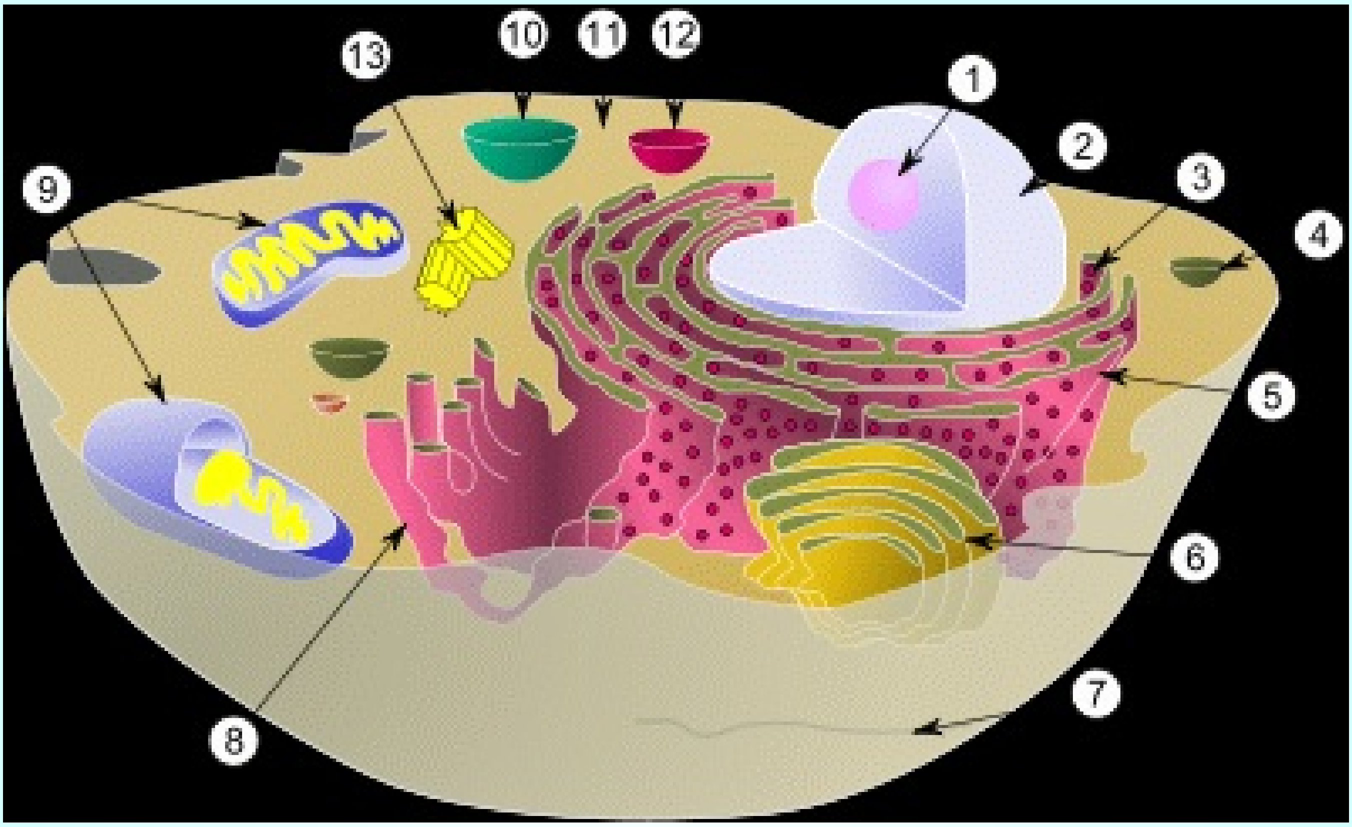
FYS-KJM-4710

Nuclear Chem., Dept.of Chem. University of Oslo

Radiation and the the cell



Organelles:(1) nucleolus(2) nucleus(3) ribosome(4) vesicle(5) rough endoplasmic reticulum (ER)(6) Golgi apparatus(7) Cytoskeleton(8) smooth endoplasmic reticulum(9) mitochondria(10) vacuole(11) cytoplasm(12) lysosome(13) centrioles within centrosome

DNA in the cell nucleus is the primary target for killing cells with radiation !!

Autumn 2009

Per Hoff

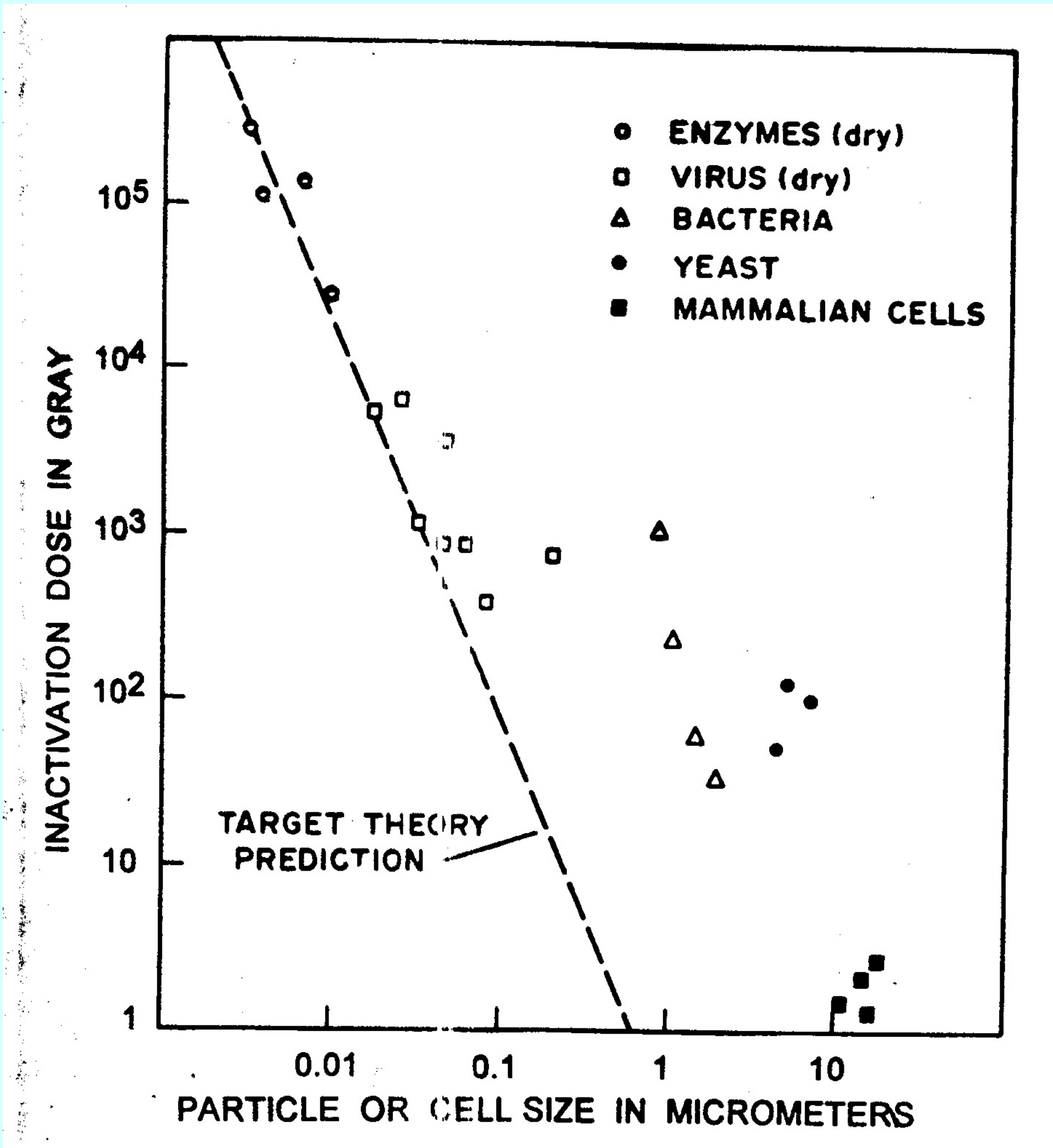
Radiation and the the cell

TABLE 18.5. *Effects of γ-radiation doses on micro organisms, pla*

Doses for inactivation (Gy):	enzymes	> 20 000	
	virus (dry)	300-5000	
	bacteria	20-1000	
	human cells	≥ 1	
Flowers (Senecio) survive at	10 Gy/d		during the
Trees do not survive at	> 1 Gy/d		growing se
Trees normally survive at	≤ 0.02 Gy/d		(normally g
$LD_{50/30}$ (Gy) for	amoeba	1000	
	fruit fly (Drosophila)	≥600	
	shellfish	200	
	goldfish	20	
	tortoise	15	
	song sparrow	8	
	rabbit	8	
	monkey	6	
	man	~4	
	dog	3.5	

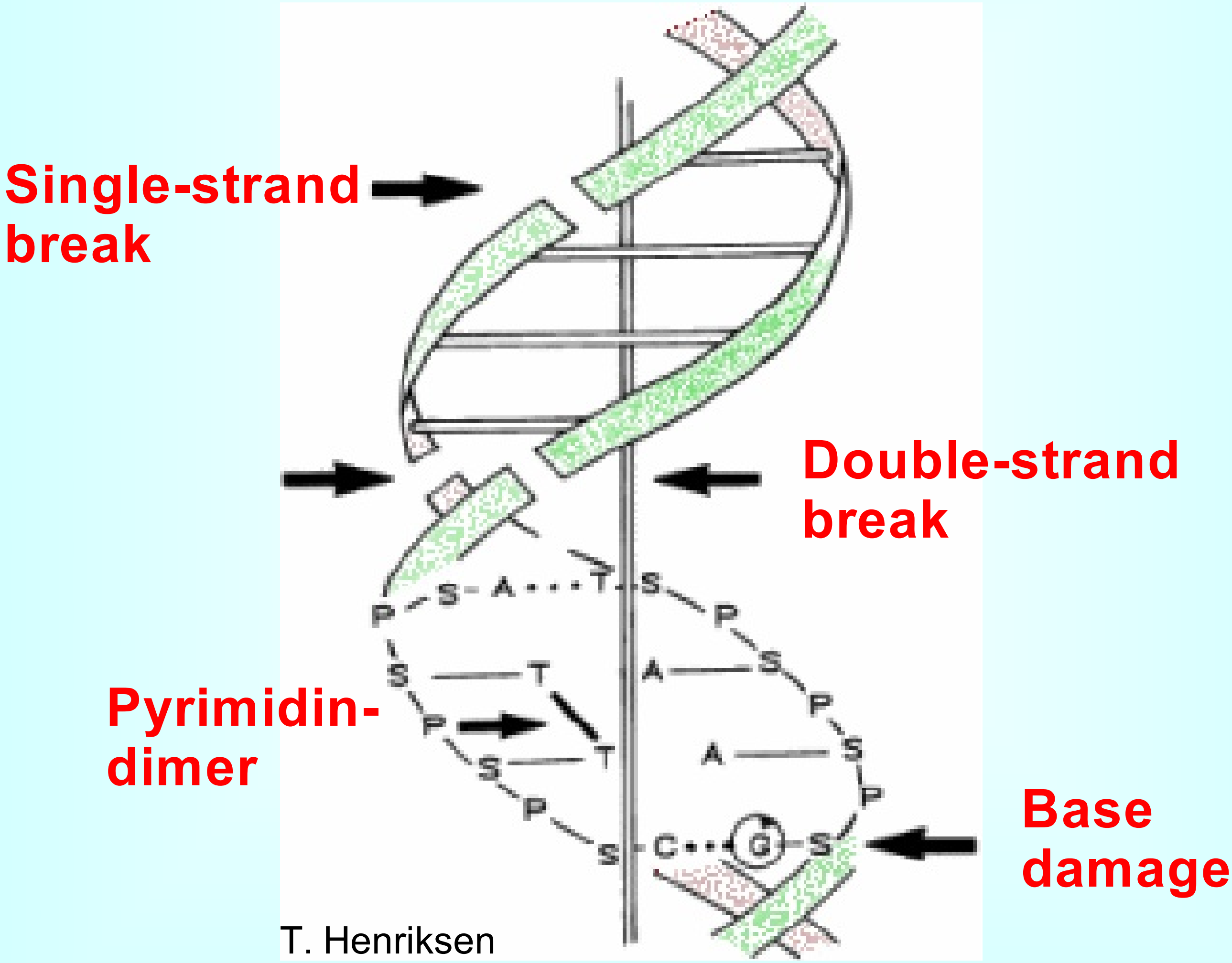
$LD_{50/30}$ - the dose at which 50 % of the individuals die within 30 days. Varies a lot.

