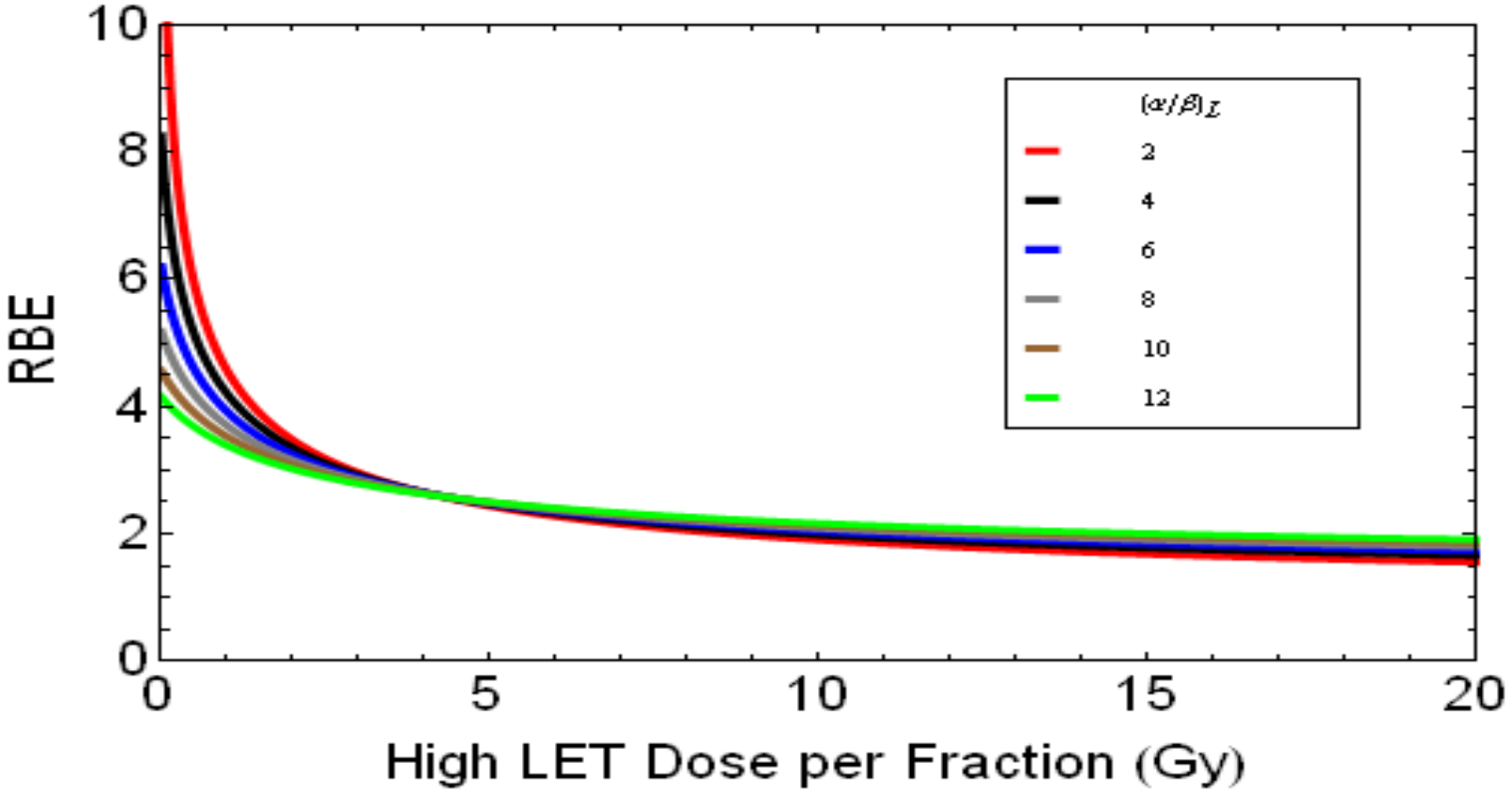
$$\mathbf{RBE_{MIN} = C+K\sqrt{(\alpha/\beta)_L}}$$




Fast neutron data Hammersmith and Clatterbridge data. Then replace the two RBE limits in:

**BED[highLET]**
**$=D_H(R_{MAX}+R_{MIN}^2 d_H/(\alpha/\beta)_L)$**
**BED[lowLET]**
**$=D_L(1+d_L/(\alpha/\beta)_L)$**

# Modelled Fast Neutron RBE and dose relationships



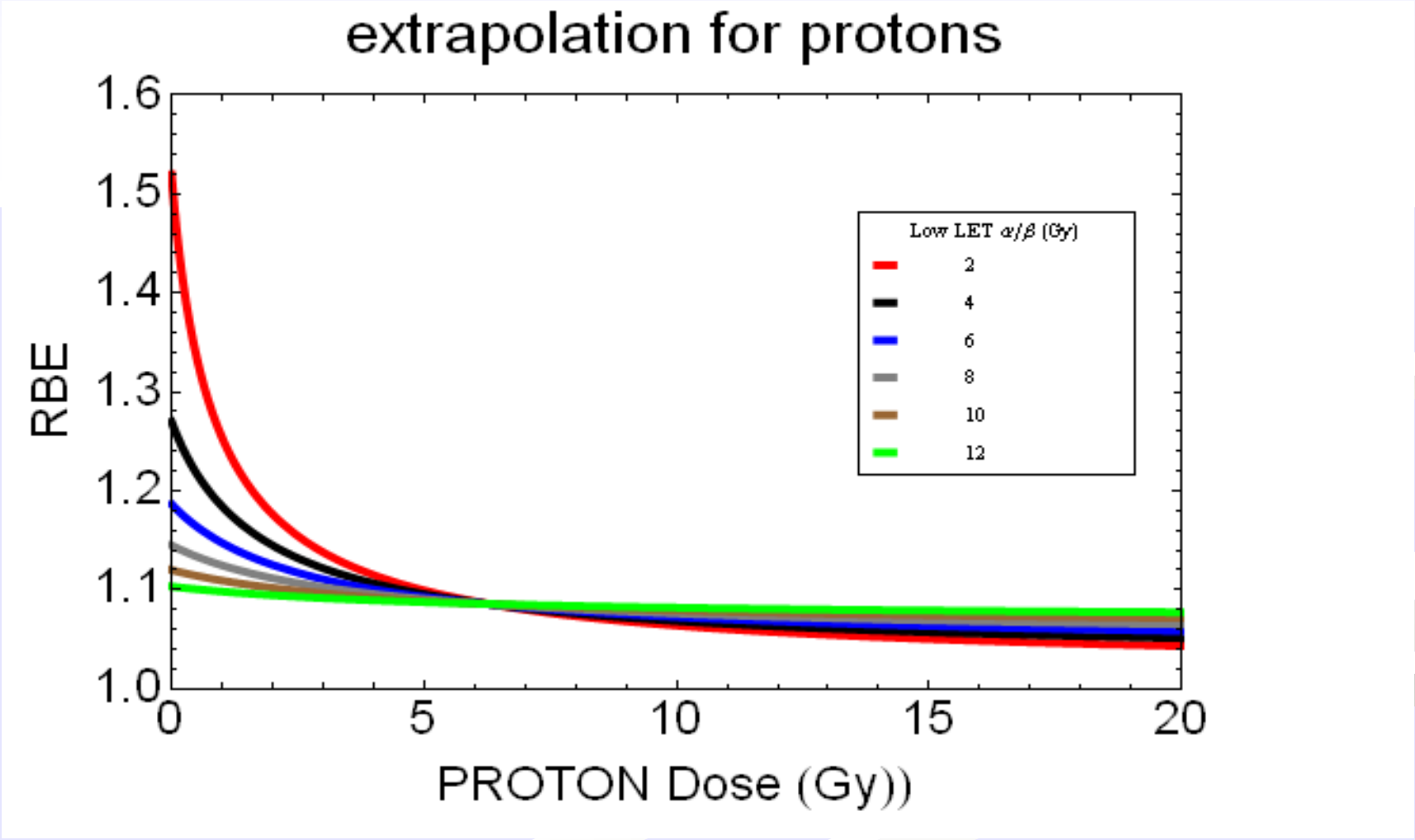

**RBE larger at low dose per fraction, with highest values in late-reacting tissues (low $\alpha/\beta$ ratio).**

**Note: most RBE assays use high $\alpha/\beta$ ratio endpoints (respond like brown and green lines).**

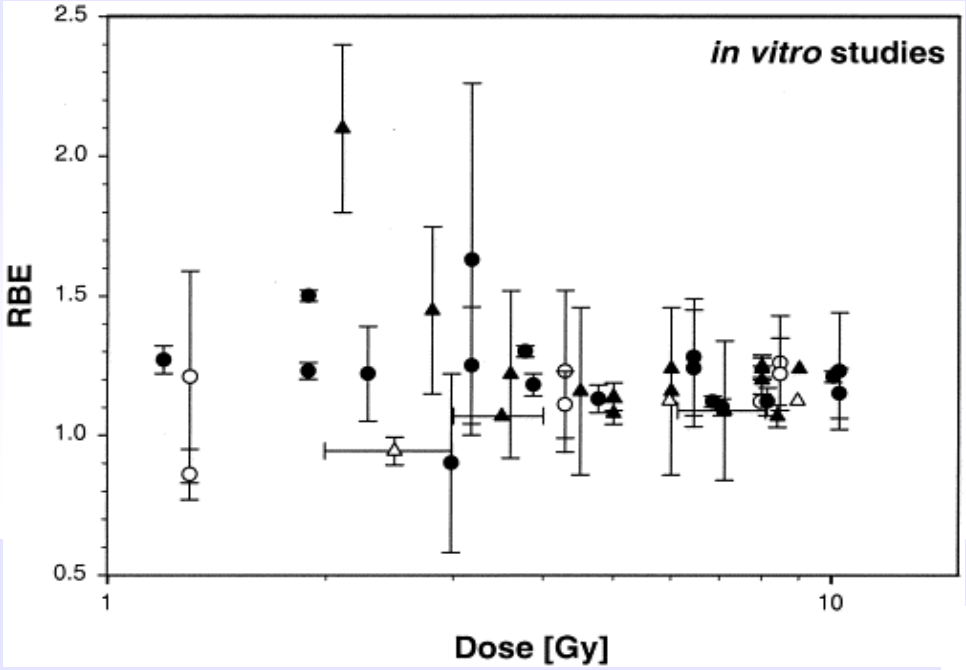
# If relationship scaled down for protons as:

$$RBEmax = 1.0 + 1.2/(\alpha/\beta)_L$$

$$RBEmin = 1.0 + Sqrt[0.0005 .(\alpha/\beta)_L]$$



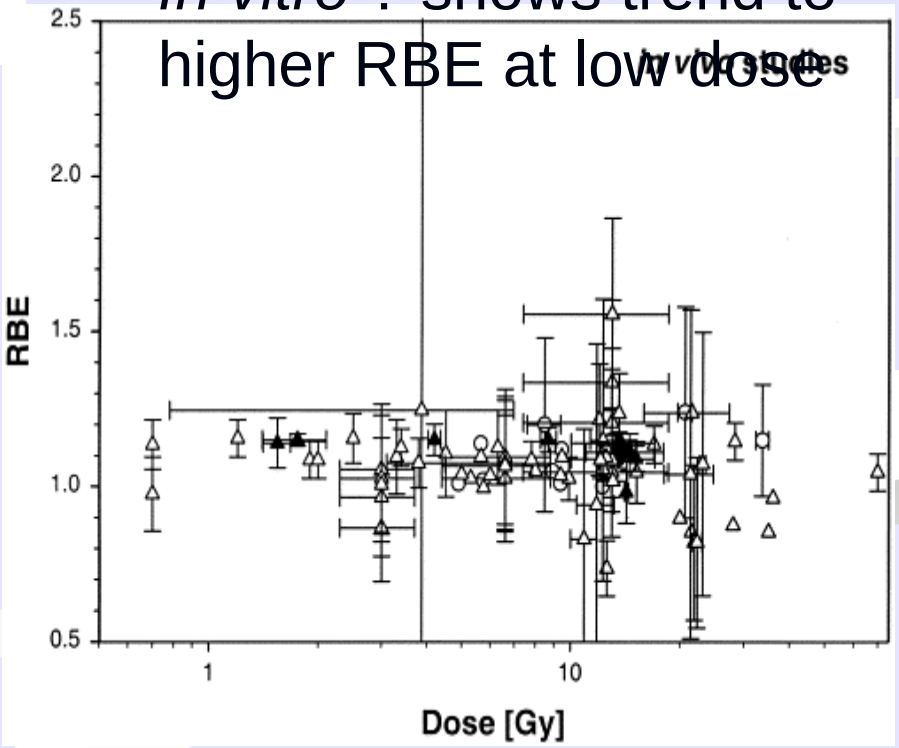

Jones, Underwood ,Timlin and Dale (Brit J Radiol – in press 2011)




**Boston review of proton RBE studies: Paganetti et al IJROBP 2002**

**IN MID Spread out Bragg peaks (SOBP`s)**

*In vitro* ? shows trend to higher RBE at low dose




*In vivo* and *in vitro* results are consistent with ***high $\alpha/\beta$ ratio endpoints***, as expected from rapidly growing CHO-V79 cells and acute small intestine crypt assay.

# Intestinal crypt regeneration in mice: a biological system for quality assurance in non-conventional radiation therapy.

**Gueulette J**, Octave-Prignot M, De Costera BM, Wambersie A, Grégoire V.

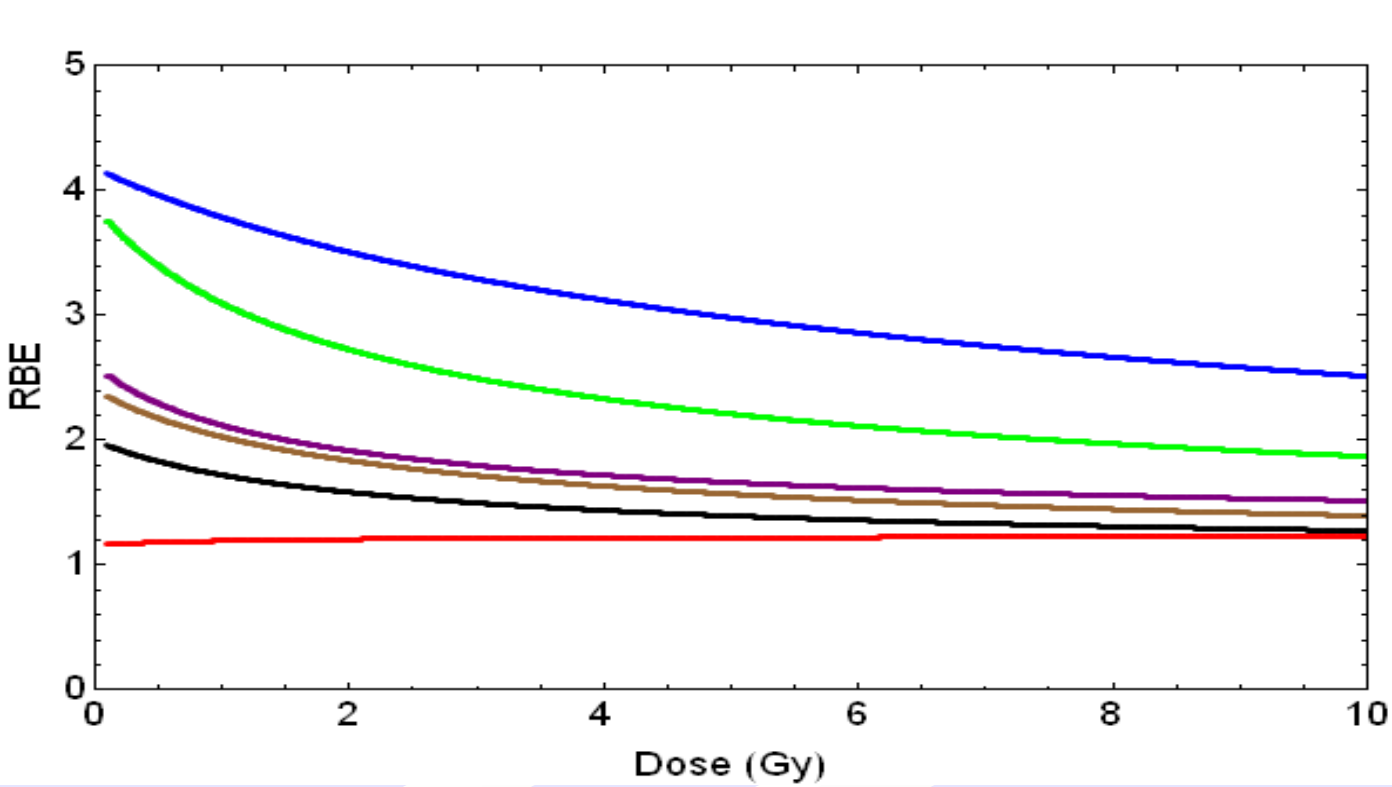
Radiother Oncol. 2004 Dec;73 Suppl 2:S148-54.

- Used throughout the world as quality assurance for neutron and proton beams; many reports.
- But it does not inform what the RBE is in humans for late effects

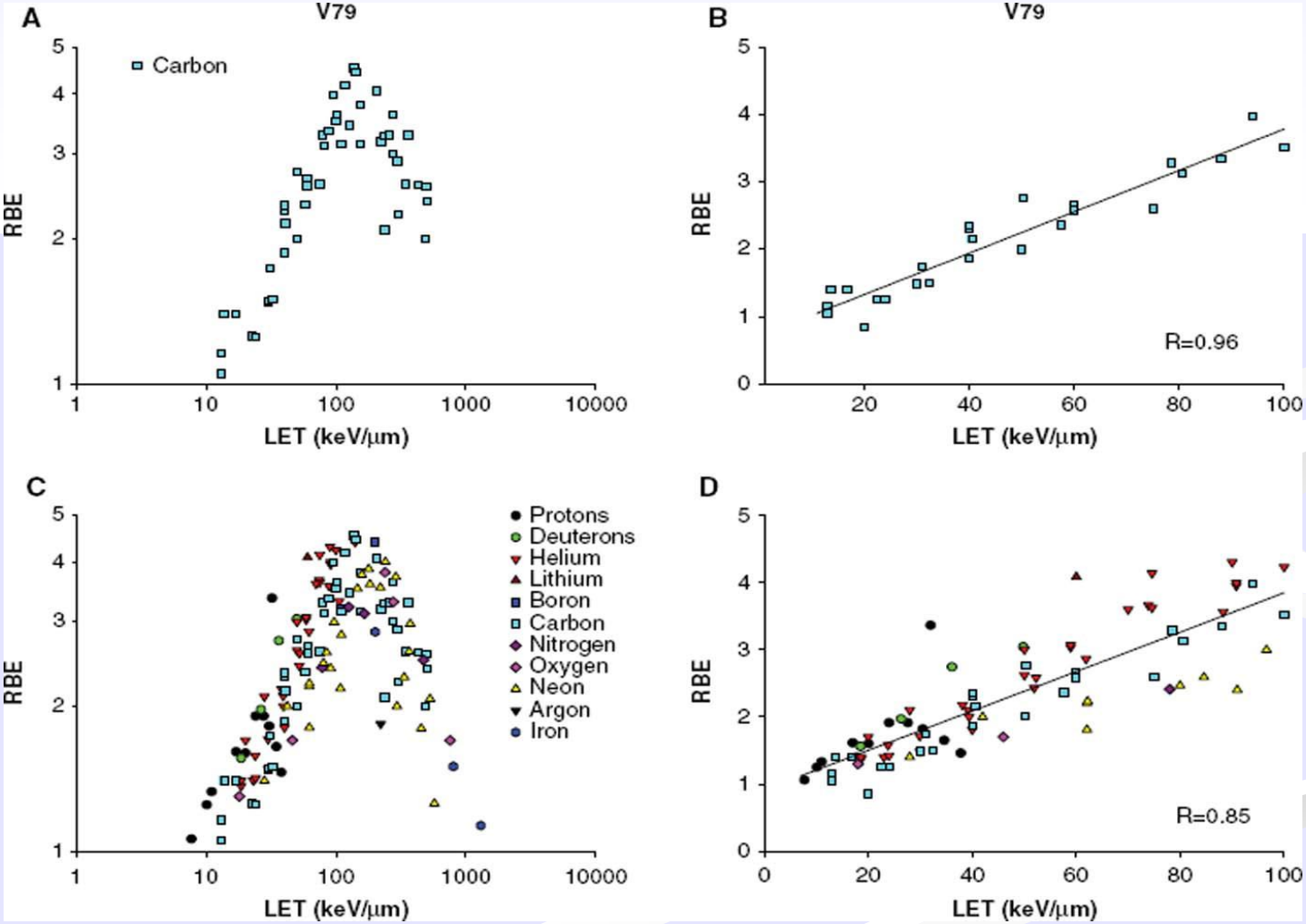
# Protons, neutrons and gammas

- Note that most of ionisation from a neutron beam is caused by recoil protons
- It follows that protons in certain energy ranges can have RBE`s as large as for neutrons.
- Increased γ-ray proportion in beam with depth

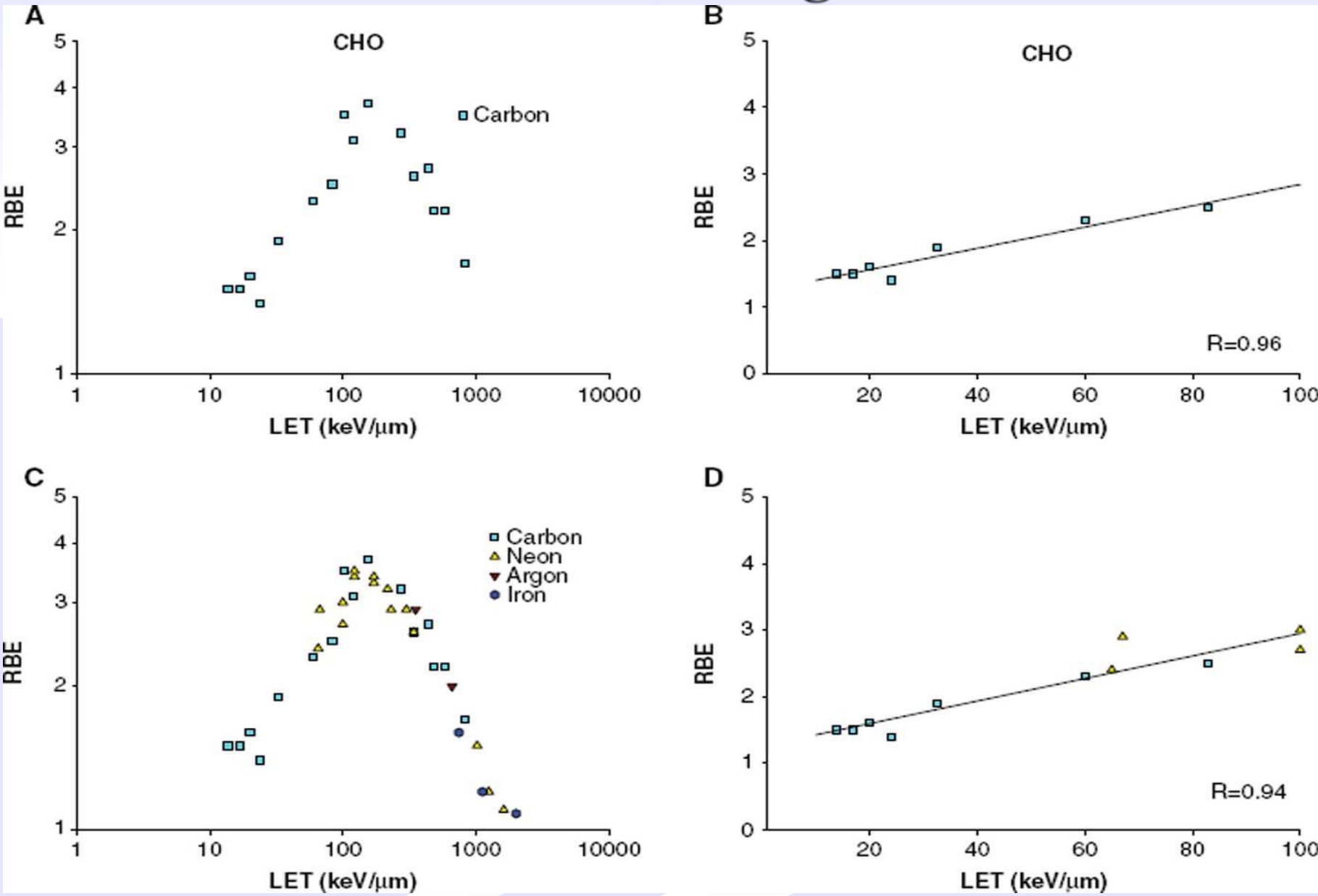
# Proton RBEs modelled in UK from cell survival expts (Human hep2 cells) done by Richard Britten et al East Virginia Univeristy, Norfolk, USA) in SOBP in Bloomington (Indiana) beam at increasing depth

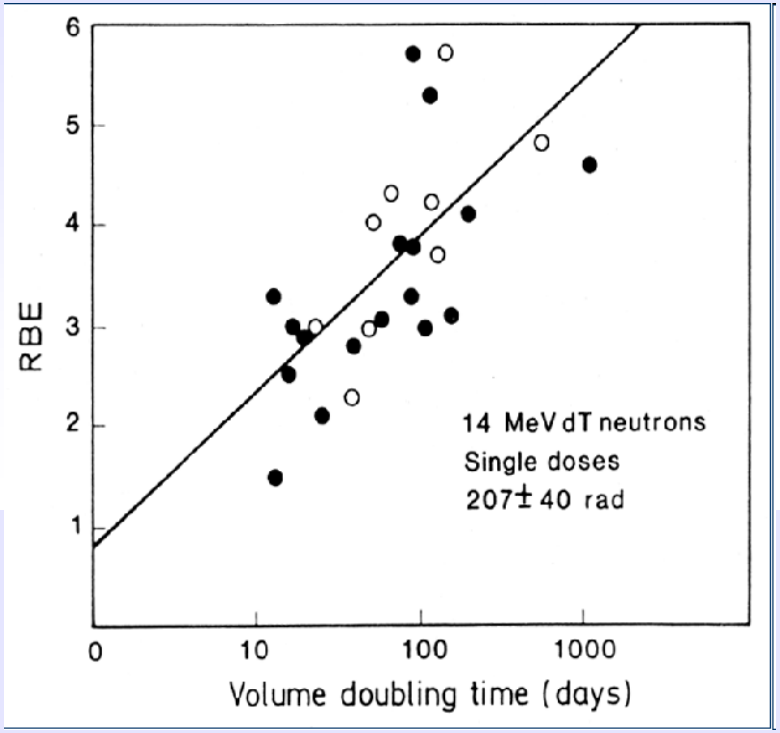


# Acta Oncol 2011: Sorensen Overgaard and Bassler….V79 cells

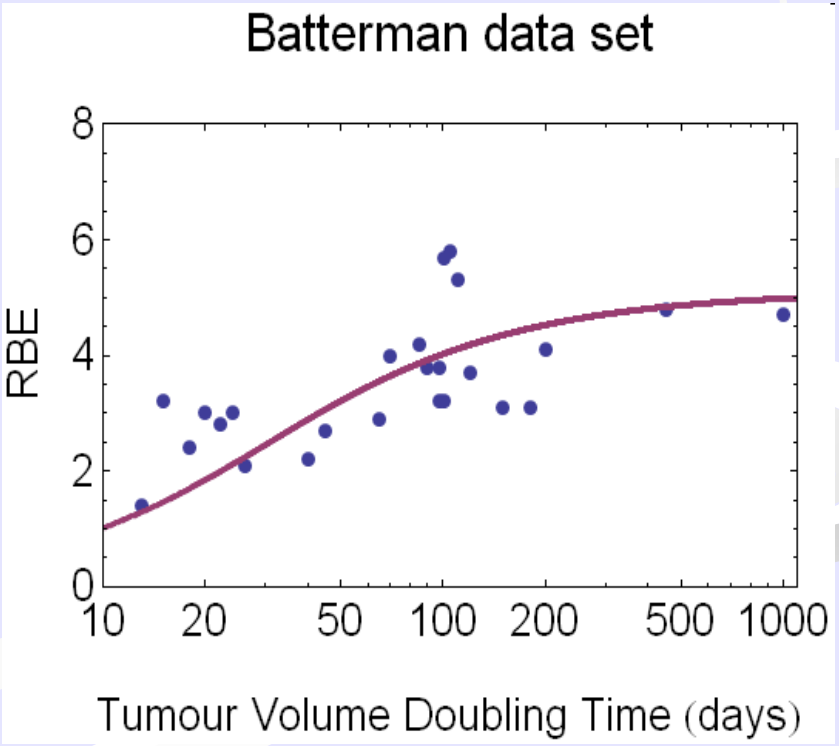


# Acta Oncol 2011: Sorensen, Overgaard and Bassler





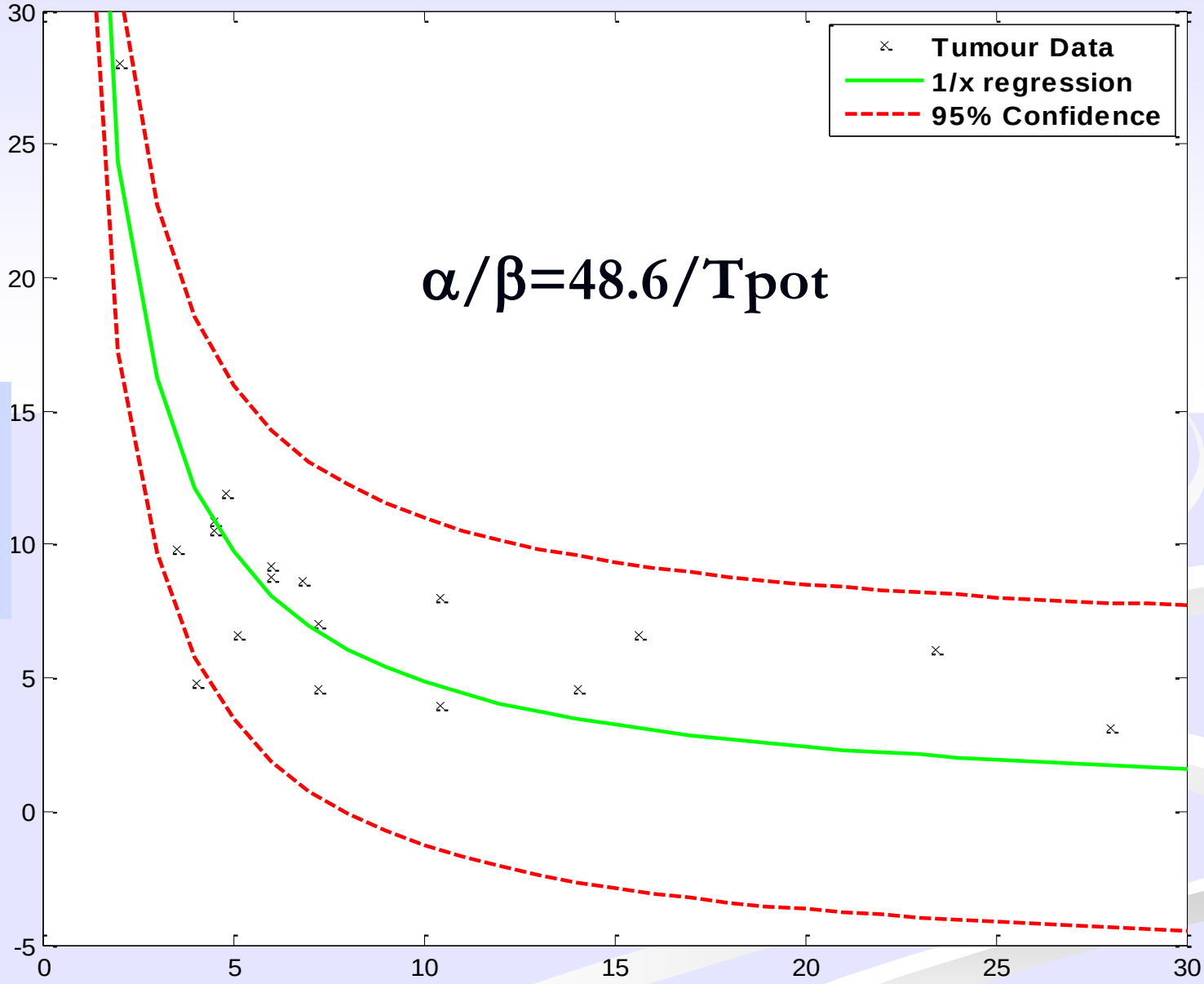

Batterman Eur J Cancer 1981 – human lung metastases given neutron exposures




Method :