Radiation and the the cell



Radiation sensitivity varies over a large range. The onset of repair mechanisms is clearly seen

DNA damage


Single-strand break
Double-strand break
Pyrimidin-dimer
Base damage
T. Henriksen

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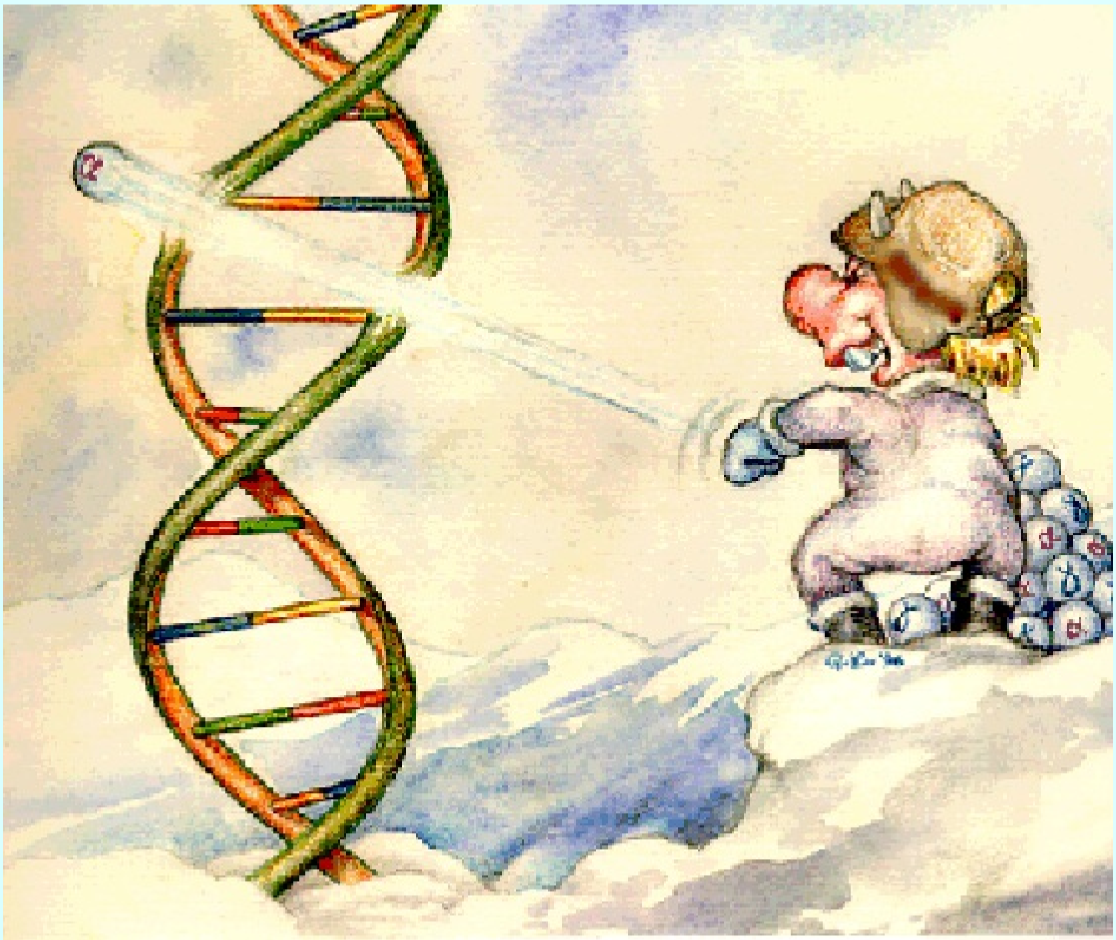
Cell-death by radiation



The double-strand break is the important mechanism of cell-kill !

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Cell-death by radiation

There are three fundamentally different ways of cell death.

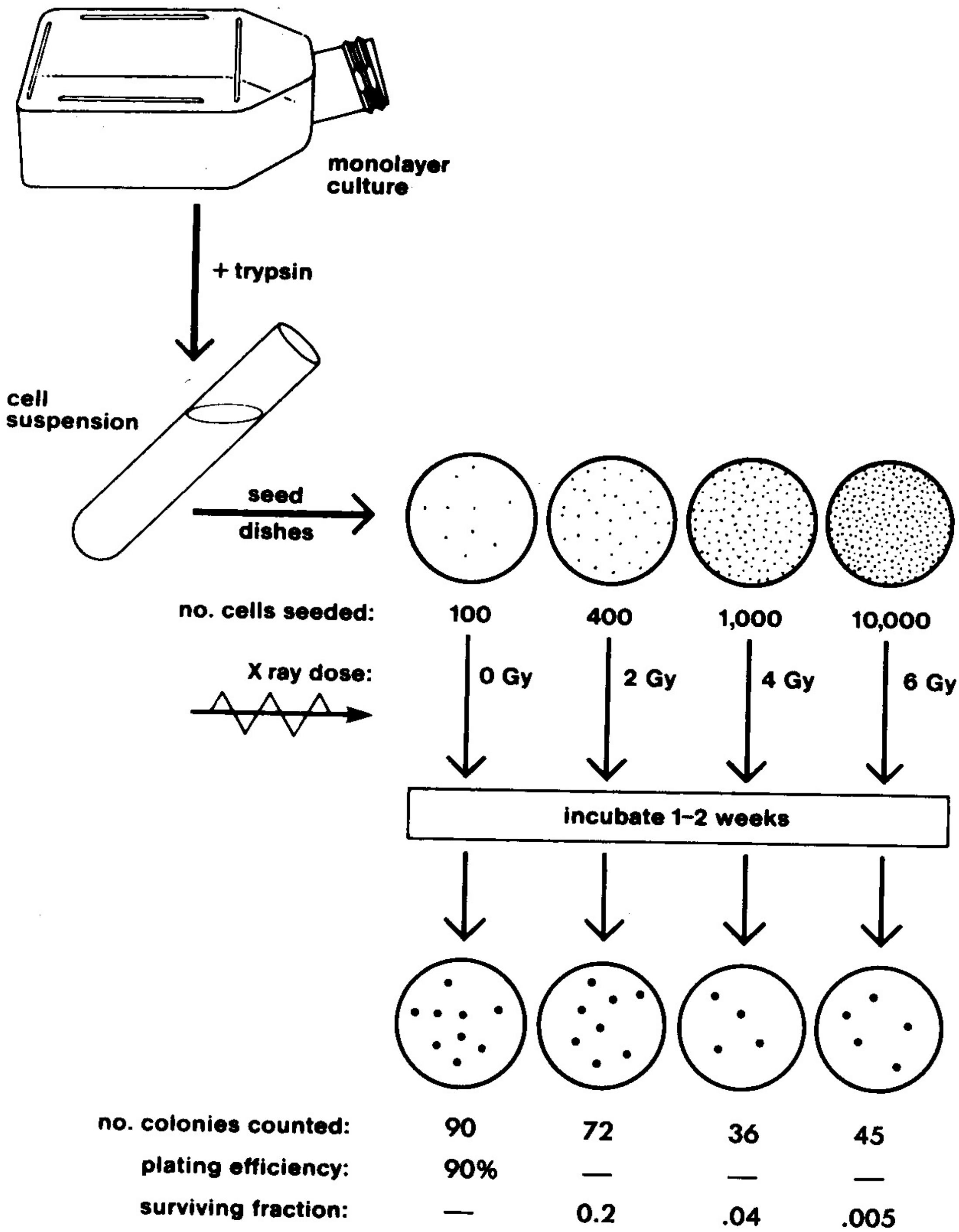
1. Mitotic cell death
   The cell is no longer able to divide itself.

2. Apoptotic cell death
   Or “programmed” cell death -activation of security mechanism against potentially harmful cells

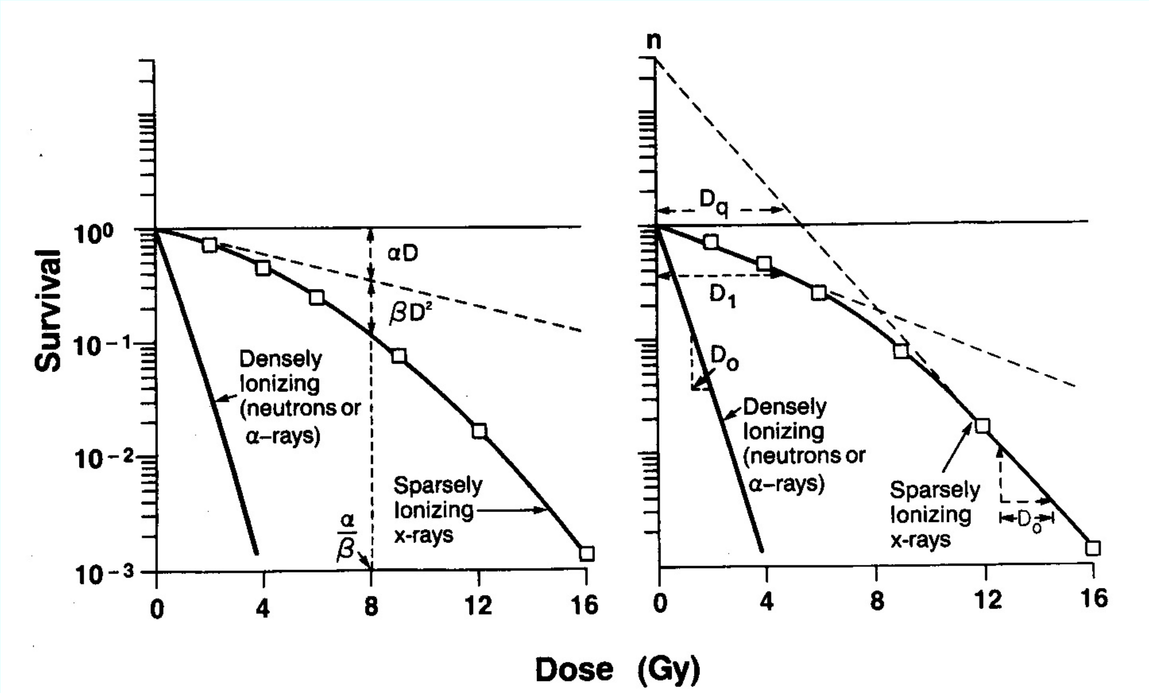
Different cell damage mechanisms are discussed in later courses. This lecture only gives a superficial survey.

3. Bystander effect
   In recent years, it has been shown that cells die more easily if neighbour cells are hit and killed. The details about this mechanism is currently frontline research

Cell survival



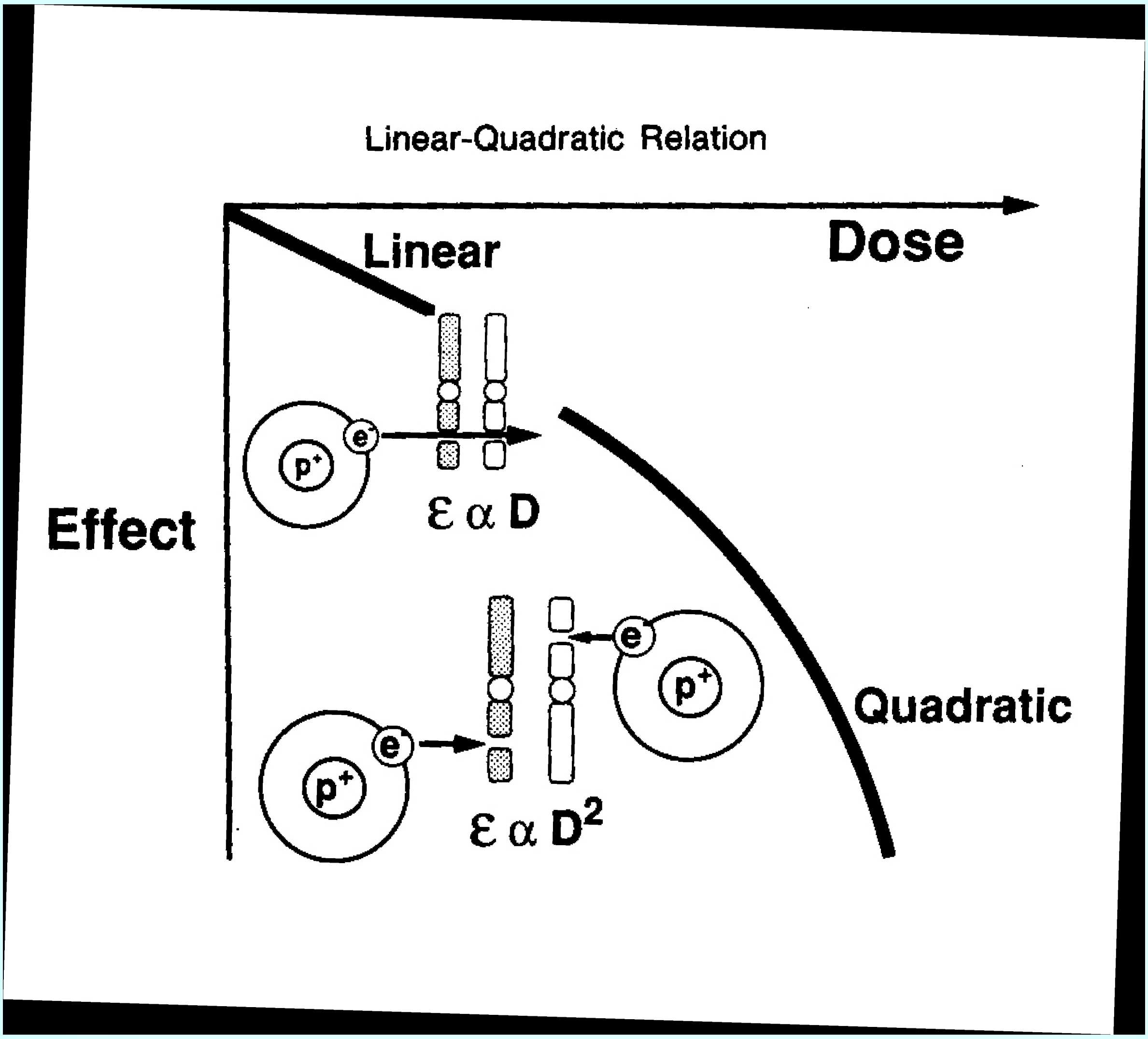
Survival curves



Typical survival curves for cells in culture with low LET and high LET radiation.
Important: "Curved shape" with low LET absent with high LET

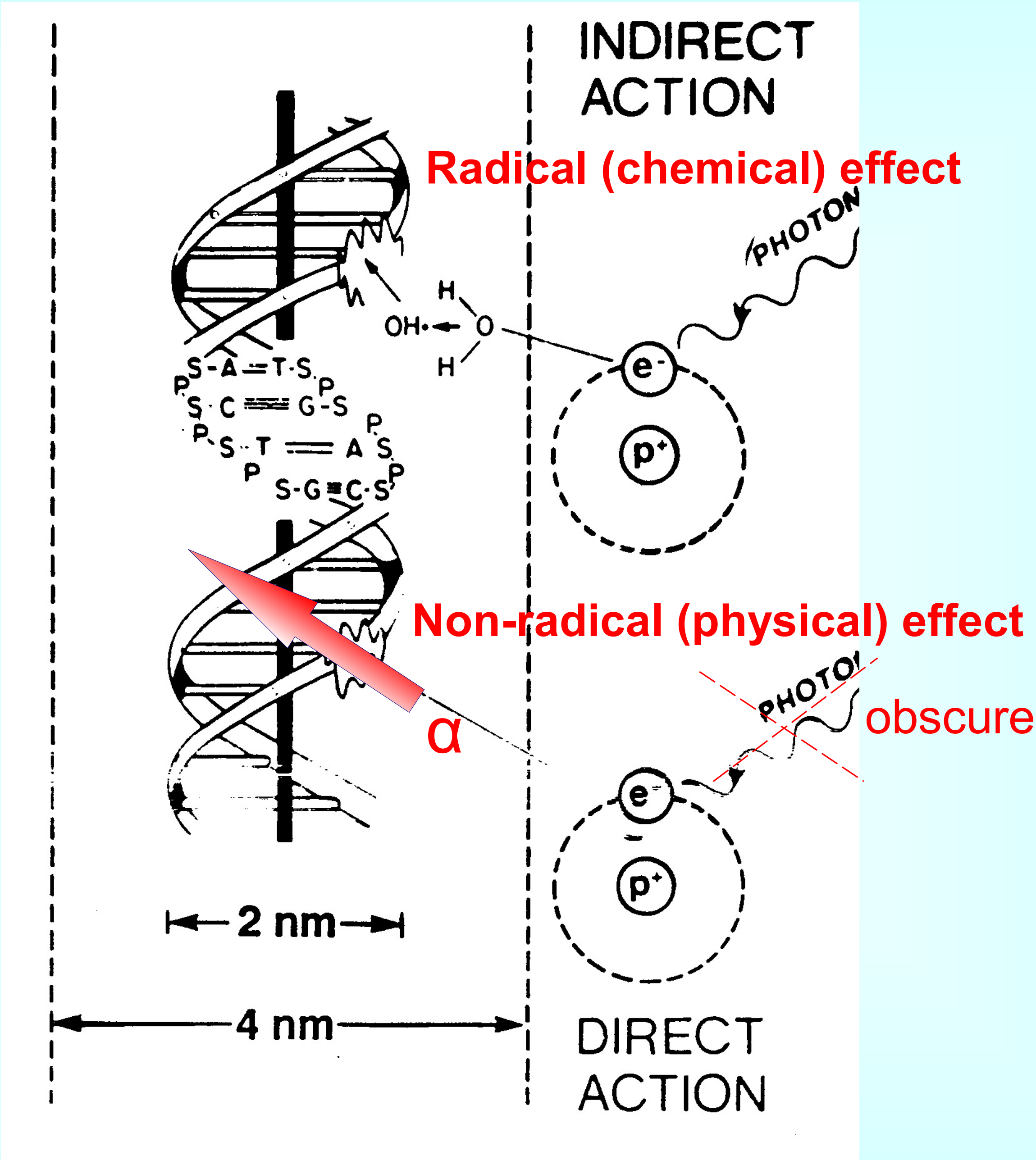
D_o - dose necessary to achieve reduction of surviving fraction to 1/e
A "shoulder" tells that a cellular repair mechanism is in action !

A primitive model



The linear part is caused by a single shot, while the quadratic part is caused by two consecutive shots

Direct and indirect mechanism



Direct action dominates at high LET radiation (α,p,n), indirect at low LET (β,γ X-rays)

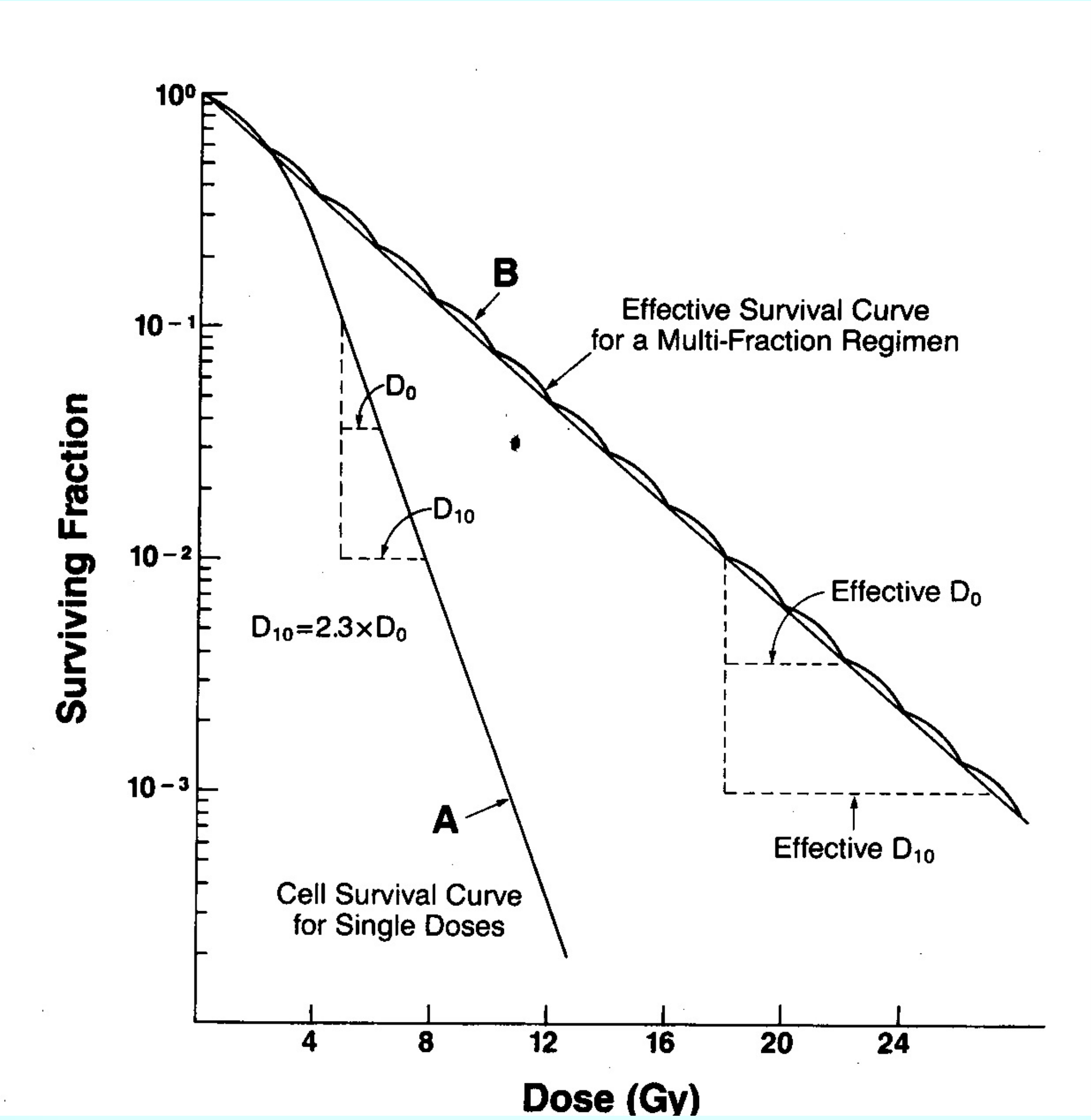
α versus β

	Range (μm) dimension	LET (keV/μm)	hits required for inactivation
cell	10 - 40		
α	40 - 90	~100	1-5
β	1000 -8000[x)]	~0.2	100-1000