- use relationship between cell doubling time and $\alpha/\beta$
- then between $\alpha/\beta$ and RBE
- use RBEmin and RBEmax concepts in BED equations

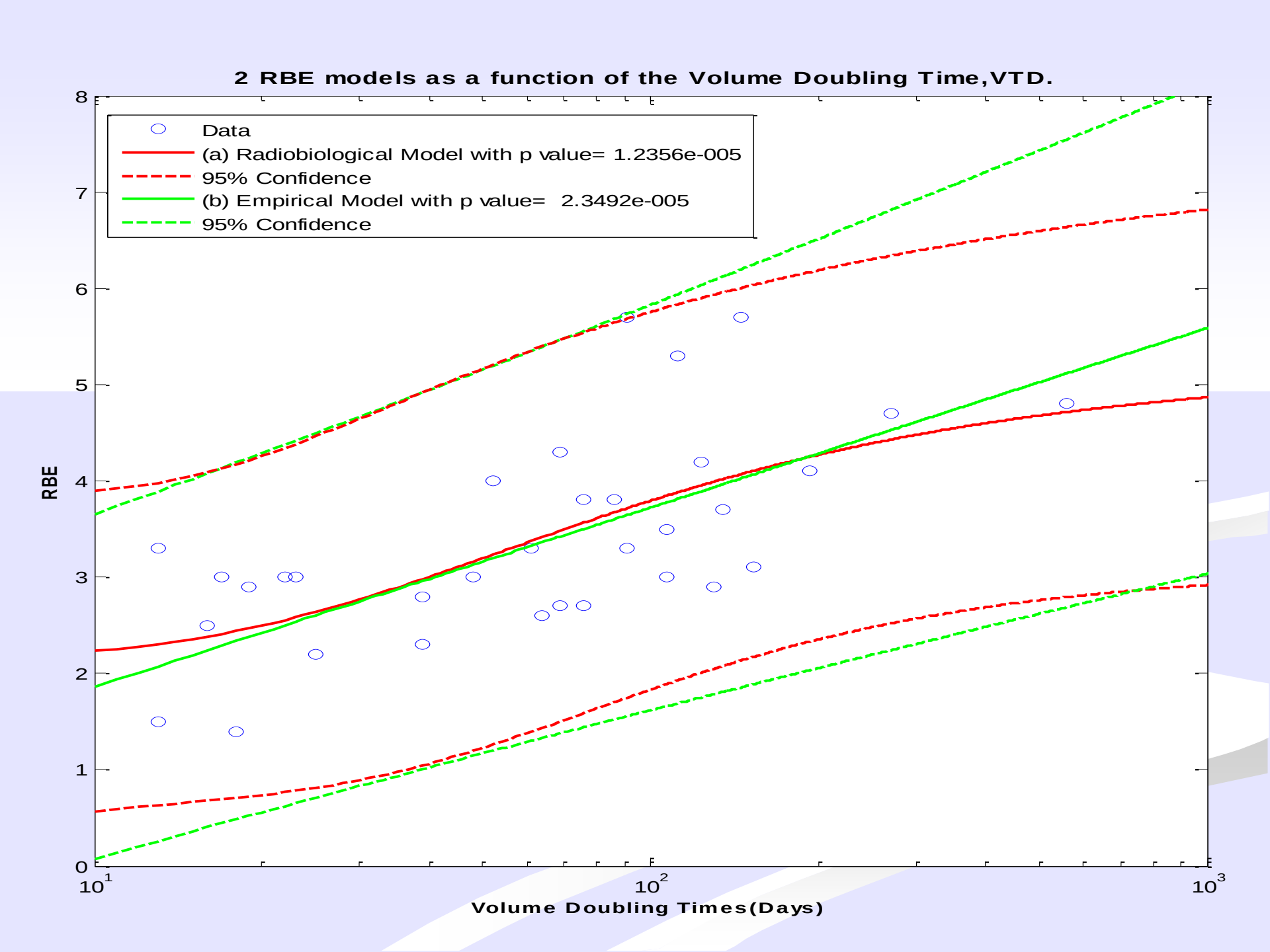
$\alpha / \beta = 48.6033 / T_{pot}$ with 95% Confidence Intervals 41.3805 & 55.8262 with p-value < 2.3459e-006



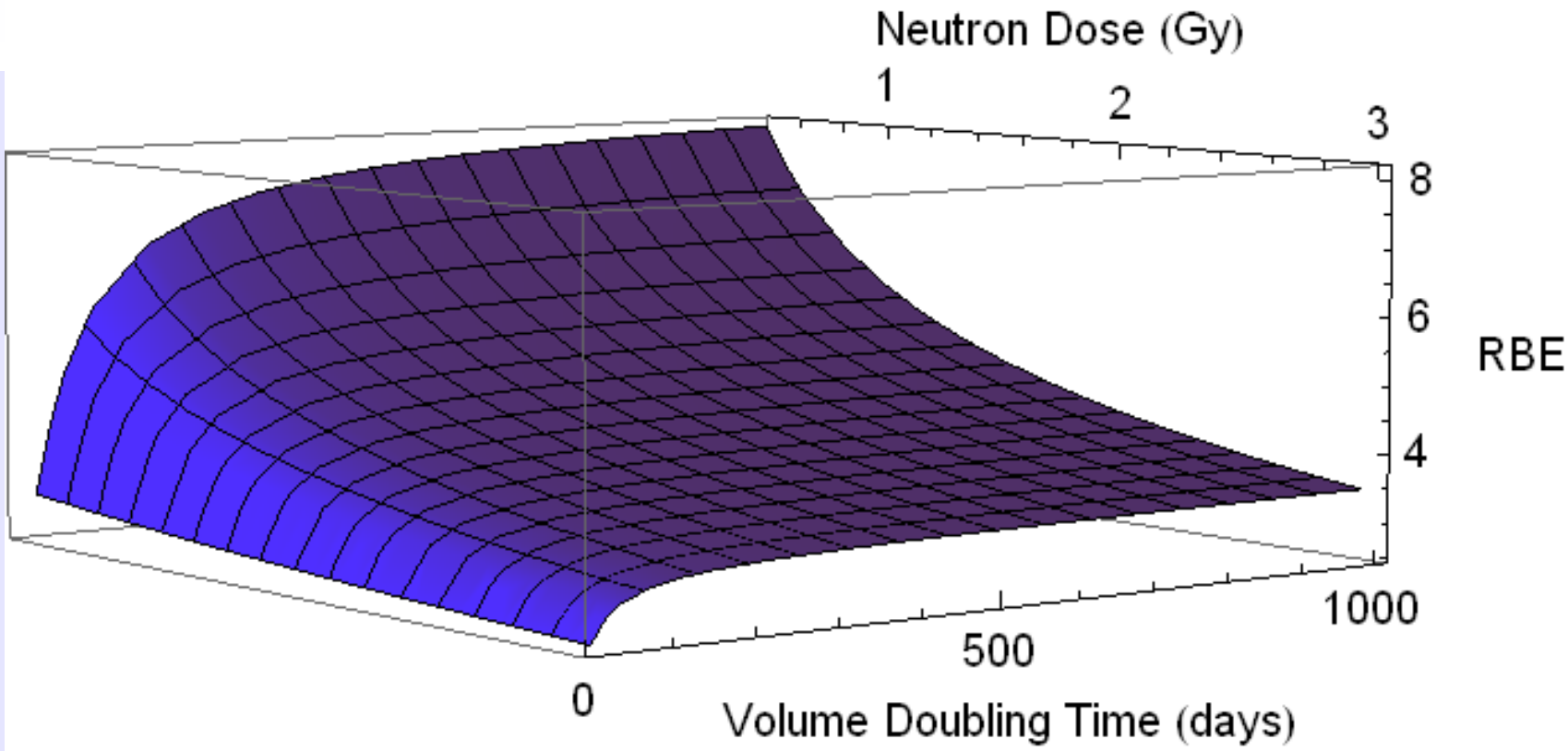
- **RBE is influenced by tumour cell doubling time and volume doubling time by the functions:**

$$RBE = \frac{-(C/T_{pot}) + \sqrt{(C/T_{pot})^2 + 4.d_H.(C/\psi).\left(A + B/(C/T_{pot})\right) + 4.d_H^2.\left(C + D.\sqrt{(C/T_{pot})}\right)}}{2.d_H}$$

$$RBE = \frac{-(C/\frac{VDT}{(1-\phi)}) + \sqrt{(C/\frac{VDT}{(1-\phi)})^2 + 4.d_H.(C/\frac{VDT}{(1-\phi)}).\left(A + B/(C/\frac{VDT}{(1-\phi)})\right) + 4.d_H^2.\left(C + D.\sqrt{(C/\frac{VDT}{(1-\phi)})}\right)}}{2.d_H}$$


2 RBE models as a function of the Volume Doubling Time,VTD.
Data
(a) Radiobiological Model with p value= 1.2356e-005
95% Confidence
(b) Empirical Model with p value= 2.3492e-005
95% Confidence
RBE
Volume Doubling Times(Days)
0
1
2
3
4
5
6
7
8
10^1
10^2
10^3

# Model of Neutron dose per fraction, RBE and doubling time



# Applications

***Converting a specific low LET BED to that for high LET, when the low LET α/β ratio is known……use***

$$BED = D_L\left(1+\frac{d_L}{\left(\frac{\alpha}{\beta}\right)_L}\right) = D_H\left(RBEmax+\frac{RBEmin^2 d_H}{\left(\frac{\alpha}{\beta}\right)_L}\right)$$

$$BED = D_L\left(1+\frac{d_L}{\left(\frac{\alpha}{\beta}\right)_L}\right) - KT_L = D_H\left(RBEmax+\frac{RBEmin^2 d_H}{\left(\frac{\alpha}{\beta}\right)_L}\right) - KT_H$$

$$K = \frac{0.693}{\alpha_L.\omega}$$

# *For isoeffect calculations in the case of two high LET schedules – need $(\alpha/\beta)_H$ value*

$$\frac{RBEmax}{RBEmin^2} = \frac{\left(\frac{\alpha}{\beta}\right)_H}{\left(\frac{\alpha}{\beta}\right)_L}$$

**And so,**

$$\left(\frac{\alpha}{\beta}\right)_H = R_C\left(\frac{\alpha}{\beta}\right)_L \text{ where } R_C = \frac{RBE_{max}}{RBE_{min}{}^2}$$

**Then, for $N_{1H}(\alpha_H d_{1H}+\beta_H d_1{}^2{}_H)= N_{2H}(\alpha_H d_{2H}+\beta_H d_2{}^2{}_H)$**
**Divide throughout by $\alpha_H$**

$$D_{1H}\left(1+\frac{d_{1H}}{\left(\frac{\alpha}{\beta}\right)_H}\right) = D_{2H}\left(1+\frac{d_{2H}}{\left(\frac{\alpha}{\beta}\right)_H}\right)$$

$$D_{1H}\left(1+\frac{d_{1H}}{\left(\frac{\alpha}{\beta}\right)_H}\right) - K_H T_{1H} = D_{2H}\left(1+\frac{d_{2H}}{\left(\frac{\alpha}{\beta}\right)_H}\right) - K_H T_{2H}$$

$$K_H = \frac{0.693}{\alpha_H . \omega}$$

# Extra constraints in treatment planning – inclusion of RBE uncertainties

$$S = \frac{P_H}{P_L} \cdot \frac{RBE_{NT}(1+error)}{RBE_{CA}(1-error)}$$

P is physical dose sparing for low (L) and high (H) LET cases

$$S = \frac{P_H}{P_L} \cdot \frac{RBE_{NT}(1+0.2)}{RBE_{CA}(1-0.2)} = \frac{P_H}{P_L} \cdot \frac{RBE_{NT}.3}{RBE_{CA}.2}$$

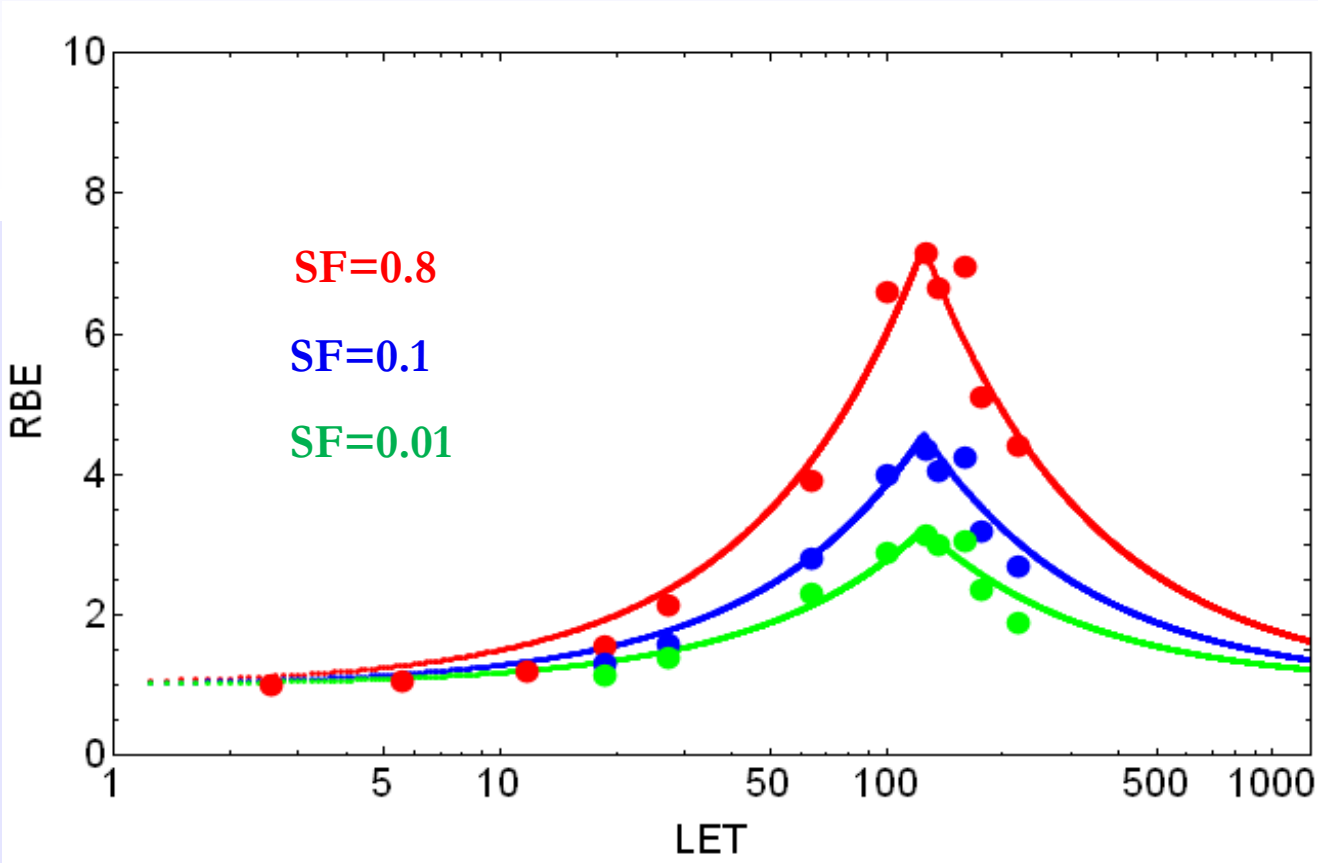
$$\therefore S = \frac{P_H\left(\frac{2}{3}\right)}{P_L} \cdot \frac{RBE_{NT}.3}{RBE_{CA}.2}$$