x) in rare cases (e.g. ^{3}H), the range is much shorter

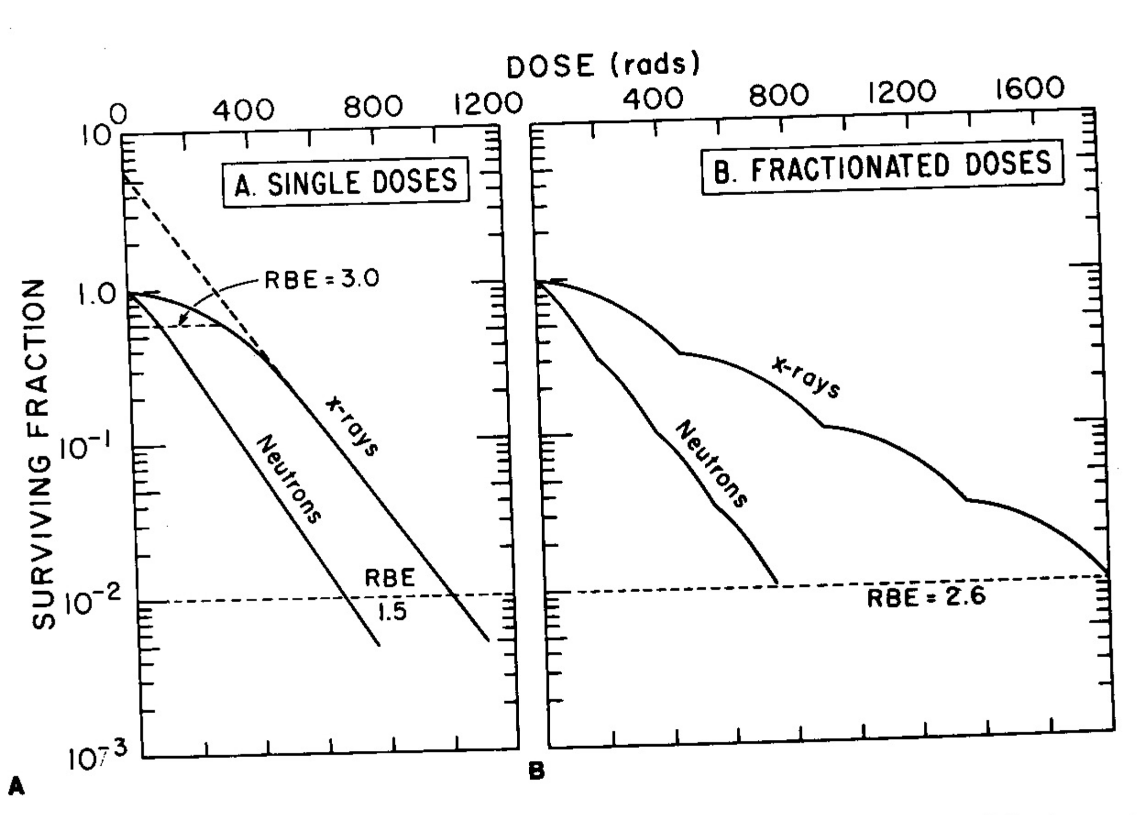
The large difference in LET between elctrons and heavy particles has several important consequences

Dose fractionation



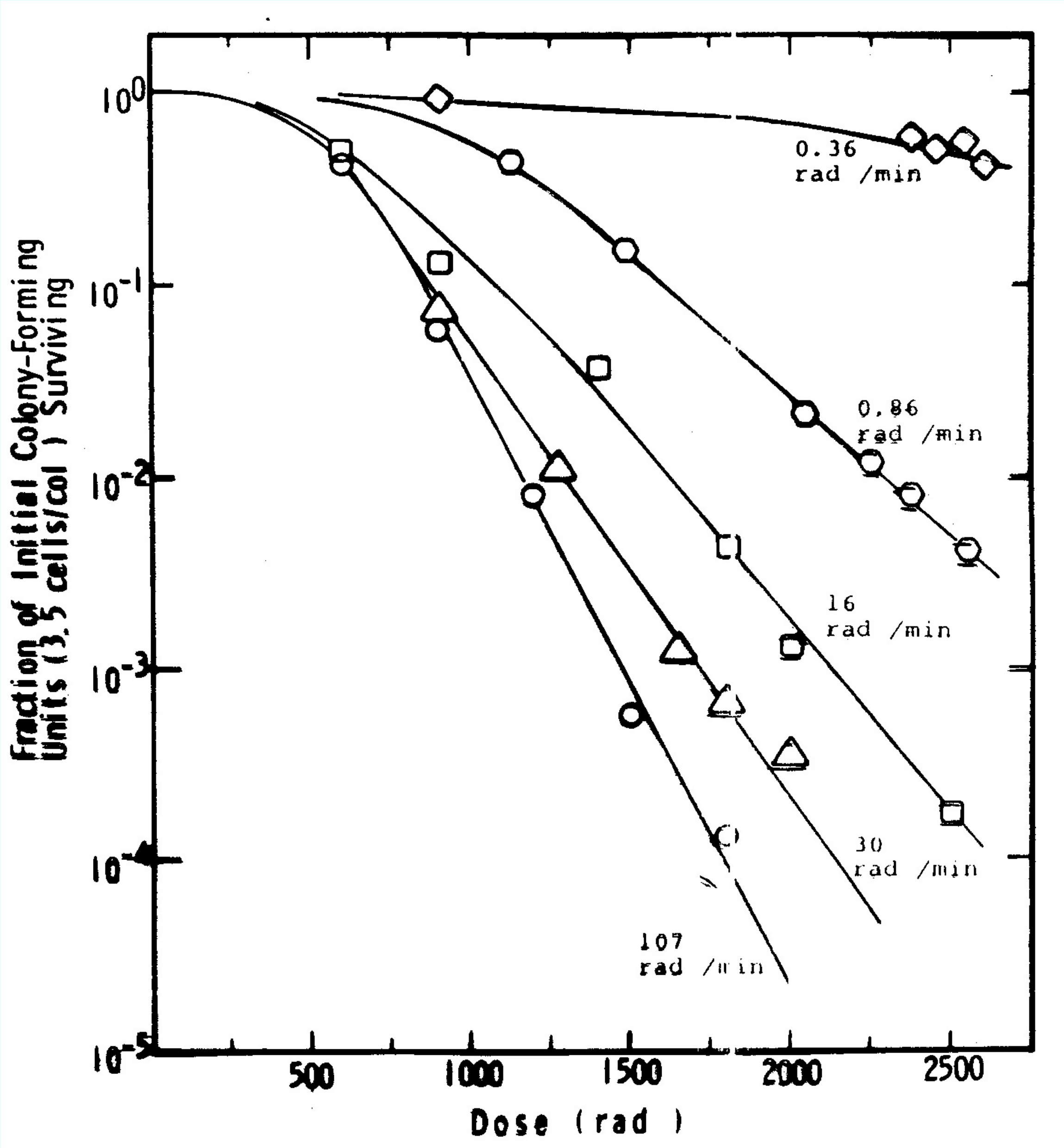
The treatment of cancer is now given in the form of highly fractionated doses given at short intervals (several per day), to spare healthy tissue and avoid damages.

Dose fractionation



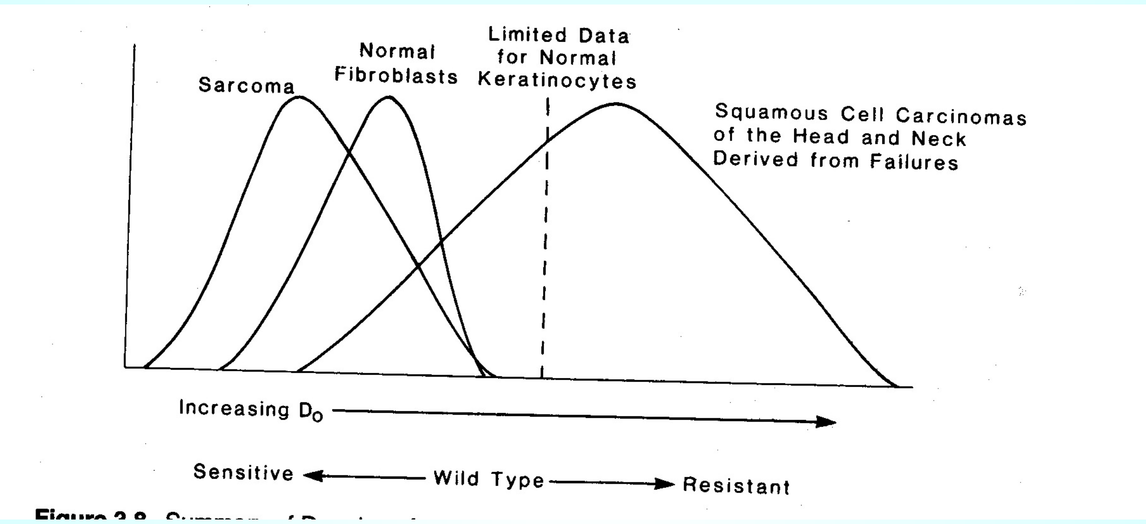
Fractionation of dose is important for low-LET radiation (due to repair mechanism), but has less or close to no importance for high-LET radiation.