**dose sparing ratio must be improved by ~33% a (1/3) ↓ in NT dose to account for worse case scenario. And lower RBE in tumour needs dose escalation**

Brit J Radiol, [Jones, Underwood & Dale] accepted in press 2011

# Data of Barendsen (1968), monoenergetic alpha particles and deuterons only for three levels of dose [cell surviving fraction]

Oxford Model

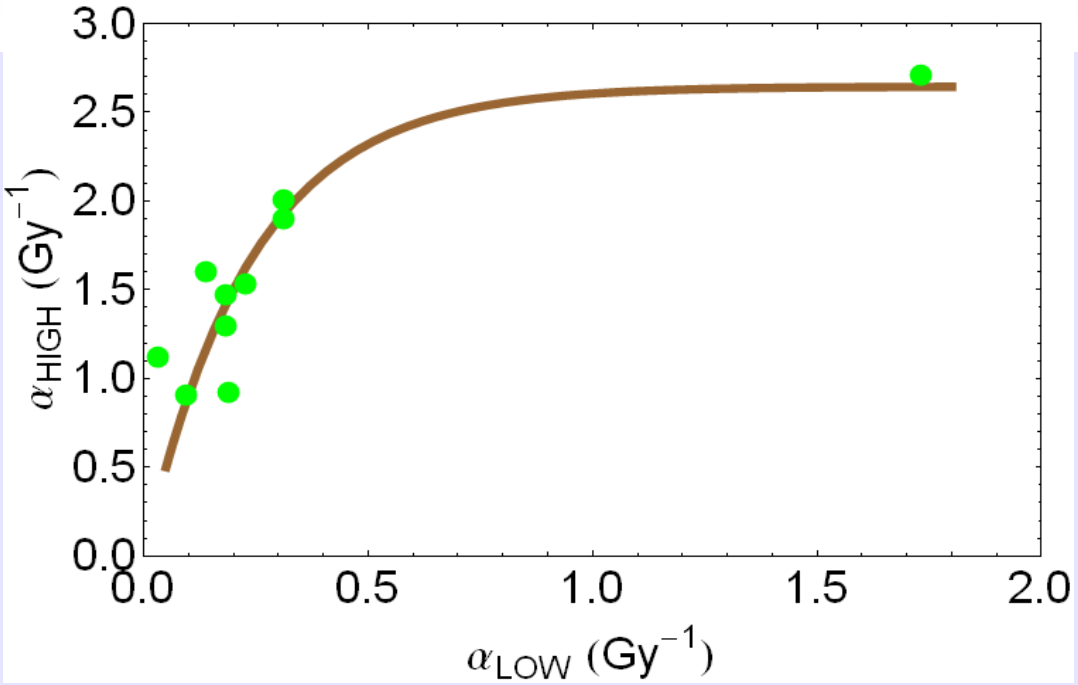


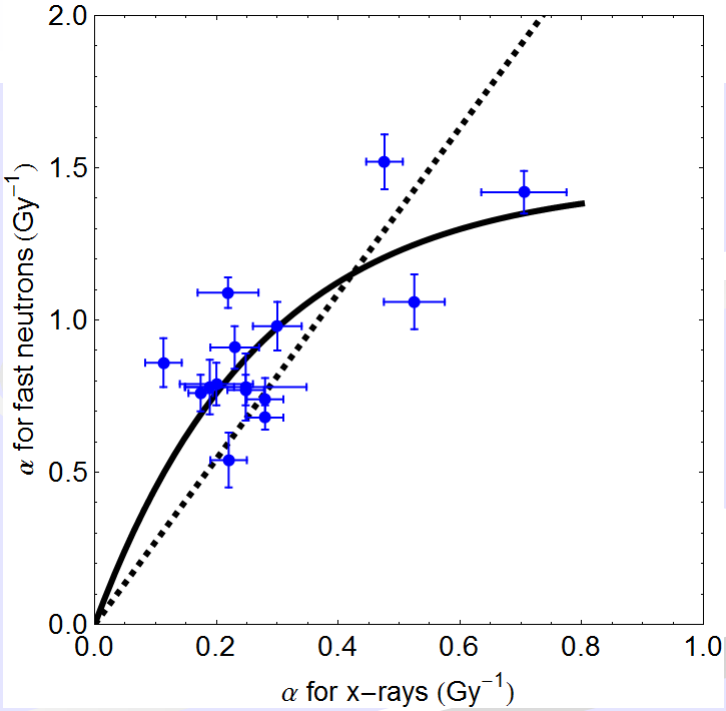
# Relationship between $\alpha_L$ and $\alpha_H$

## (for various ions, protons and neutrons).

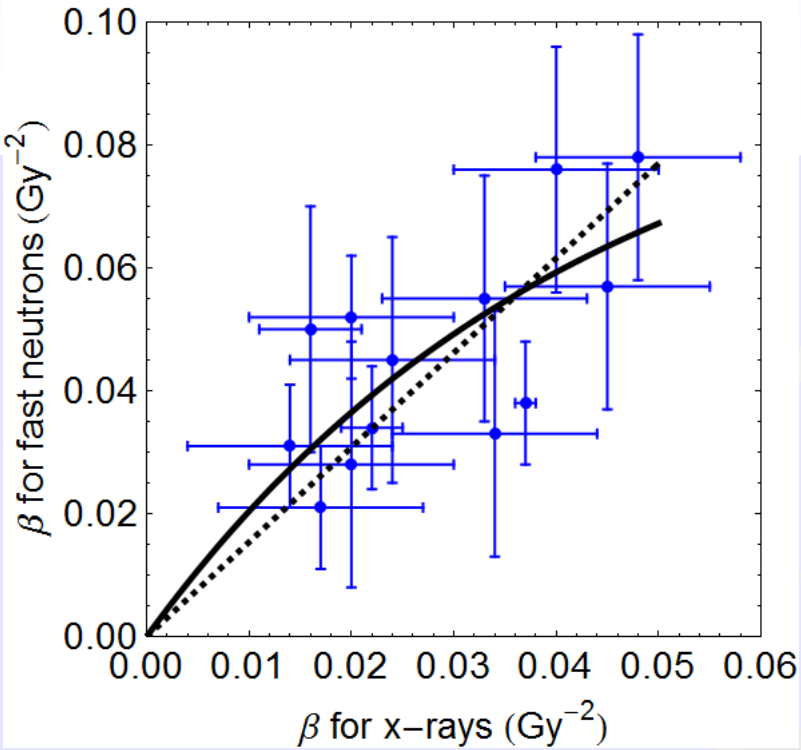
Fitted by $\alpha_H = 11.1/4.2\ (1-\mathrm{Exp}[-4.2\ \alpha_L])$

$P<0.01$



# Changes in beta



# Before turnover point

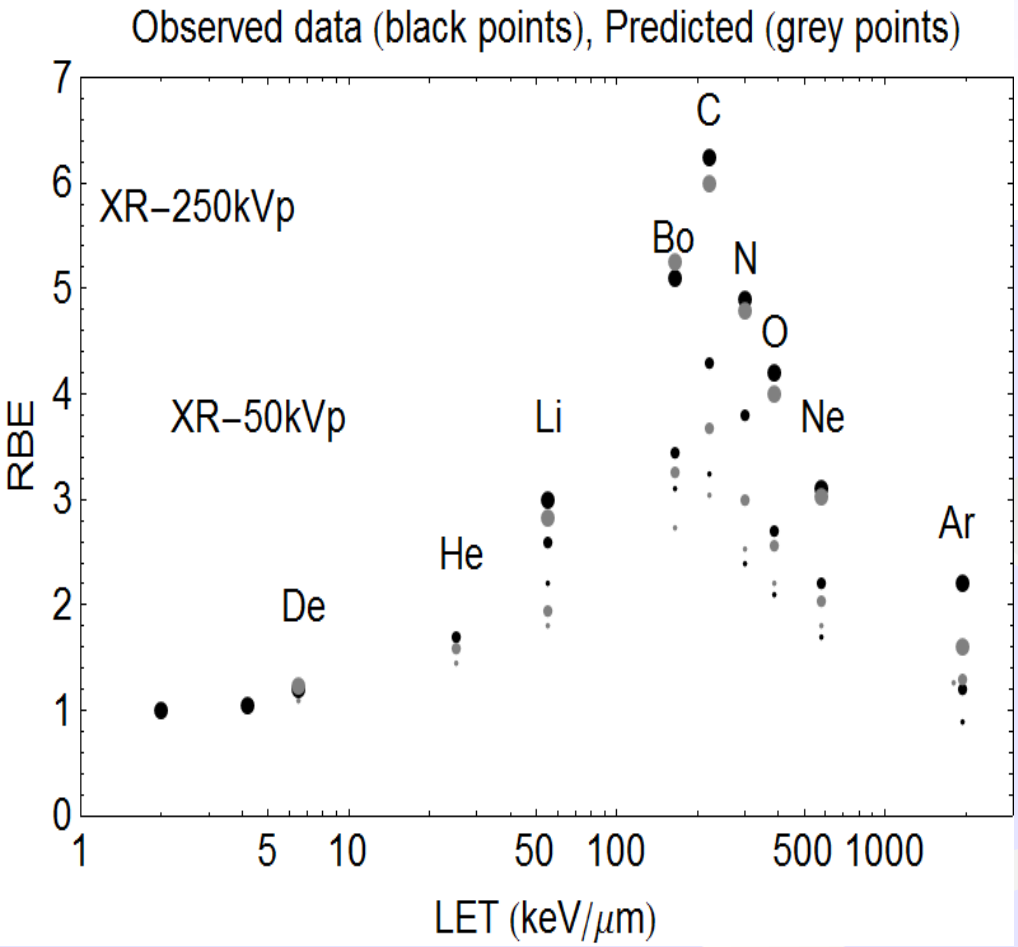
- $\alpha_H = \frac{LETx - LET_C}{LET_U - LETc} . (\alpha_U - \alpha_C)$ In this way if $LET_c$ and $LET_U$ are 1.2 and 120 Kev/μm respectively, with $\alpha_C$ and $\alpha_U$ of say 0.3 and 1.3 $Gy^{-1}$, then for LETx values of 60 and 90 respectively, the process is only (1.3-0.3)/(120-2)× 60 = ~ 50% efficient, or (1-3-0.3)/(120-2)× 90 = approximately 75% efficient. Lethal events per unit dose will increase linearly with LET, leading up to maximum efficiency

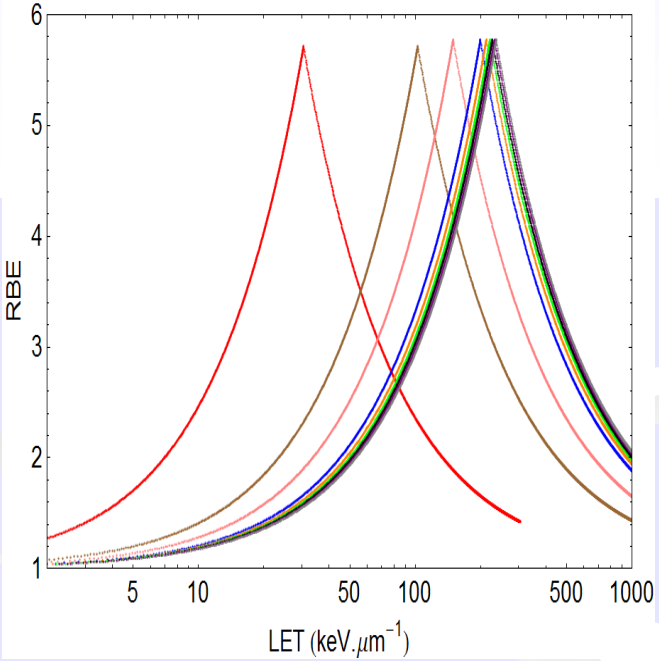
# After turnover point, for LET>$LET_U$

- % efficiency = 100 - %inefficiency
- $a_H = \left(1 - \frac{LETx - LET_U}{LET_U}\right).(\alpha_U - \alpha_C)$

expresses the reduction in α with increasing LET. In this way if $LET_x$ is 180 and $LET_U$ is 120, the value of $\alpha_U$ at the turnover point of 100% efficiency will fall to 1-(180-120)/180, which provides around 67% efficiency. For a LETx of 240, we obtain 1-(240-120)/240 to be 50% efficient.

# Reduced RBE with increasing dose – data of Todd (1967) modelled in Oxford

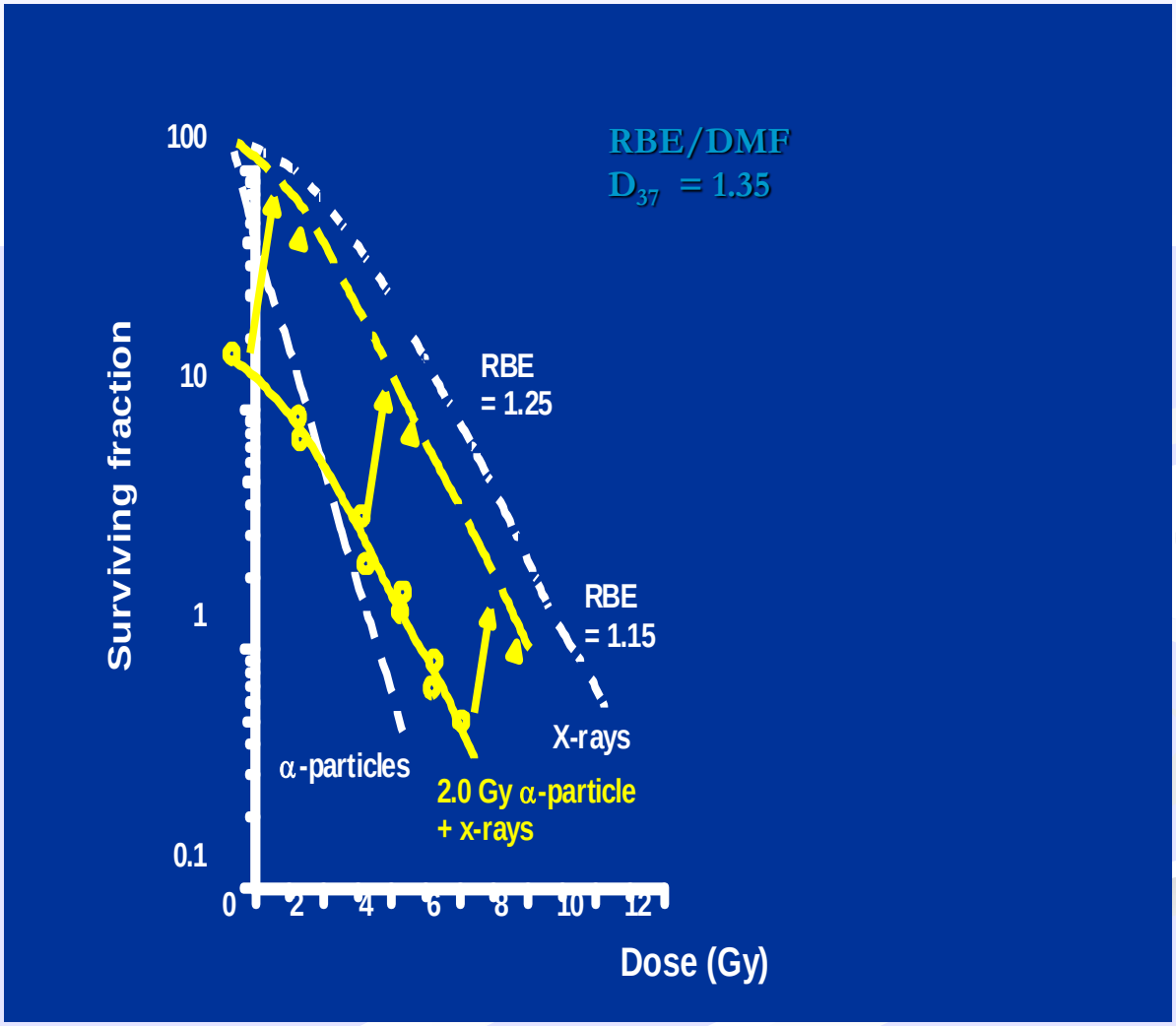


# Mixed fields (different percentages of photons and neutrons, which vary in neutron beams and with depth in tissue)

- Data of McNally et al showed non-linear effects, with lower doses of neutrons dominating the effectiveness, but also dose dependent. Int J Radiat Biol Relat Stud Phys Chem Med. 1984 Apr;45(4):301-10
- Zaider and Rossi proposed quadrature addition of beta component of cell kill, but no model is adequately predictive.
- It is probably necessary to include entire LET-RBE functions and the neutron LET spectrum.

# Effect of a fixed sequential α-particle (high LET) dose on the x-ray cell survival of V79 cells

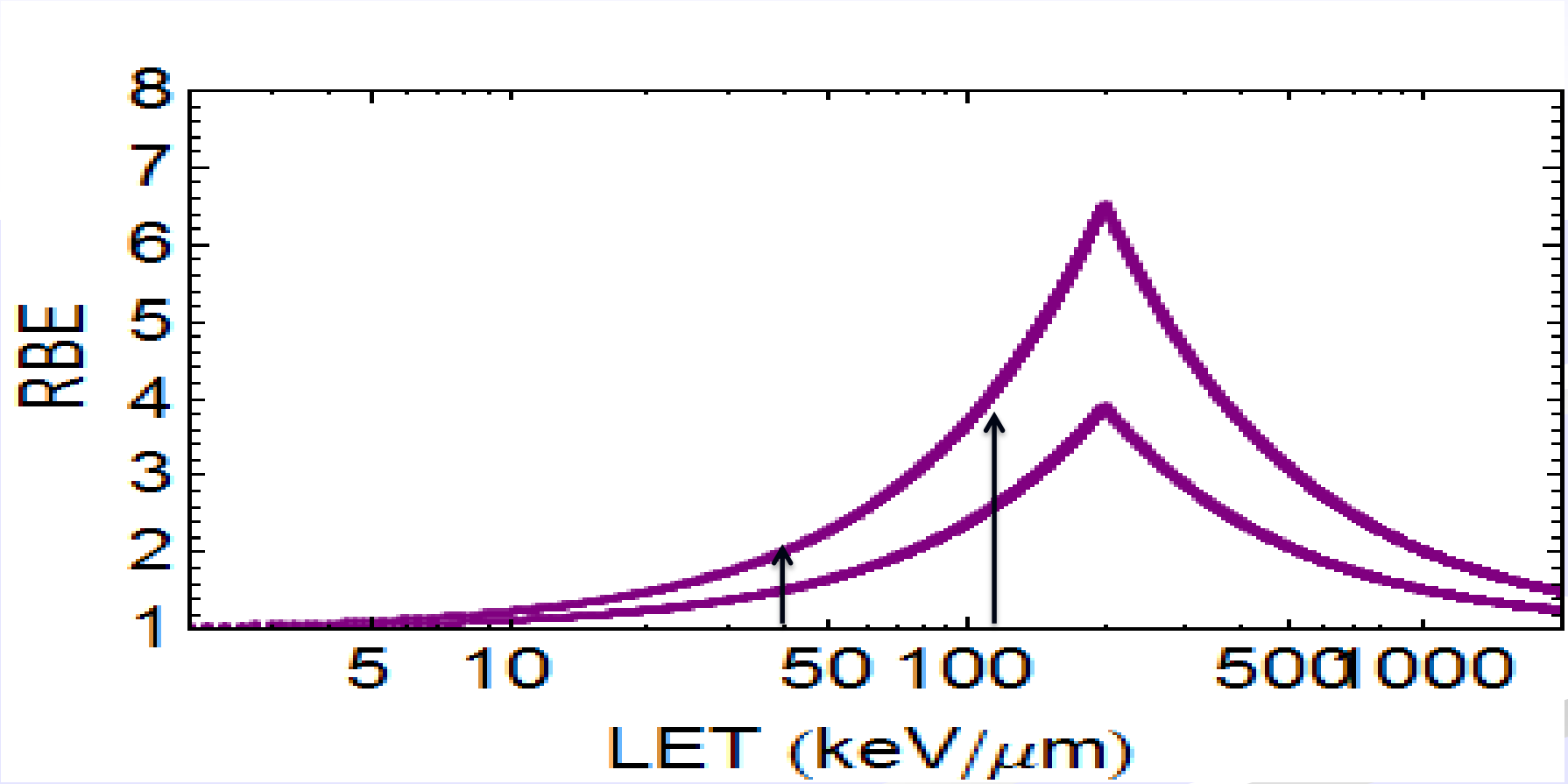



McNally et al., 1988

# McNally data sets on mixed fields

- V79 Chinese hamster cells exposed to X-rays or fast neutrons or to both radiations sequentially. Cells exposed priming X-rays then given a series of neutron doses regard the X-ray dose as equivalent to a neutron dose giving the same surviving fraction.
- If the cells are exposed to neutrons followed by X-rays the resulting survival is higher than would be obtained if first dose had been an iso-effective X-ray dose. But, it is lower than would be expected if the two radiations acted independently. Results imply an interaction between X-rays and fast neutrons.
- If the two radiations are given 3 hours apart they act independently.
- BED[X-R]+X.BED[NEUT}=Combined BED, where X is Variable

# It may involve further processes, integrating neutron spectrum on this type of plot; with dose related changes in the plot

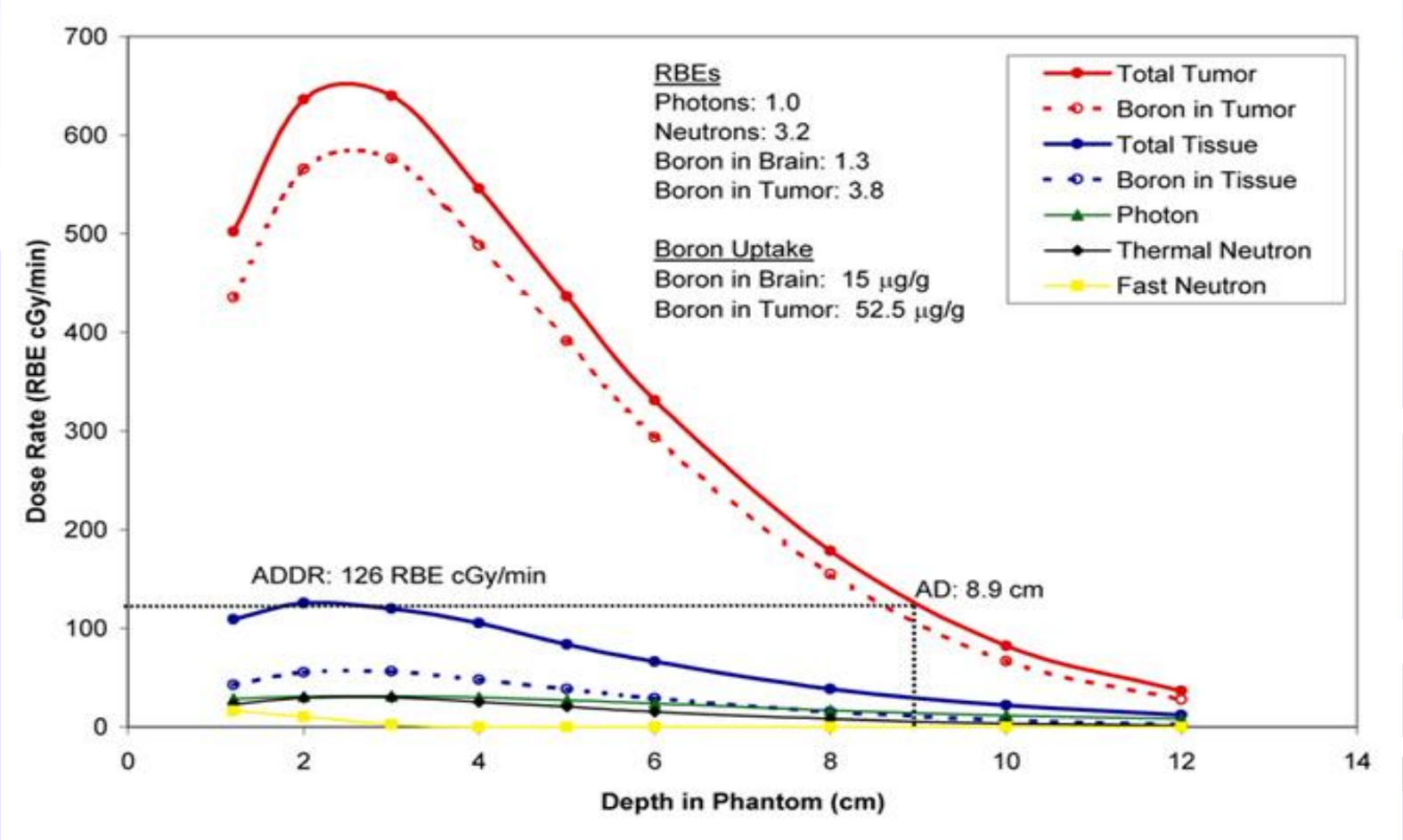


- **Journal of Cancer Therapy, 2014, 5, 1388-1398**
- Ishiyama, S. (2014) Deterministic Parsing Model of the Compound Biological Effectiveness (*CBE*) Factor for Intracellular 10-Boron Distribution in Boron Neutron Capture Therapy. *Journal of Cancer Therapy*, **5**, 1388-1398.

The individual RBE`s for C, N, O, H are included with a factor for the Boron distribution.

- The *CBE* factor = [(X-ray ED50) − (thermal beam component of ED50 × RBE]/10B(*p*, *a*)7Li component of ED50

# Typical Depth-Dose Curve for Fission Converter Beam at MITR-II using BPA



- Appl Radiat Isot. 2011 Dec;69(12):1756-9. **The radiobiological principles of boron neutron capture therapy: a critical review.** Hopewell JW[1], Morris GM, Schwint A, Coderre JA.

Effect of exposure time in determining the biological effectiveness of γ-rays, due to the repair of sublethal damage, has been largely overlooked in the application of BNCT. Recoil protons from fast neutrons vary in their RBE as a function of energy and tissue endpoint. Thus the energy spectrum of a beam will influence the RBE of this dose component. Protons from the neutron capture reaction in nitrogen have not been studied but in practice protons from nitrogen capture have been combined with the recoil proton contribution into a total proton dose. The relative biological effectiveness of the products of the neutron capture reaction in boron is derived from two factors, the RBE of the short range particles and the bio-distribution of boron, referred to collectively as the compound biological effectiveness factor. Caution is needed in the application of these factors for different normal tissues and tumors

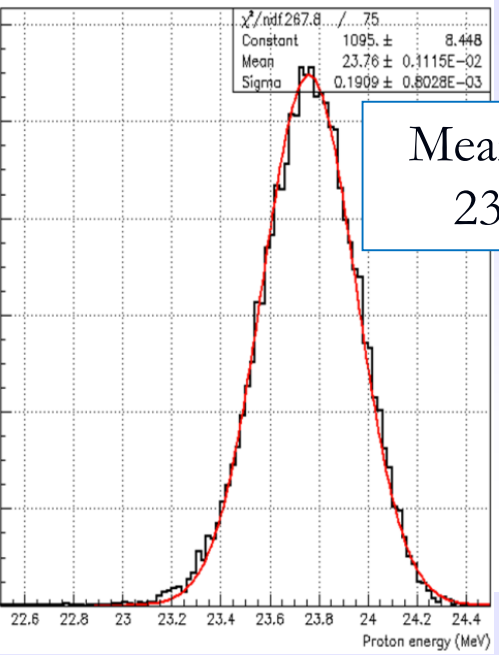
# Charged particle radiobiology

In addition to alpha-particle work in Oxford, starting to use charged particles at Birmingham

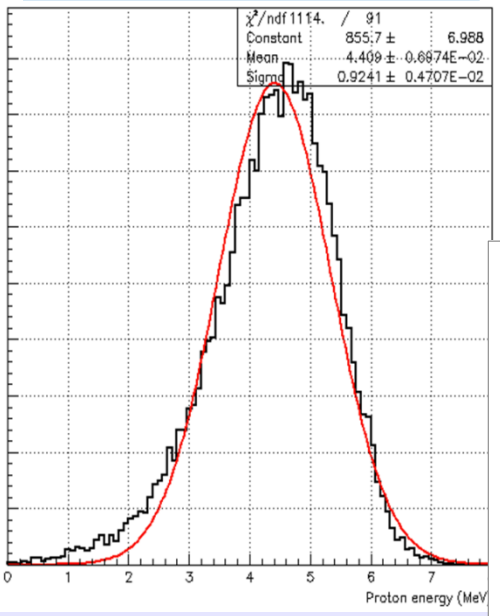

Routine use:

- proton beams at 36, 29 and 15 MeV
- alphas at 38 MeV
- Nitrogen ions possible
- Dose rates: approx 1 Gy/s up to a few hundred Gy
- Uniform beams can be produced up to a diameter of 4 cm