Effect of dose-rate



High dependence on dose-rate at low-LET radiation, due to repair mechanisms

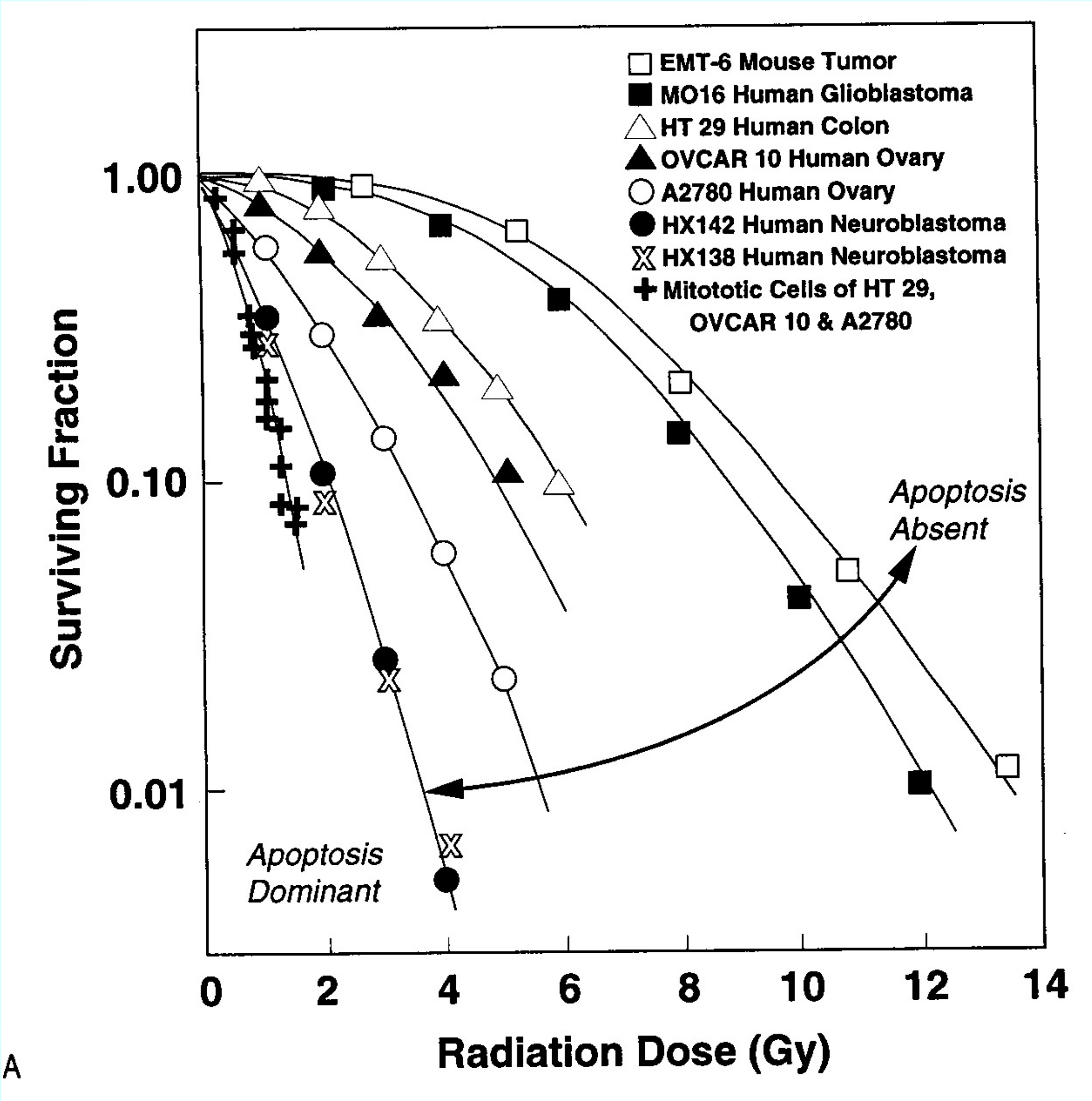
Radiation sensitivity



Different types of cells show pronounced differences in radiation sensitivity. Most cancers are more radiation sensitive than healthy cells

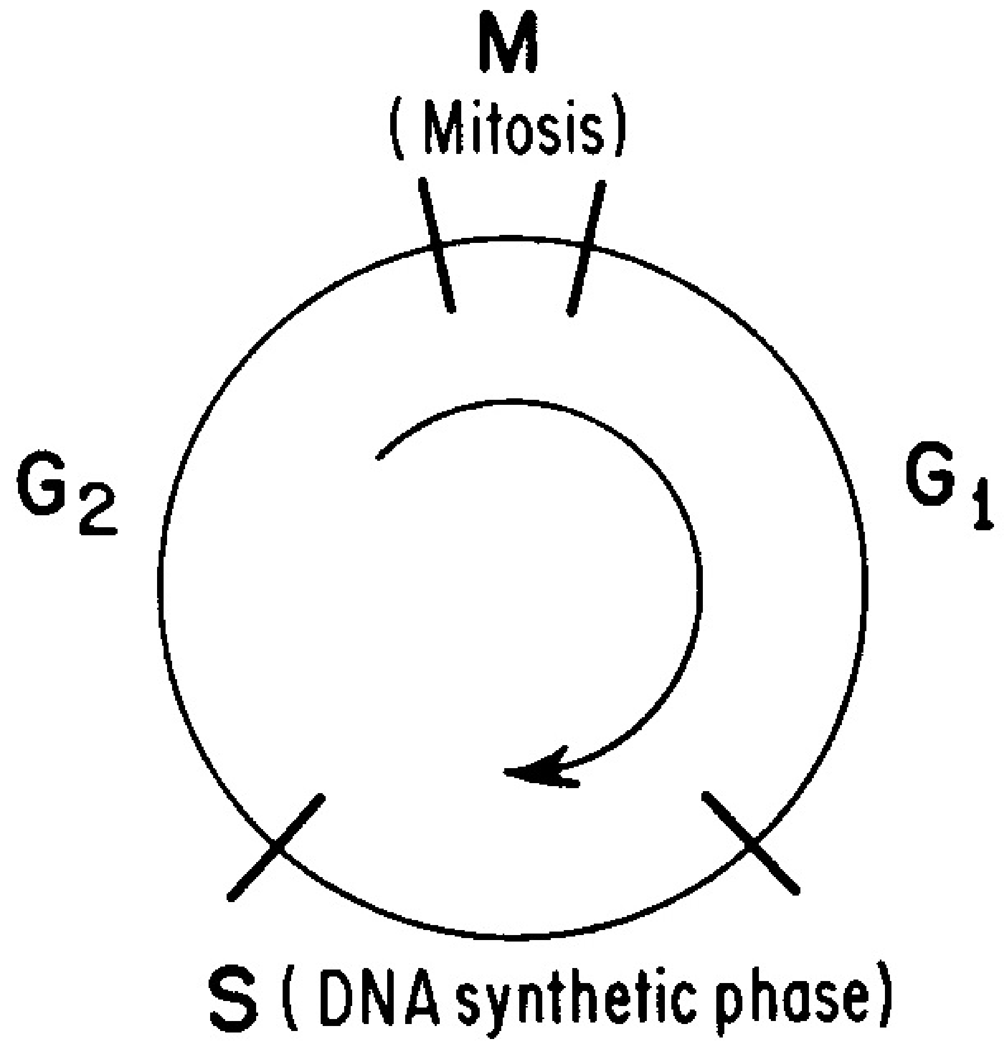
Some inherited syndromes cause increased radiation sensitivity,e.g. ataxia telangiectasia (AT), Fanconi's anemia, and several others

Radiation sensitivity

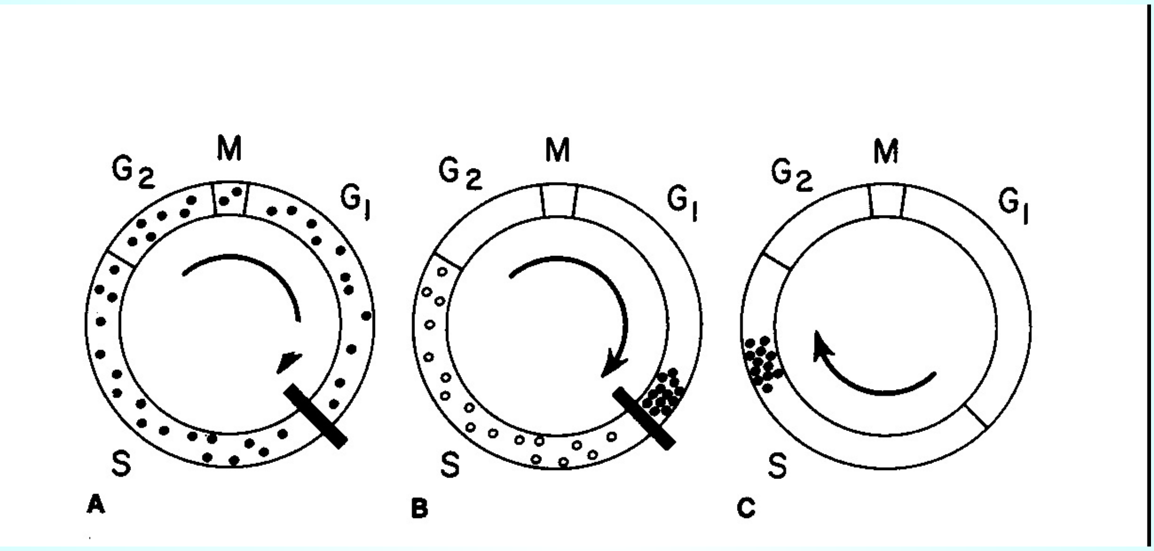


Some cancers showing very different radiosensitivity

The cell cycle



Synchronised cells



Cultured cells can be synchronised, facilitating investigations of sensitivity in different stages of its life.

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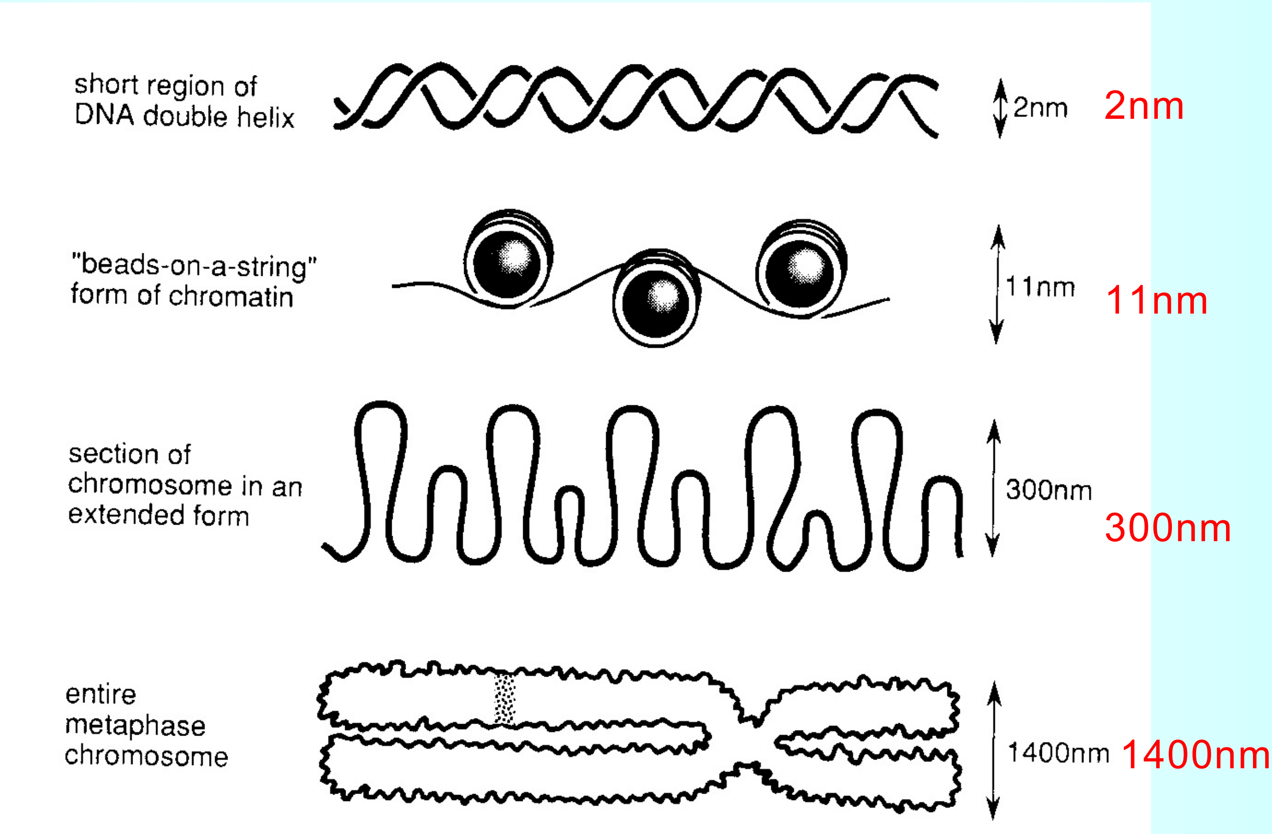
From DNA to chromosomes