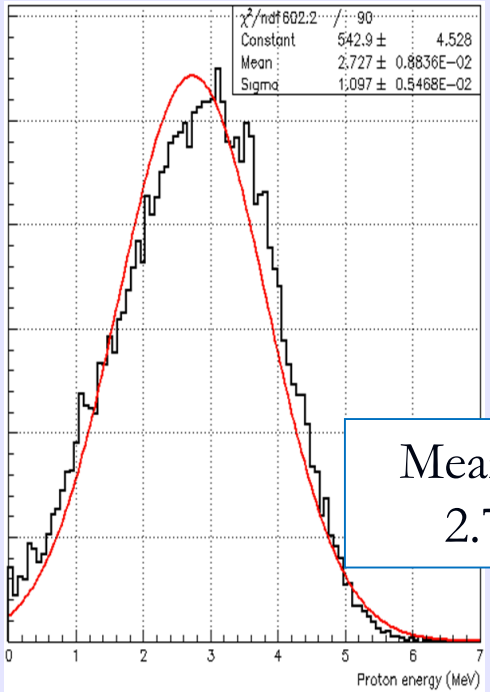
# Initial biological studies



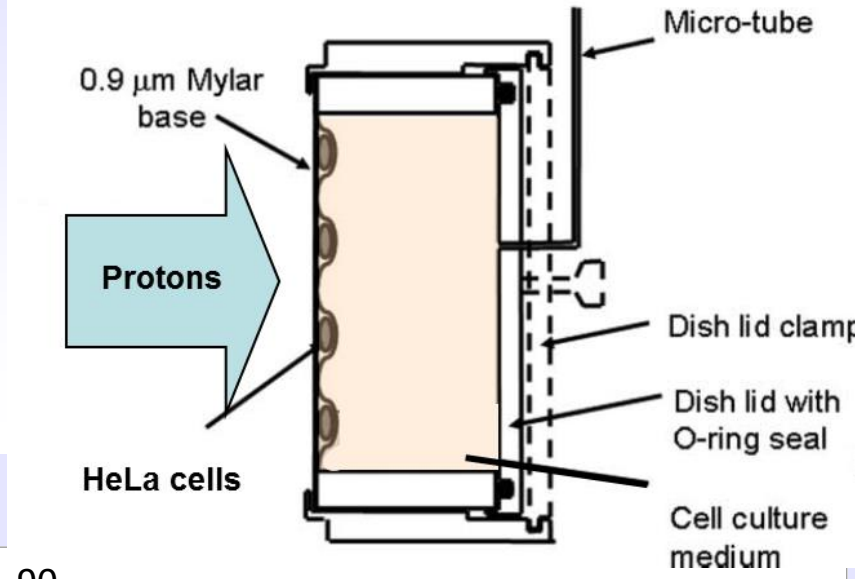

Mean Energy:
23.8 MeV

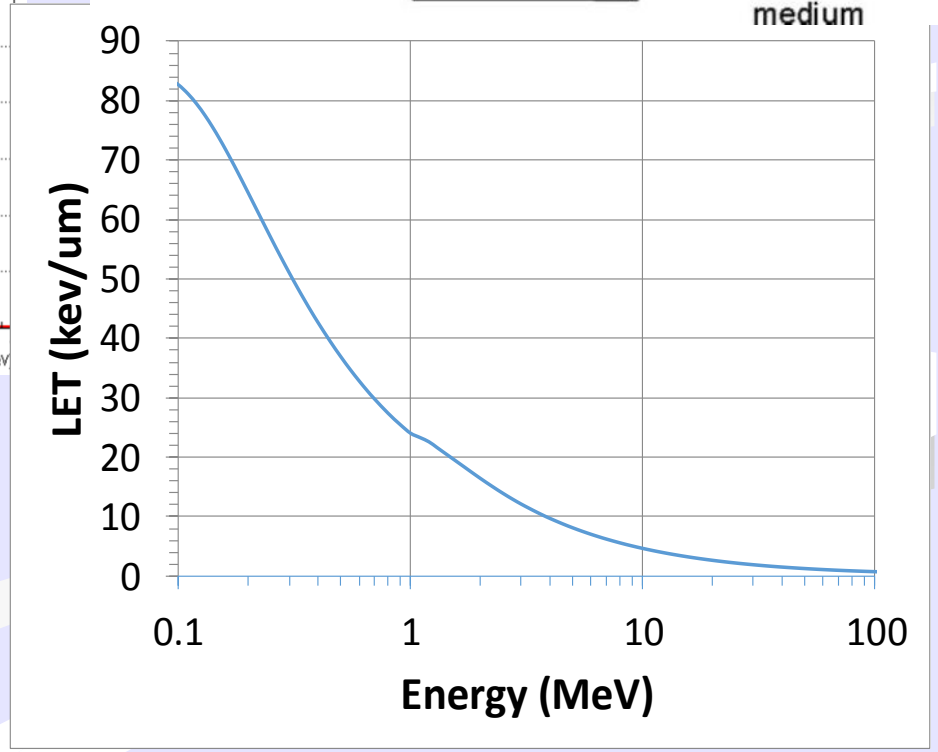



Mean Energy:
4.4 MeV



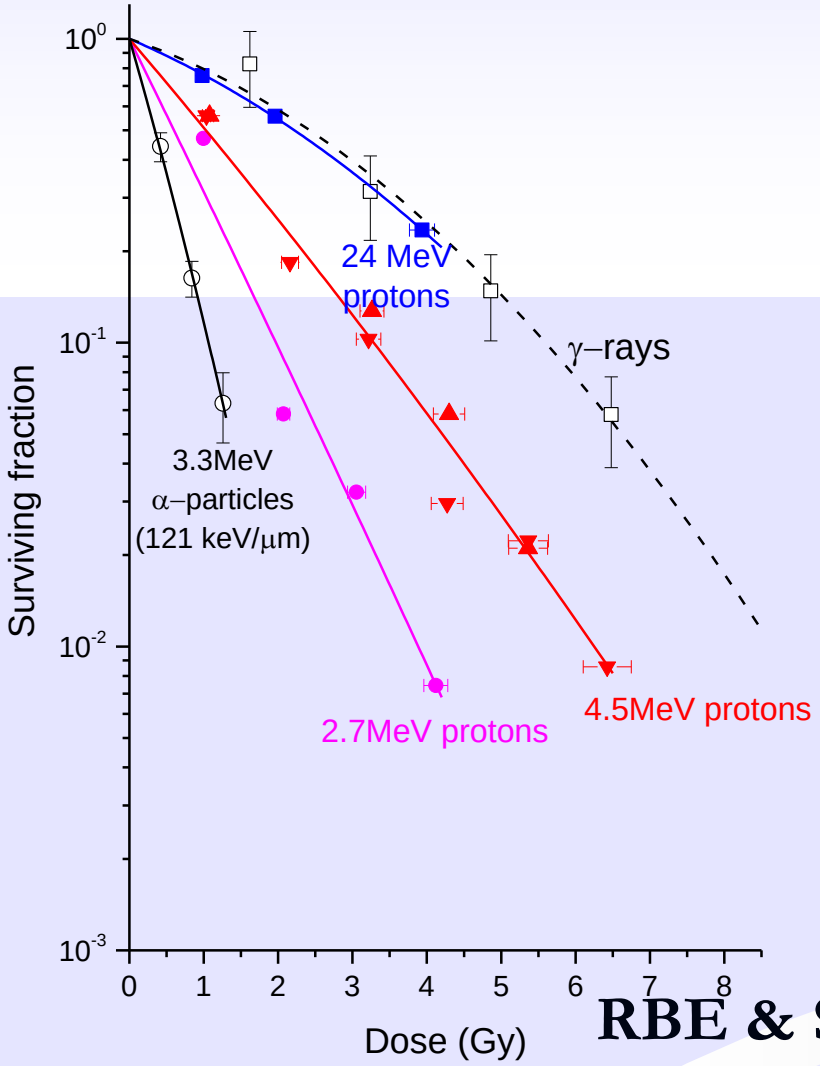

Mean Energy:
2.73 MeV



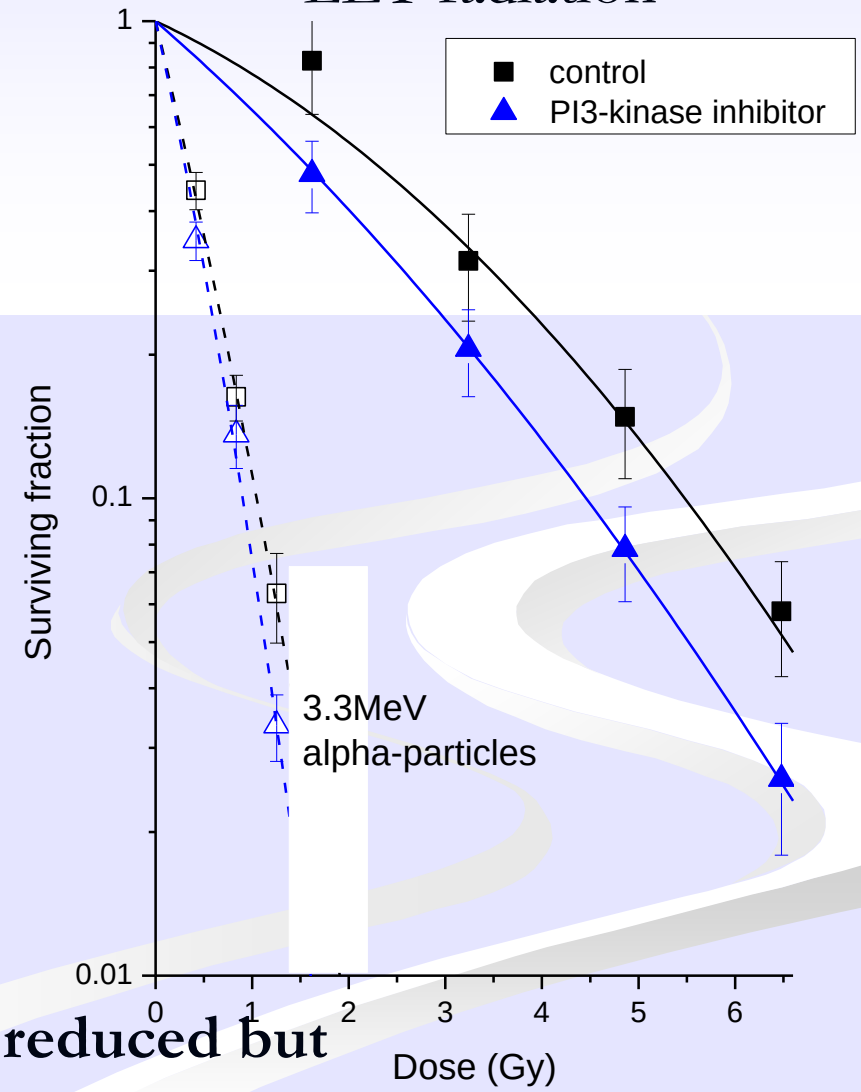



# Preliminary data

## Proton survival data




## Radio-sensitizers and high-LET radiation




**RBE & SER reduced but sensitisation remains**

# Drugs and ion beams

- ↑RBE is due mainly to ↑ in α radiosensitivity parameter , the increase in β being small.
- Drugs which sensitise β selectively may be useful …especially is tumour has "low RBE" due to poor repair capacity
- Drugs which normalise blood vessels and reduce tumour progression…..
- Ensure IB BED+ChemoBED > X-ray BED+ChemoRxBED in tumour BUT that IB BED+ChemoBED < X-ray BED+ChemoRxBED in NTissues

# Malignant Induction Probabilities with fractionation and high LET effects

**Let x be proportion of chromosome breaks → cell kill, and (1-x) → cancer**

$$MIP = (1-x)n(\alpha d R_{\max} + \beta d^2).e^{-xn(\alpha d R_{\max} + \beta d^2)}$$

Jones B – J Radiat Protection 2009

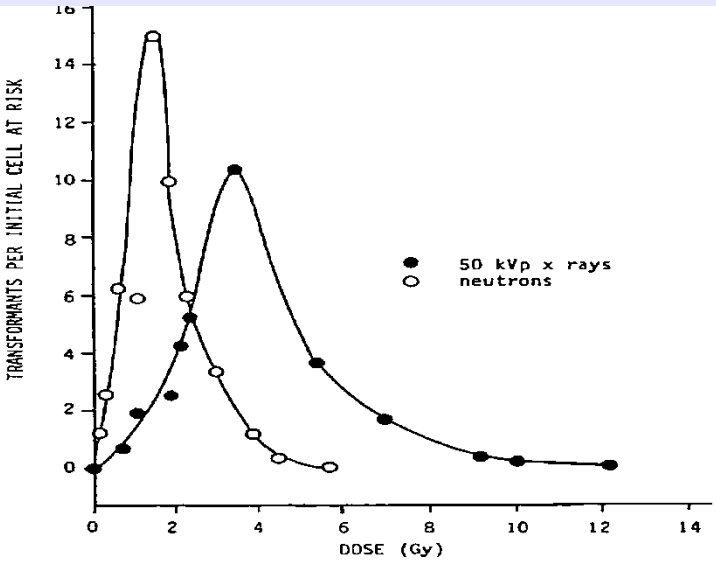
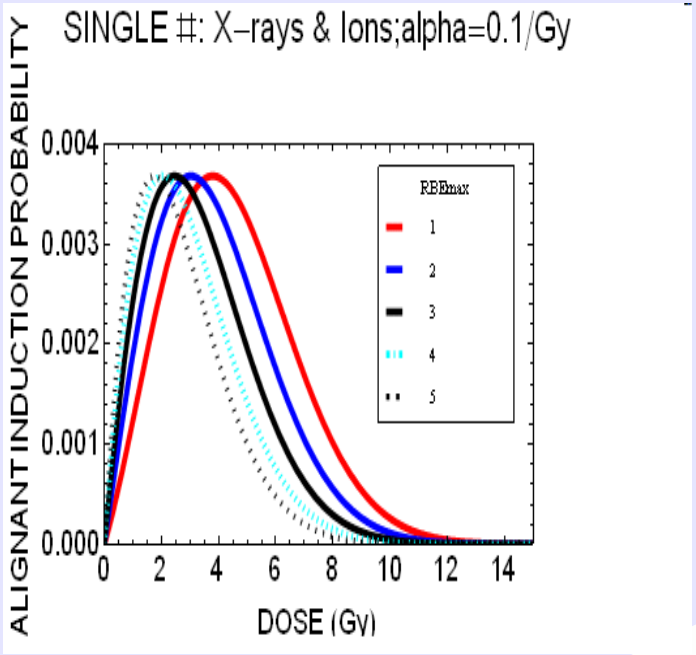
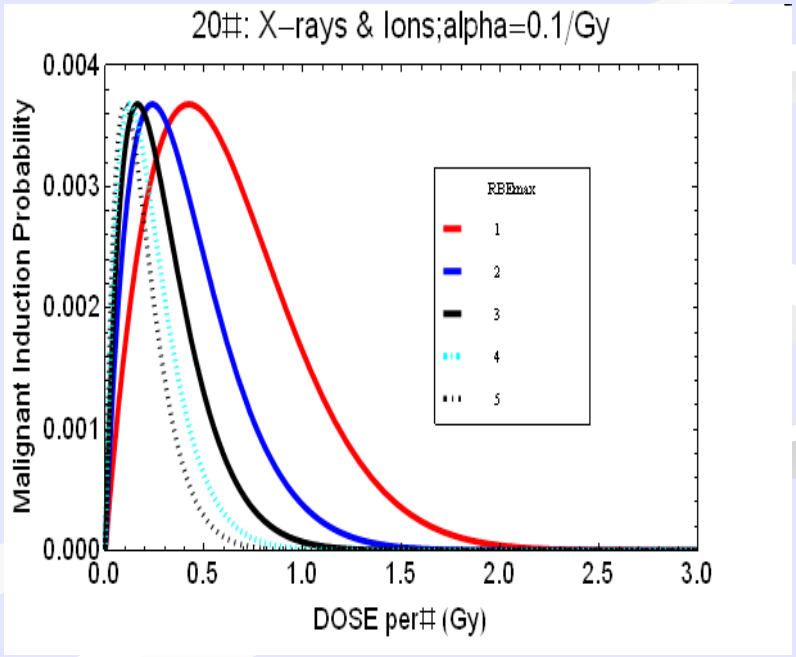



Figure X. Changes in transformation frequency of C3H10T1/2 cells after single exposures to x rays or fission-spectrum neutrons.
[H1]



2015 Apr 12. pii: ncv158. [Epub ahead of print]

**THE ANDANTE PROJECT: A MULTIDISCIPLINARY APPROACH TO NEUTRON RBE. Radiat Protection and Dosimetry**

Ottolenghi A, Baiocco G, Smyth V, Trott K; ANDANTE Consortium.

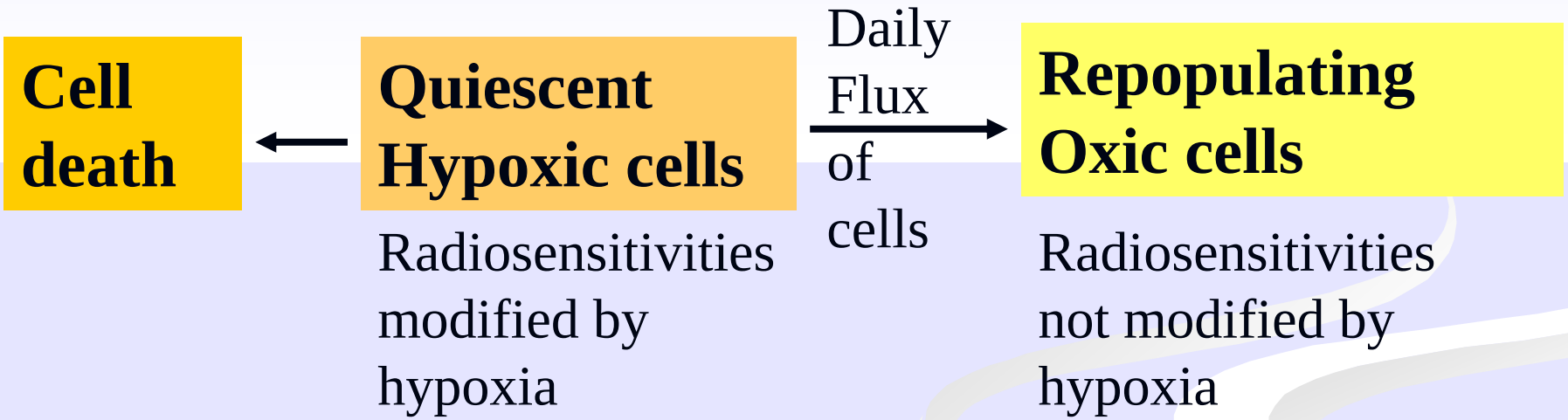
**Abstract**

Neutron risk estimation uses concept of RBE to compare photon risk. RBE has been evaluated using cellular and animal models, which causes difficulties in human applications. The ANDANTE project takes a new approach using : **Physics: track structure** model is used to contrast the patterns of damage to cellular macro-molecules from neutrons compared with photons. The simulations reproduce the same energy spectra as are used in the other two approaches. **Stem cell radiobiology**: stem cells from thyroid, salivary gland and breast tissue are given well characterised exposures to neutrons and photons. A number of endpoints are used to estimate the relative risk of damage from neutrons compared with photons. Irradiated cells will be transplanted into mice to investigate the progression of the initial radiation effects in stem cells into tumours in a physiological environment.

# Consequences of not using dose distribution & RBE to full advantage?

- Null hypothesis could be favoured in a clinical trial if tumour RBE is less than prescription RBE. Dose escalation can overcome this.
- Results in pragmatic studies may not be as good as expected…….for tumour control and mild-severe normal tissue side effects.
- 'Unexpected' findings !

# Models of Tumour Hypoxia – iterative




Initial conditions and variables: hypoxic fraction, reoxygenation rate, OER, repopulation rates, radiosensitivities and mean inter-fraction interval. Model repeats every day until TCP > 0.05.

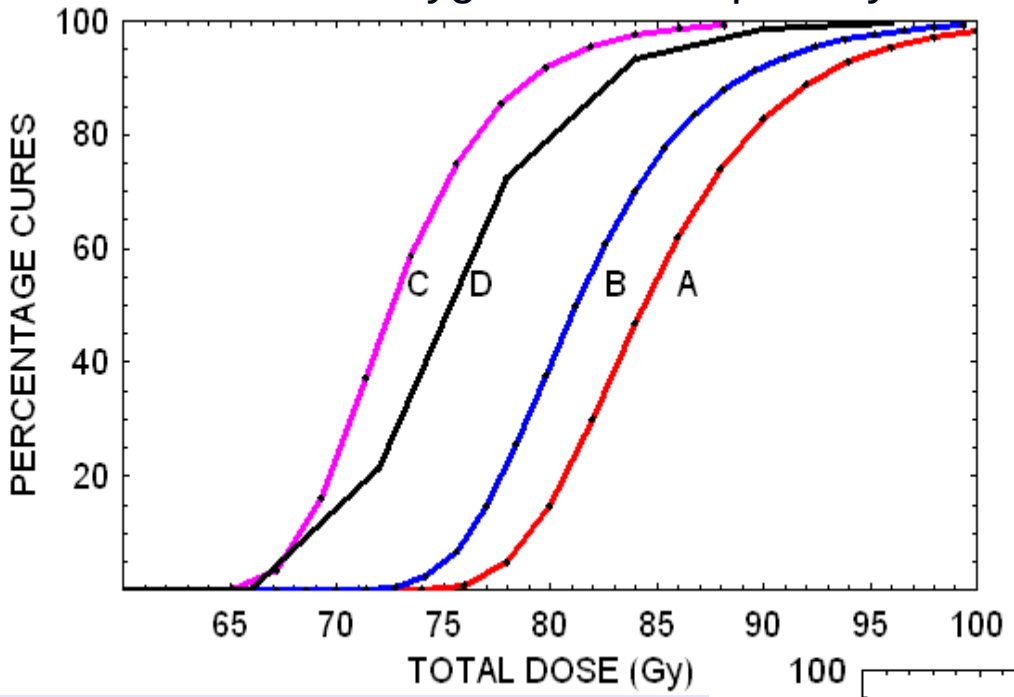
Modified from Scott (1988); alternative is to use analytical models with integration of effective OER with time to give average values. Results very similar.

# Example of iterative loop in 'Mathematica'

```
nox = nox Exp[ -αlist d- βlist d^2 + 0.693 f /ωlist ]
nhyp = nhyp Exp[ -αlistd/q- βlistd^2/q^2];
ntot = nox + nhyp;
Tcp = Exp[-ntot];
n = n+1;
Reox = x nhyp;
ntot = nox + nhyp;
nhyp = nhyp – xnhyp - ynhyp;
Nox = nox + reox
```

Heterogeneity is included by having long lists of separate tumours each with different **α, β,** and w, the cell repopulation parameter; f is the inter-fraction time interval.

For slow reoxygenation 1% per day



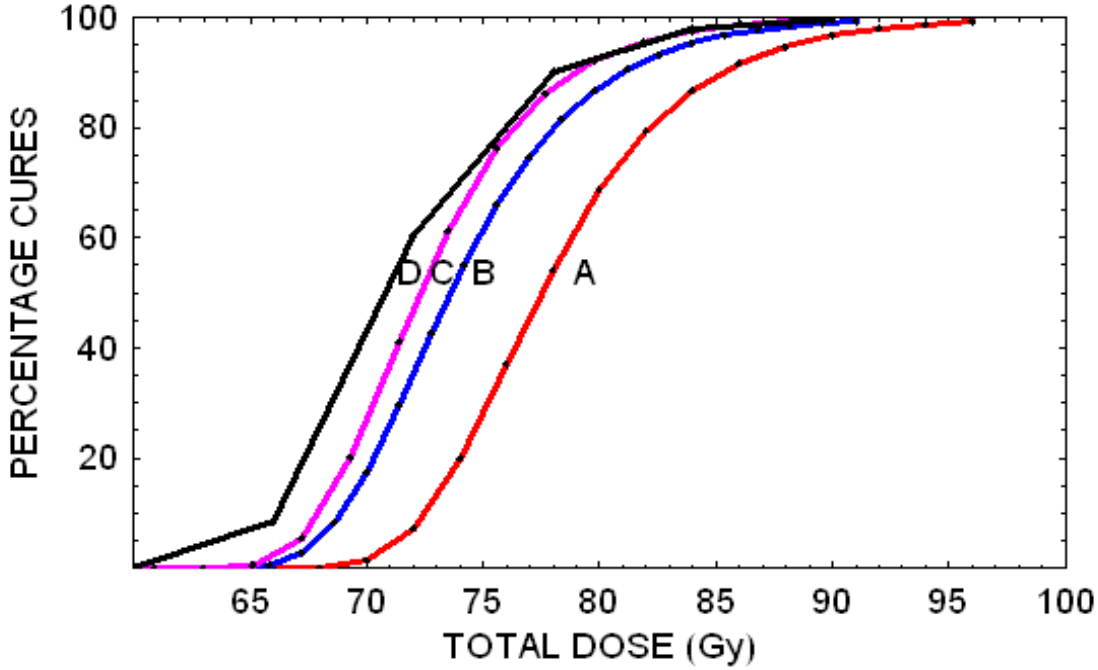

A=2 Gy per day x-rays, 5# per week

B= 1.4 Gy x-rays 10#~ per week

C=C ions 2.1 Gy per fraction 5# per week

D=C ions 6 Gy per fraction 5# per week

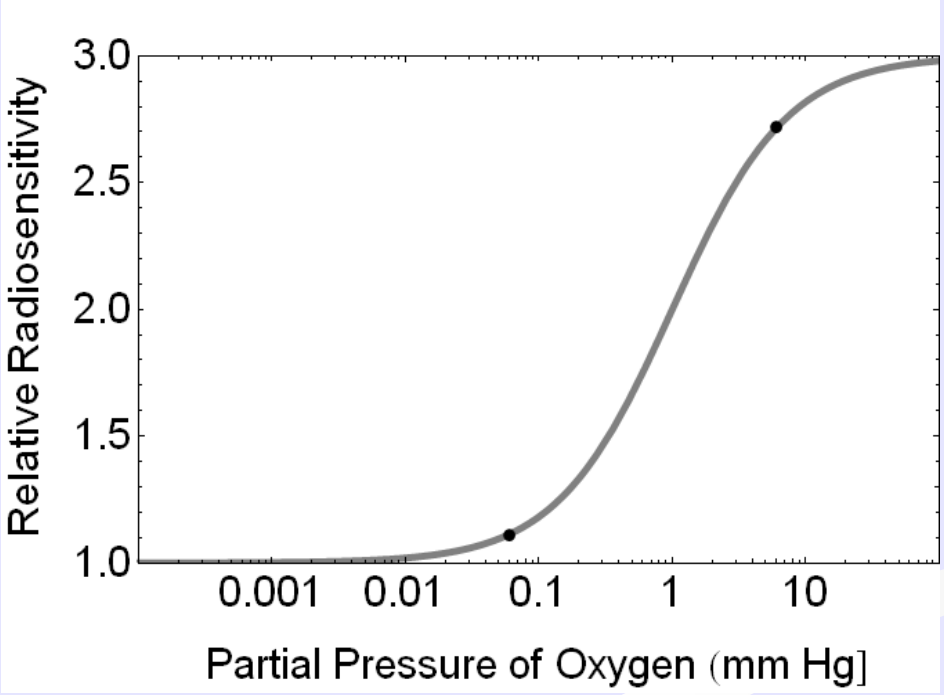
Faster re-oxygenation, mean of 3% per day




In 'Radiobiological Modelling in Radiation Oncology' [Eds Dale and Jones, Brit Insititute of 2007]

# Ultra-high dose rate effects

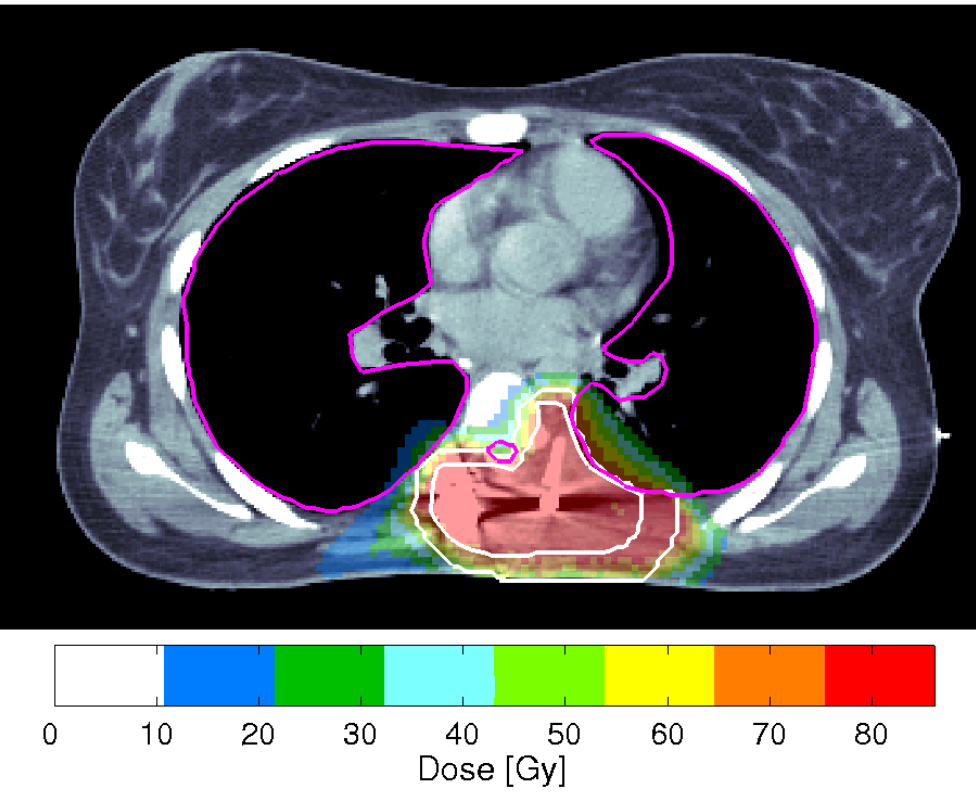
- Several Studies (1960-1980, e.g. Berry et al, Ling et al) showed that X-ray and electron doses of 5-10 Gy delivered at $10^9$ Gy/sec dose rate depletes oxygen from ~ 3mm Hg to 0.08mm Hg



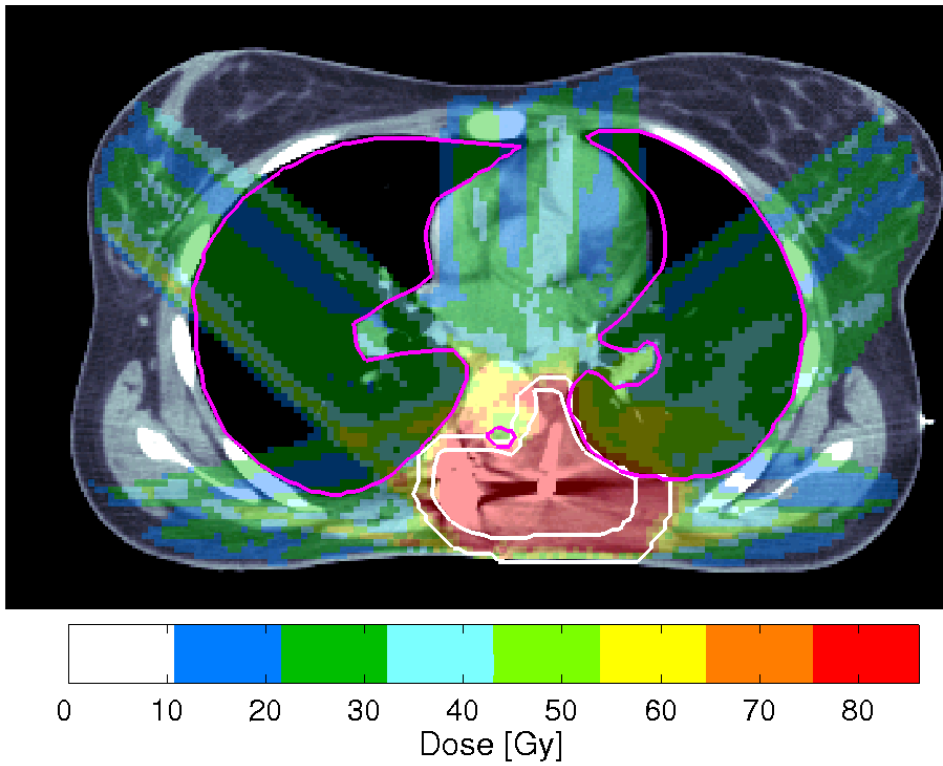

No body of work on protons, neutrons or ions…could effect differ by an order of magnitude?...e.g. dose of 2 Gy ions at $10^8$ Gy/sec

# Paravertebral Epithelioid Sarcoma Intensity Modulated Protons (IMPT) vs. Intensity Modulated X-ray (IMXRT) 7 (field)

IMProtons




IMXRT



# Circulatory Disease Risk

Report of the independent Advisory Group on Ionising Radiation (UK)