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Chromosomes aberations

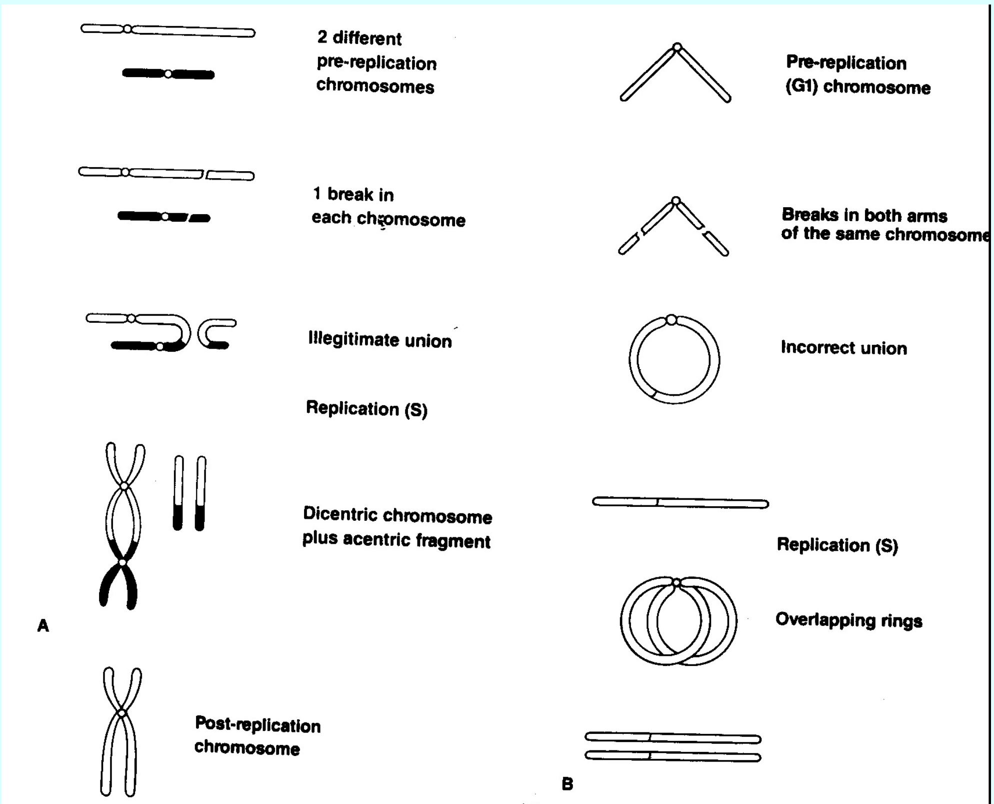
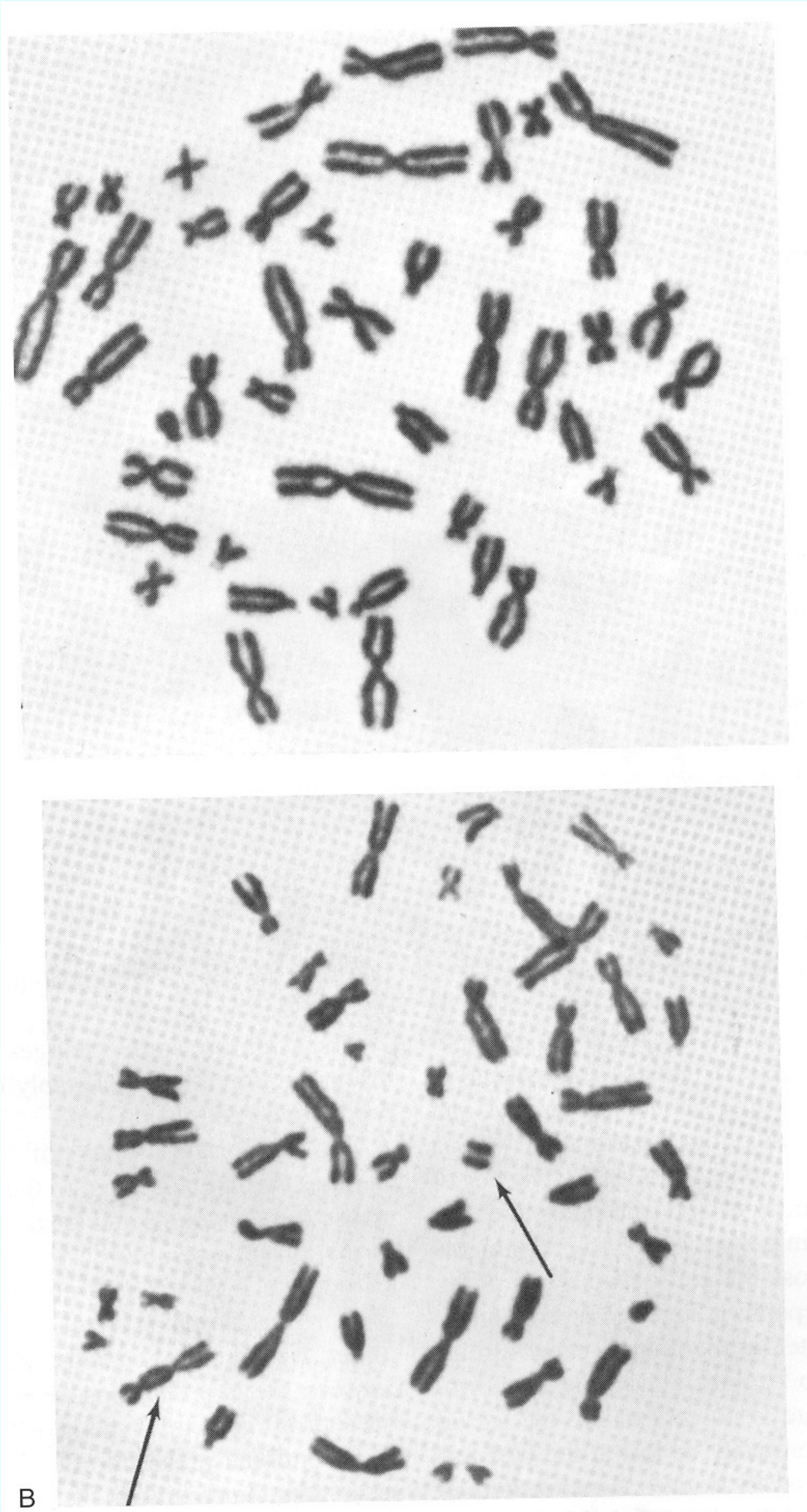


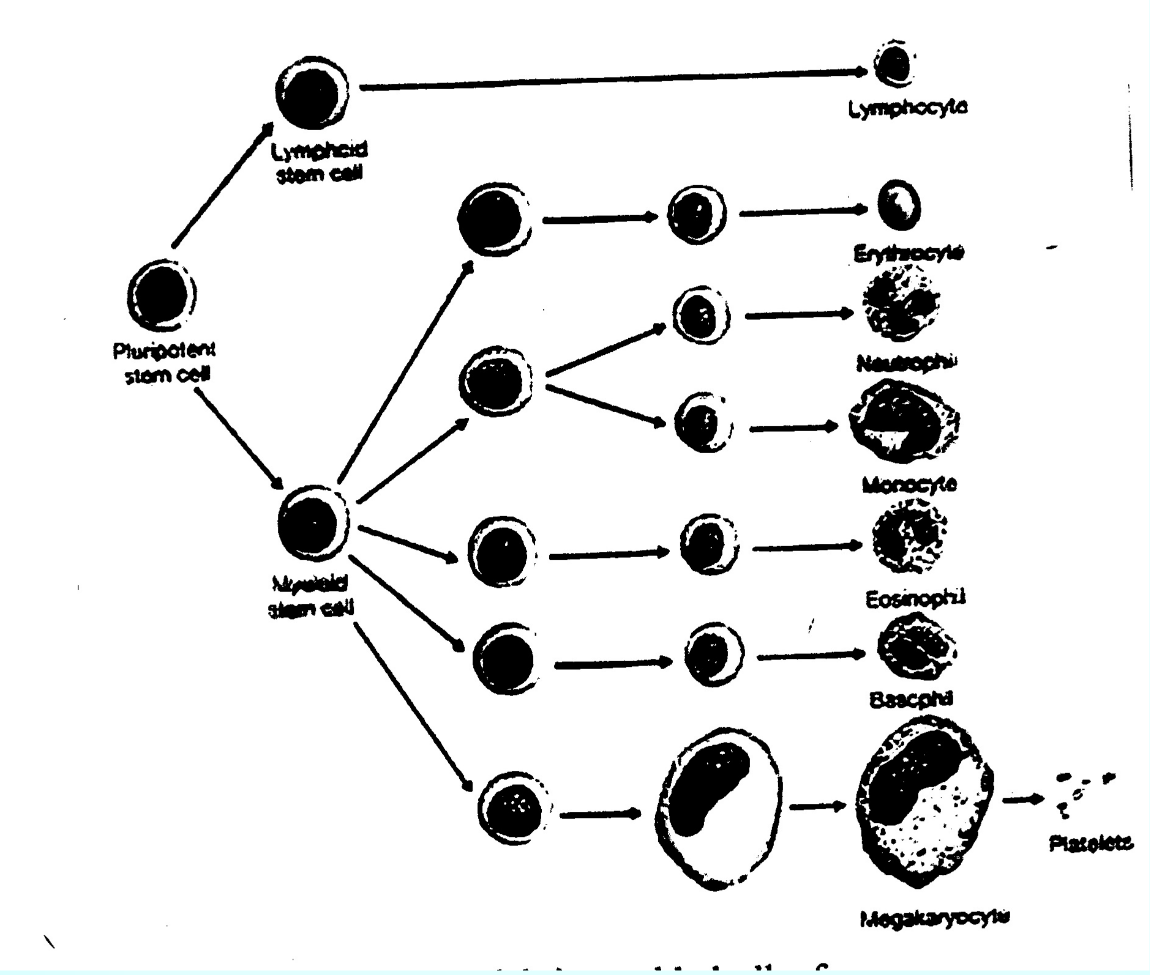
Figure 2.6. A: The steps in the formation of a dicentric by irradiation of prereplication (*i.e.*, G_1) chromosomes. A break is produced in each of two separate chromosomes. The "sticky" ends may join incorrectly to form an interchange between the two chromosomes. Replication then occurs in the DNA synthetic period. One chromosome has two centromeres: a dicentric. The other is an acentric fragment, which will be lost at a subsequent mitosis because, lacking a centromere, it will not go to either pole at anaphase. **B:** The steps in the formation of a ring by irradiation of a prereplication (*i.e.*, G_1) chromosome. A break occurs in each arm of the same chromosome. The sticky ends rejoin incorrectly to form a ring and an acentric fragment. Replication then occurs. **C:** The steps in the formation of an anaphase bridge by irradiation of a postreplication (*i.e.*, G_2) chromosome. Breaks occur in each chromatid of the

Different aberations. Rings and di-centrics normally cause cell death

Chromosome aberations

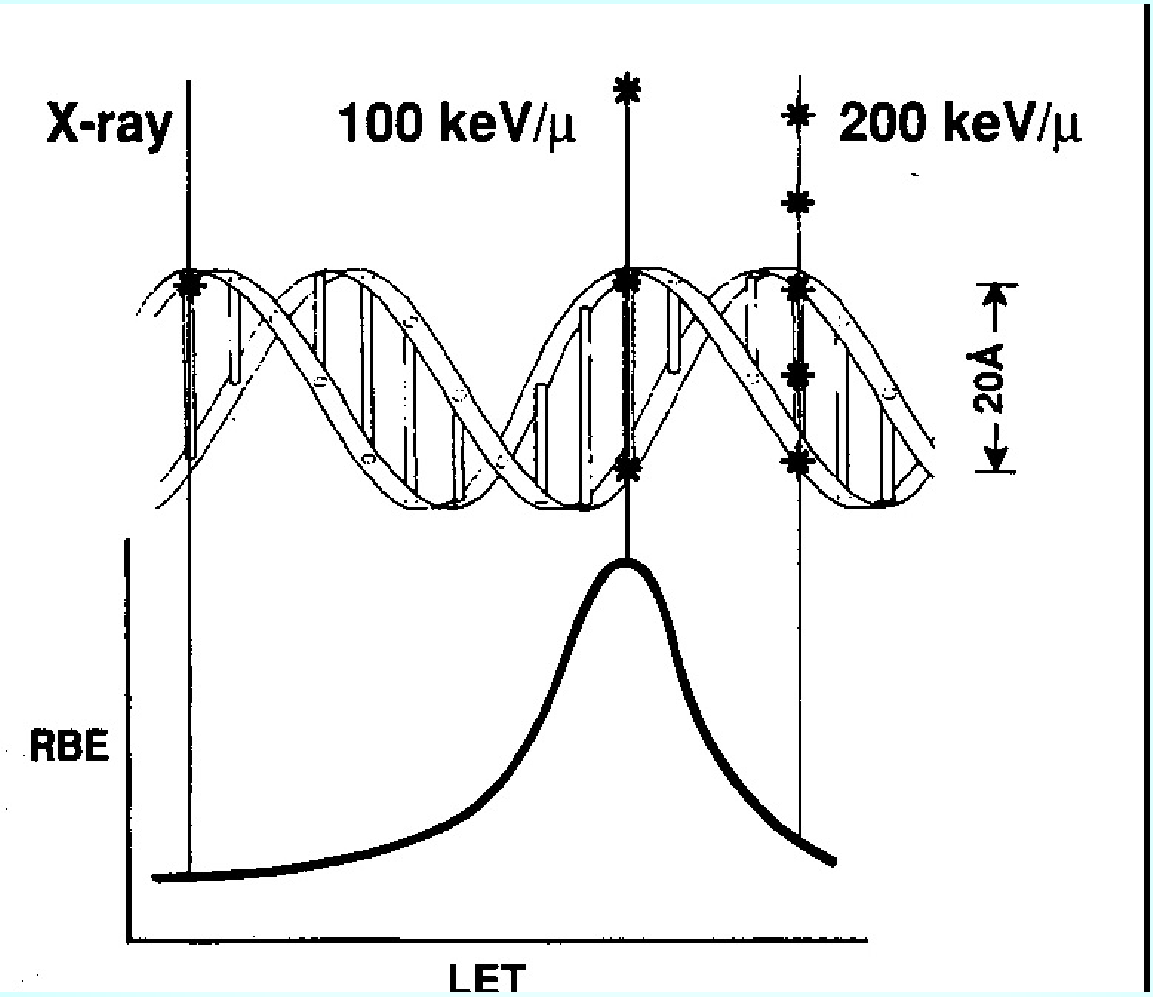


Stem cells



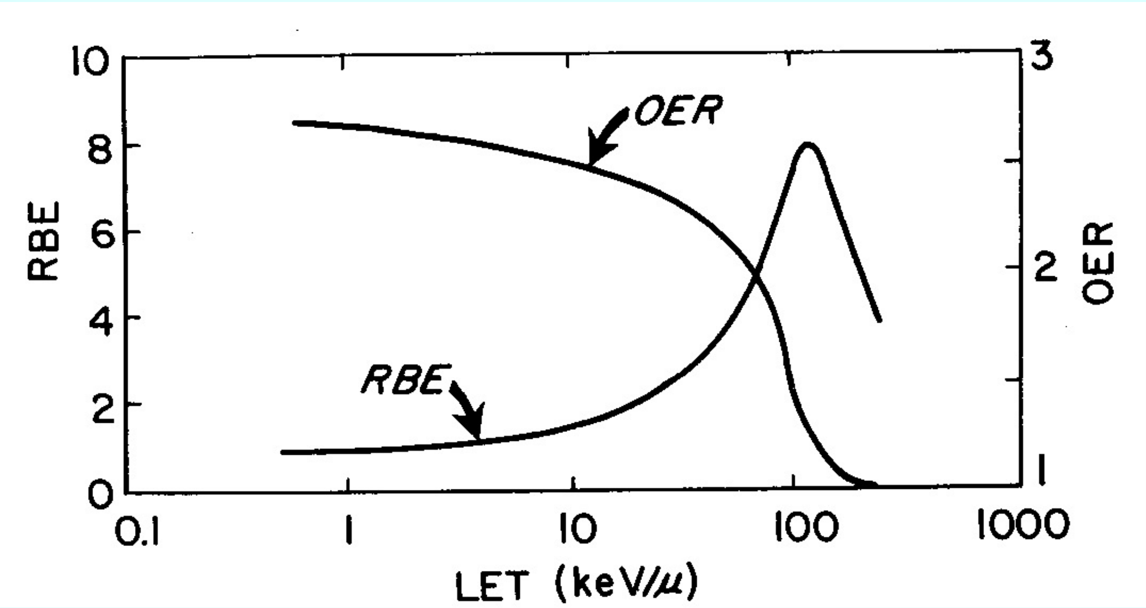
Stem cells may develop into a number of different cell types

High LET radiation



By 100 keV/μm, the average distance between ionising events is similar to the distance between the DNA strands. Hence, there is the maximum RBE (relative biologic effectiveness)