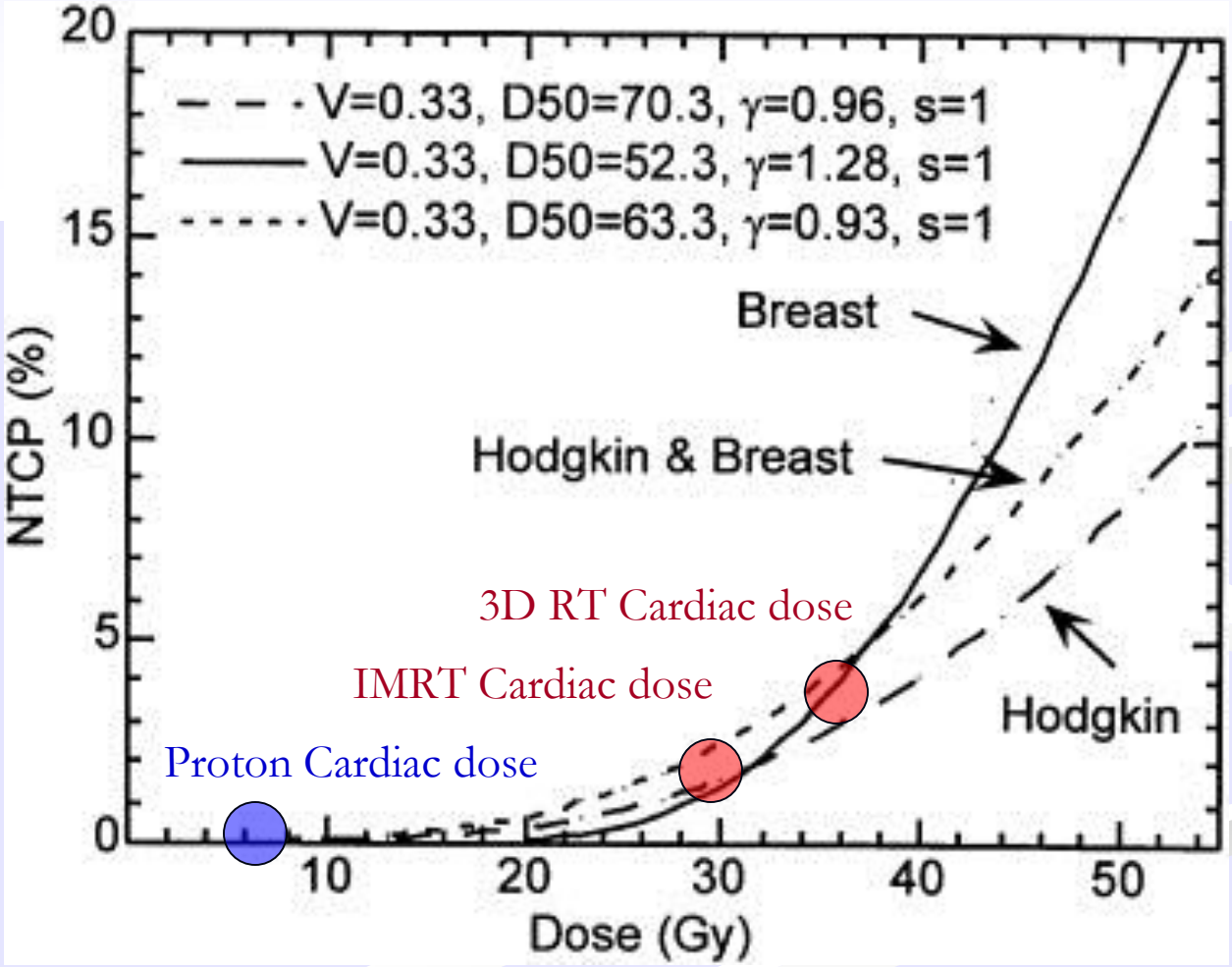
2010 (web)

2011 (book form)

Free on www.hpc.gov.uk

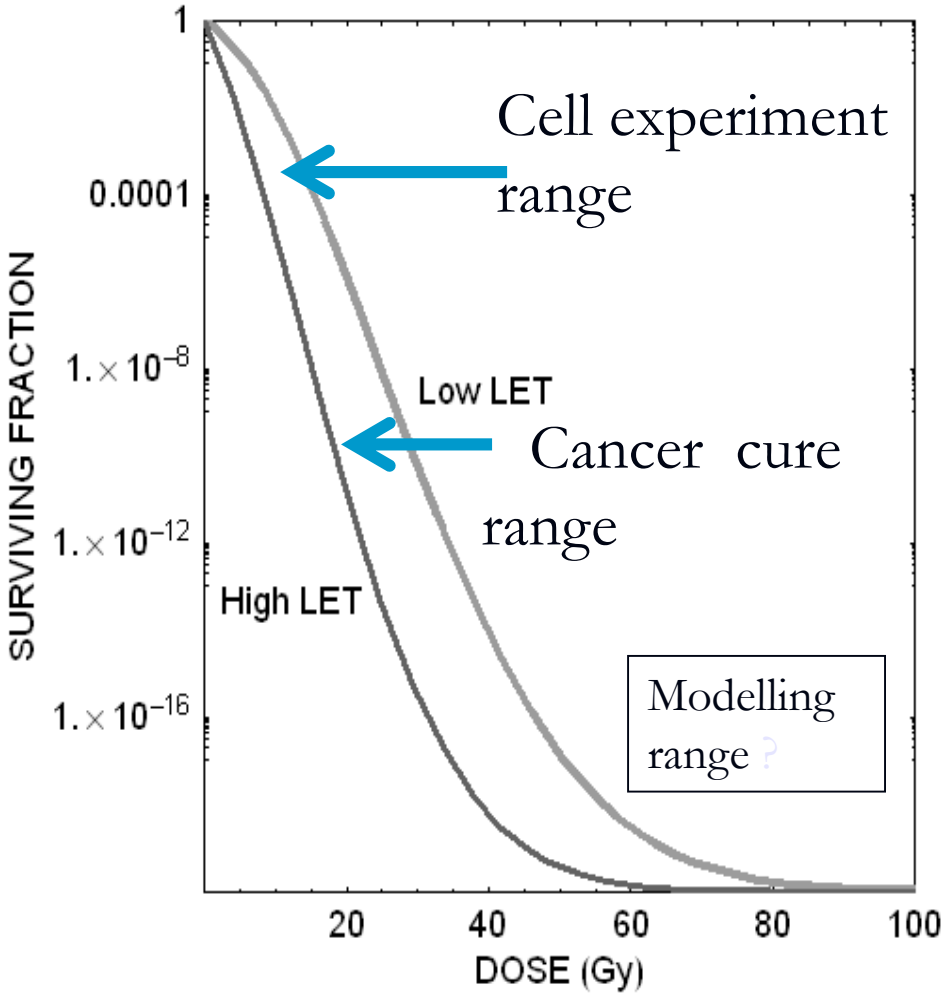
Doses as low as 2 Gy might cause increased late circulatory effects.

# QUANTEC: Risk of toxicity after cardiac radiotherapy



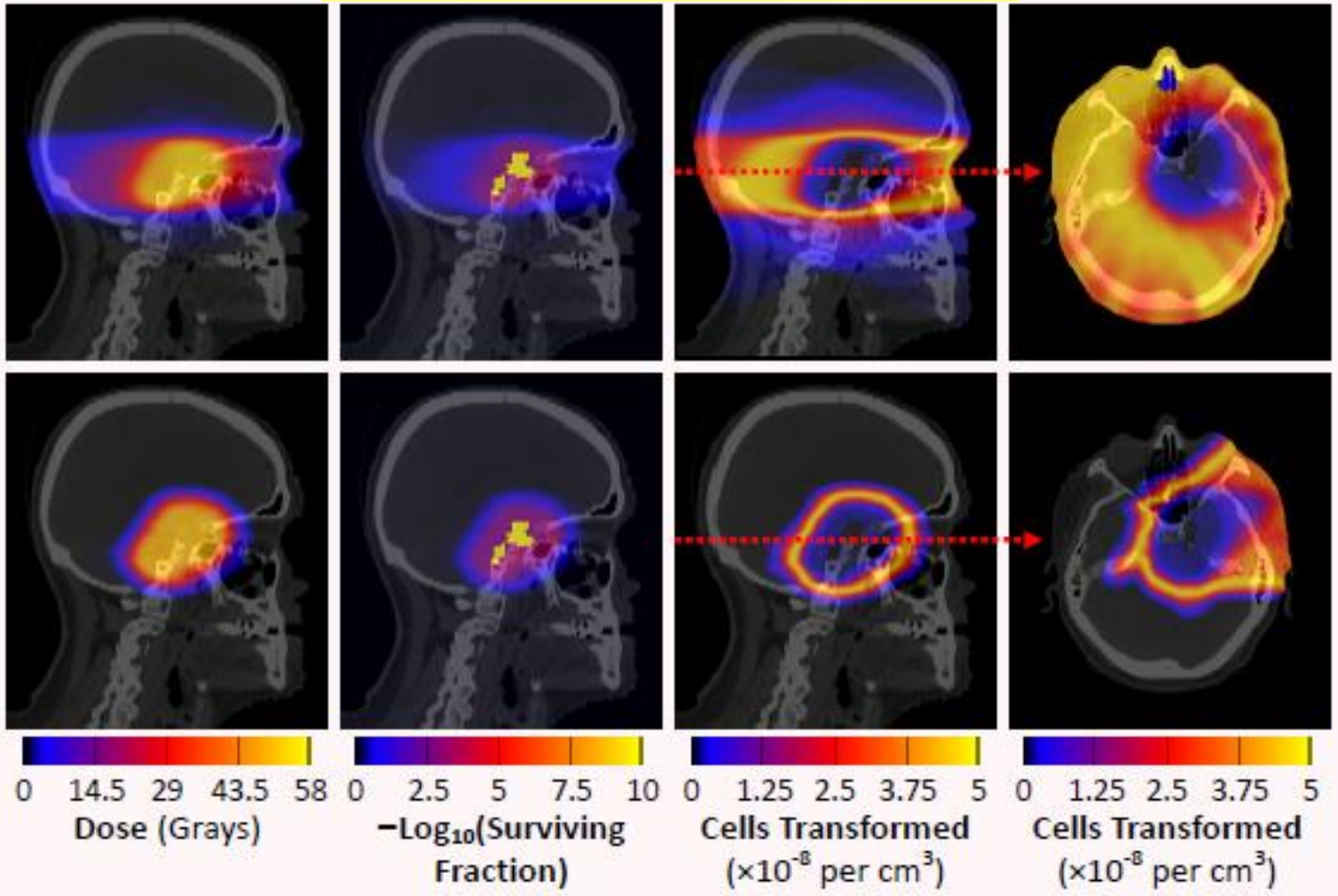

Gagliardi, et al. "Radiation Dose-Volume Effects in the Heart", IJRBOP, 76 (3S1), 2010, S77-S85.

# Cancer & Space flights !




**Prospects for long term survival of humans/cells in space will depend on improved knowledge of low and high LET radiation effects and their reduction to very high dose over long time durations.**

# Meningioma Therapy




Mayo Clinical planned scans for IMRXT and Protons transformed to Malignant Induction maps at Oxford Particle Therapy Cancer Research Institute (D Warren, C Timlin, B Jones et al)

# Some general principles

**Malignant risk** is proportional to irradiated tissue volume and dose

Reduction in tissue volume (and cells exposed) by

- reducing **number** of fields and
- using **gantries**

# RBE studies required in tissues:

- CNS + eye
- Lung & Heart
- Kidney, Bladder
- Gastro-intestinal Tract
- Connective tissues, Arteries + Bone
- Gonads

+ NEED RBE STUDIES IN ALL CANCERS

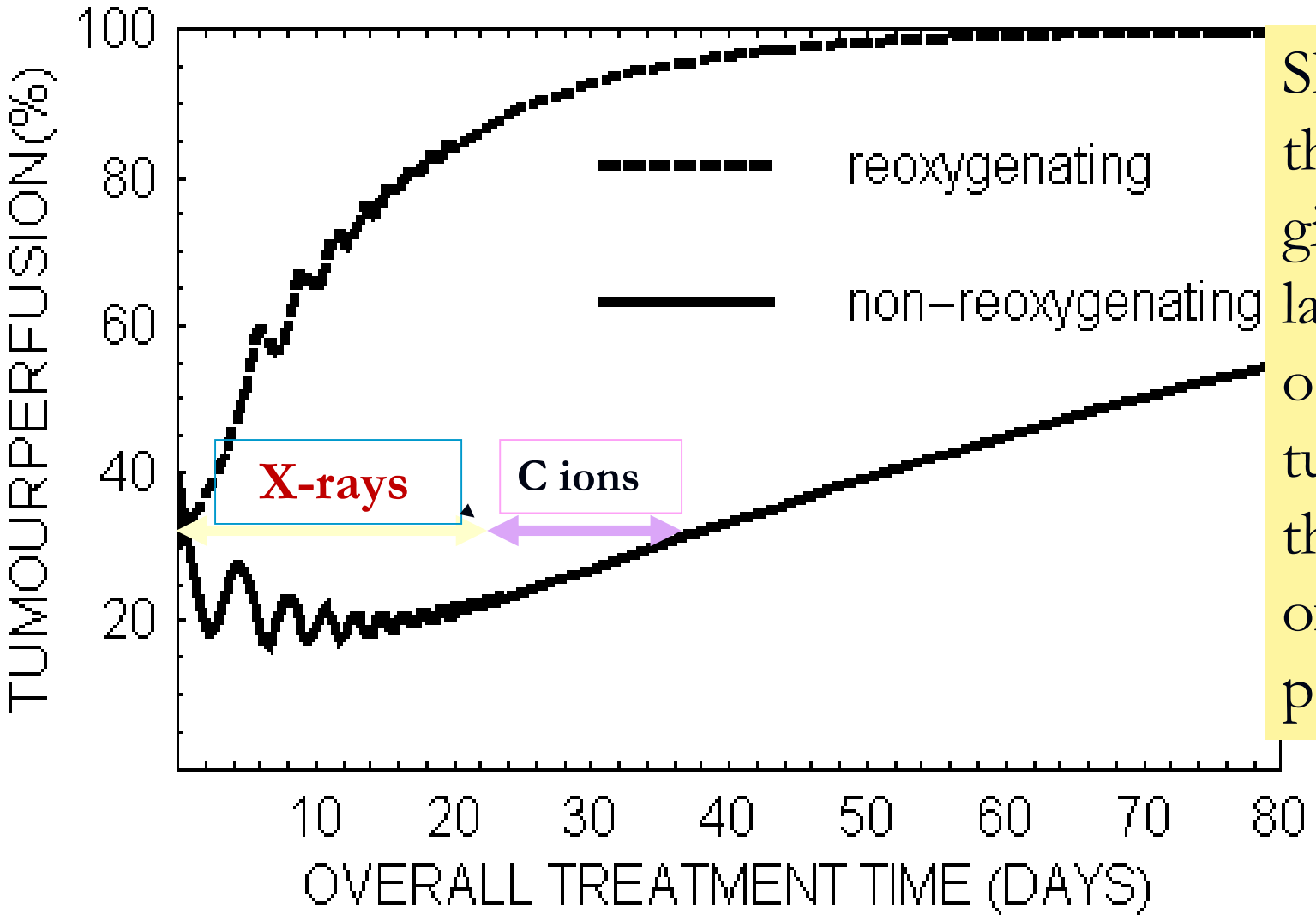
# Clinical Trial Design

Randomisation of patients to different

- Normal Tissue constraints (2)
- Tumour doses (2)

can investigate some RBE concerns

Compare results with standard – x-rays: if results better or worse than expected indicates if RBE > or < than expected, providing dose QA satisified.




Should ion therapy be given in later phase of R/T for tumours that re-oxygenate poorly?

These plots represent two extremes: there will inevitably be intermediate lines

# RBE - ? 2 additive components

$$RBE = X_{Phys} + Y_{Biol}$$

X = Physical RBE (due to LET ↑)
[influencing denominator of RBE definition]
Y= Biological contribution due to cell cycling, and dose per fraction.
[influencing numerator of RBE definition and changes with α/β ]

**Experiments with same cells in fast and slow proliferative states → magnitude of two components**