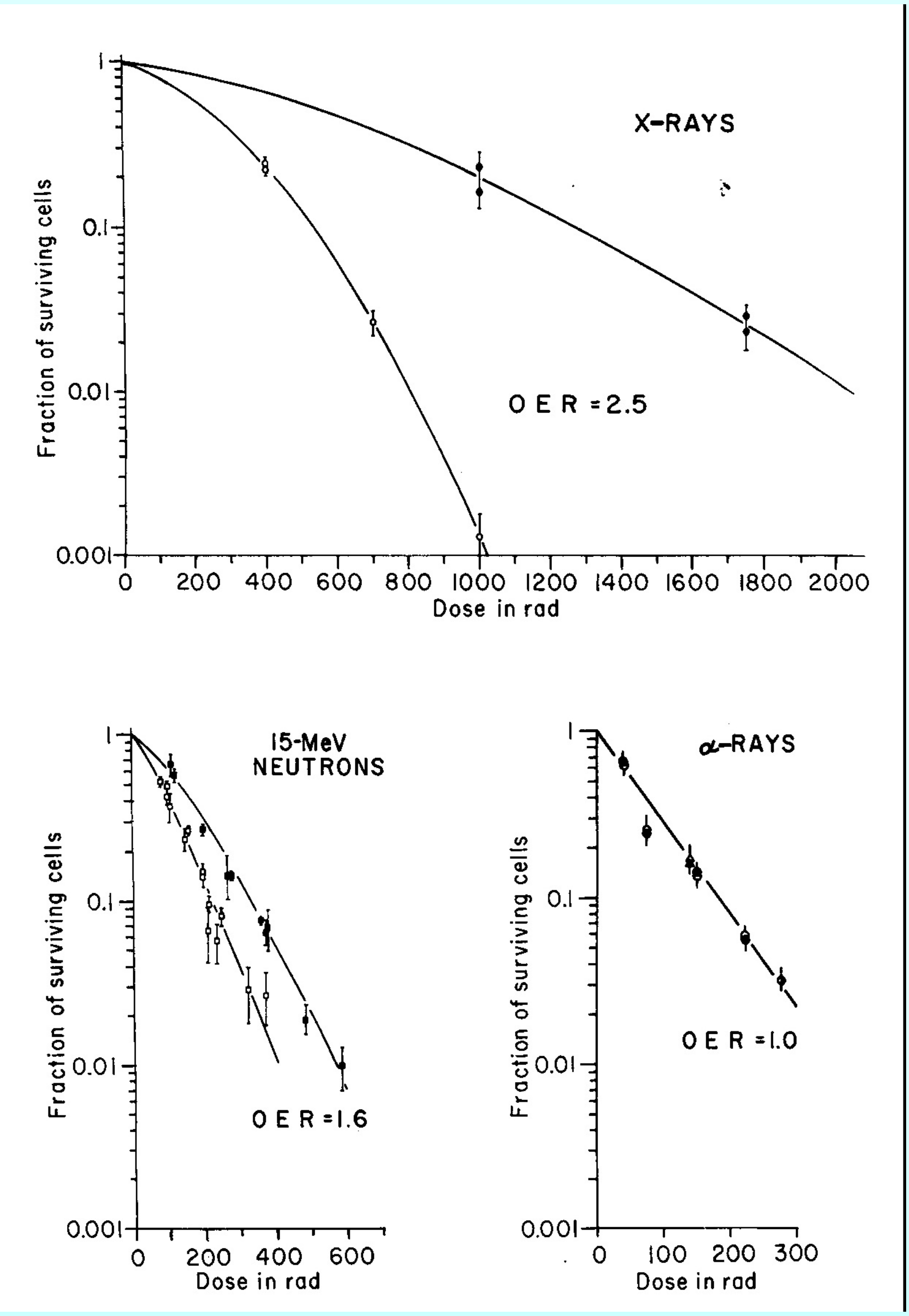
High LET radiation and O_2



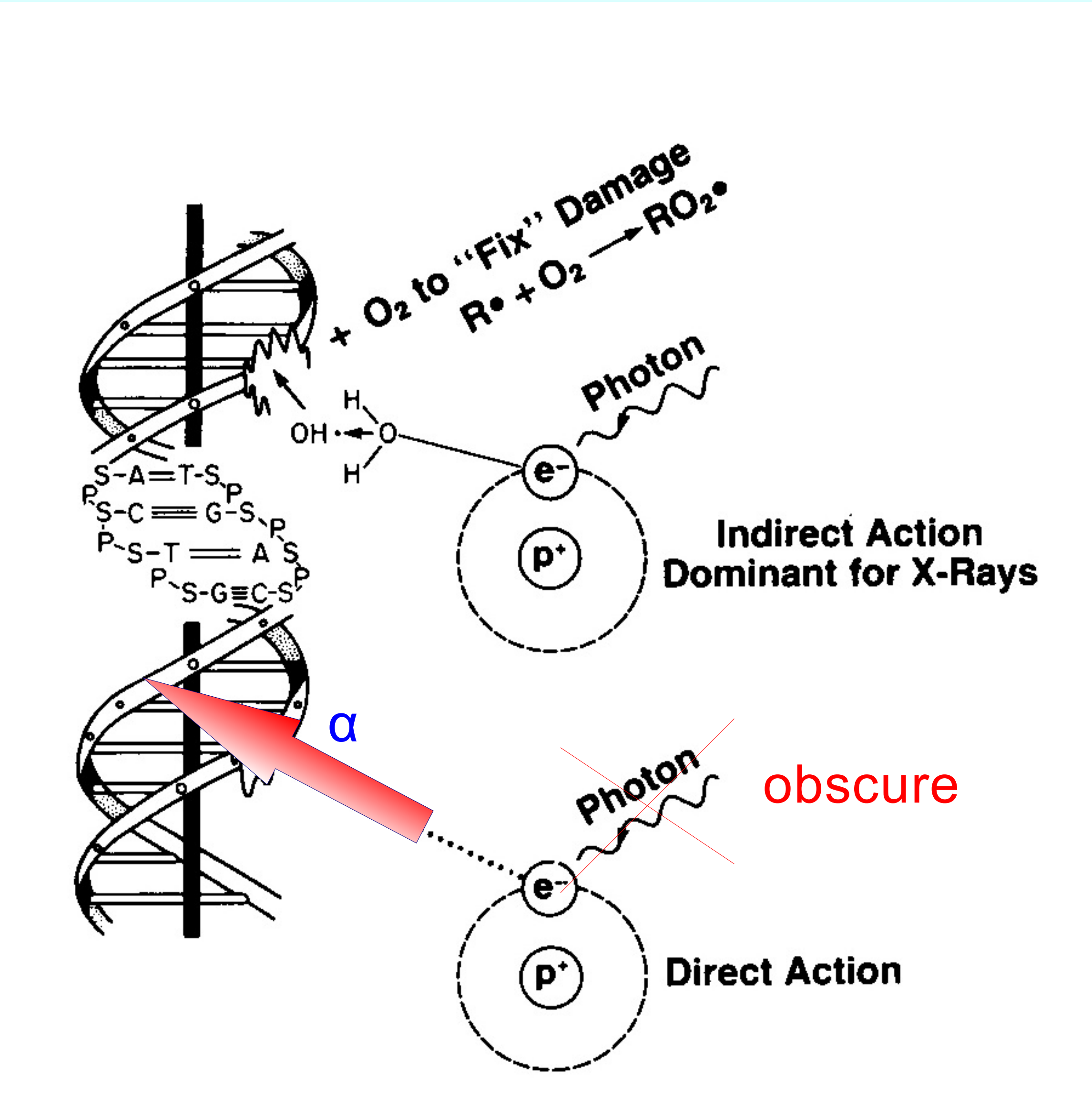
The importance of oxygen and other radiosensitizers decreases when the direct interaction mechanism takes over. Chemistry loses its importance

RBE - Relative biologic effectiveness
OER - Oxygen enhancement ratio

Oxygen effect at different LET

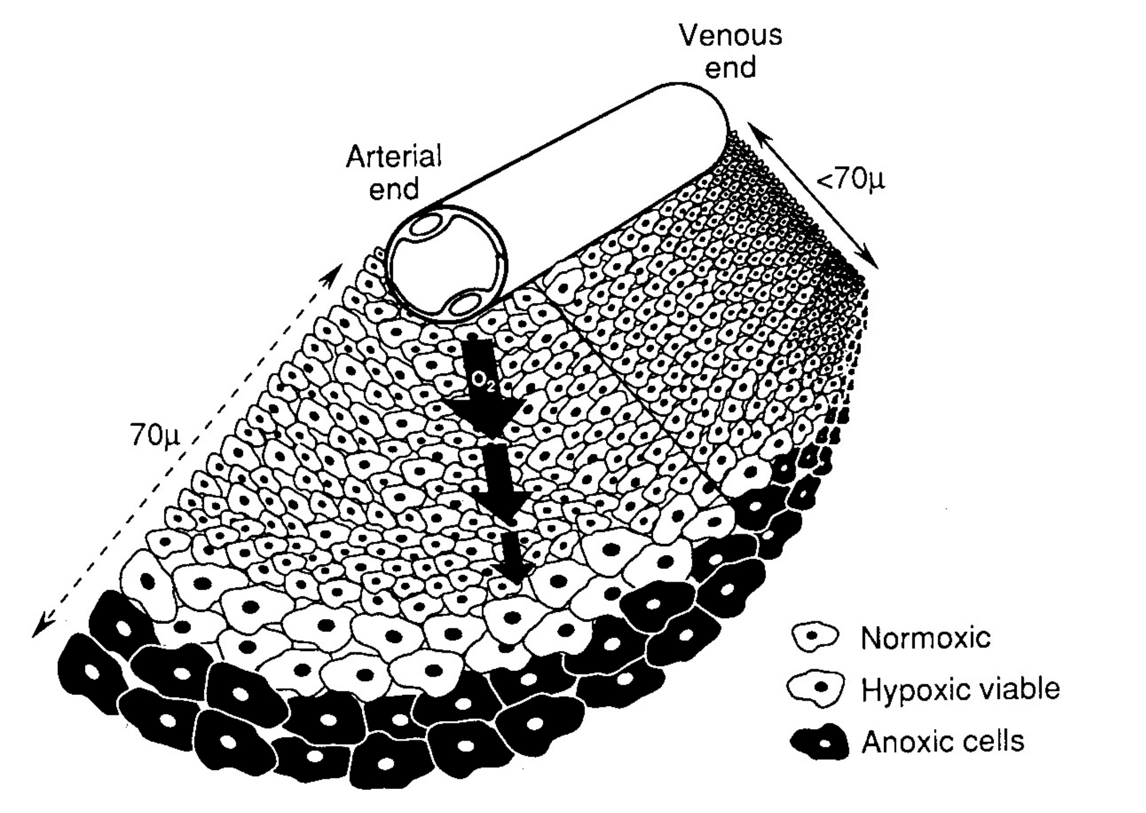


Oxygen effect at different LET



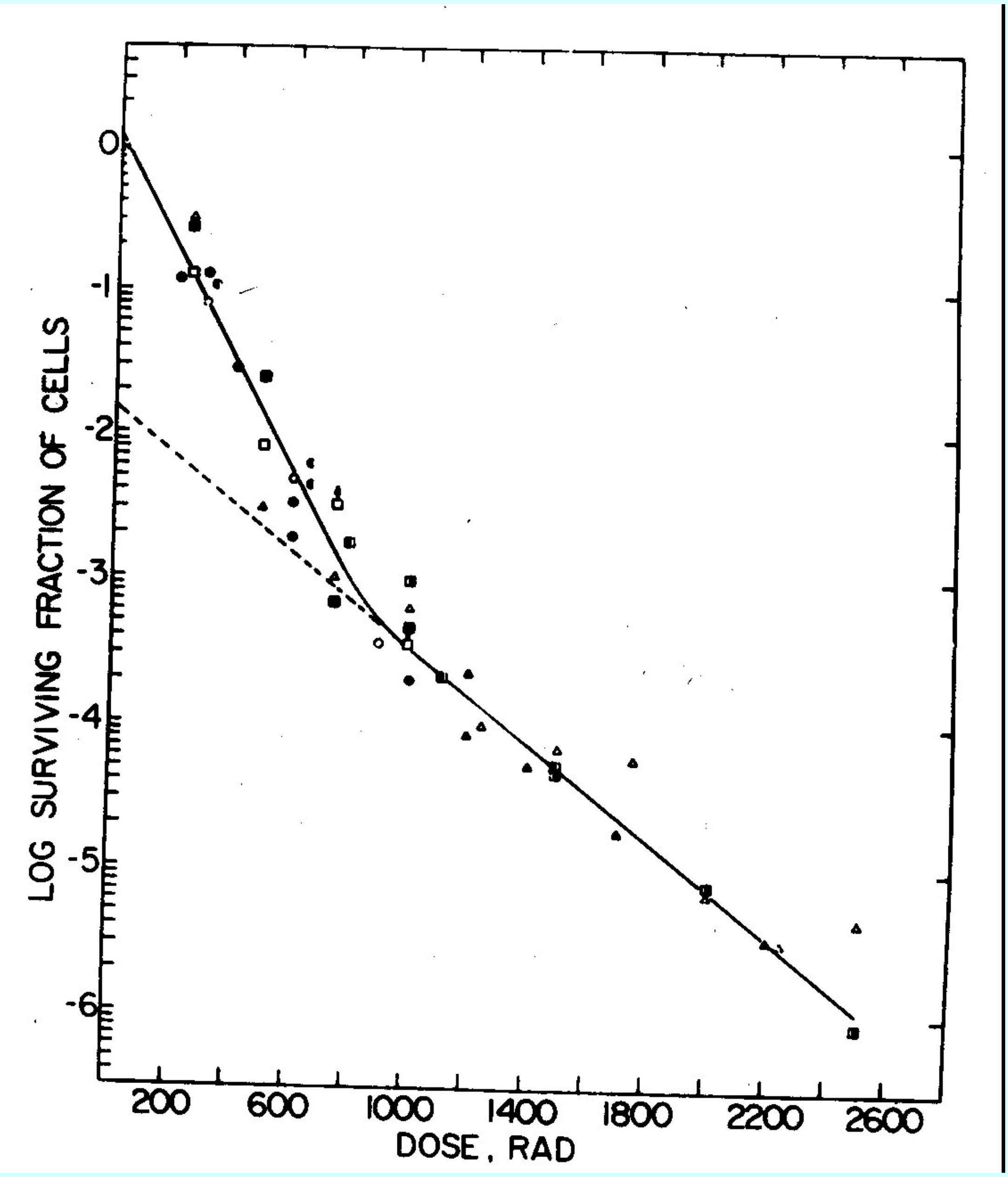
O_2 + low LET: important effect
O_2 + high LET: practically no effect

Oxygen effect in a tumor



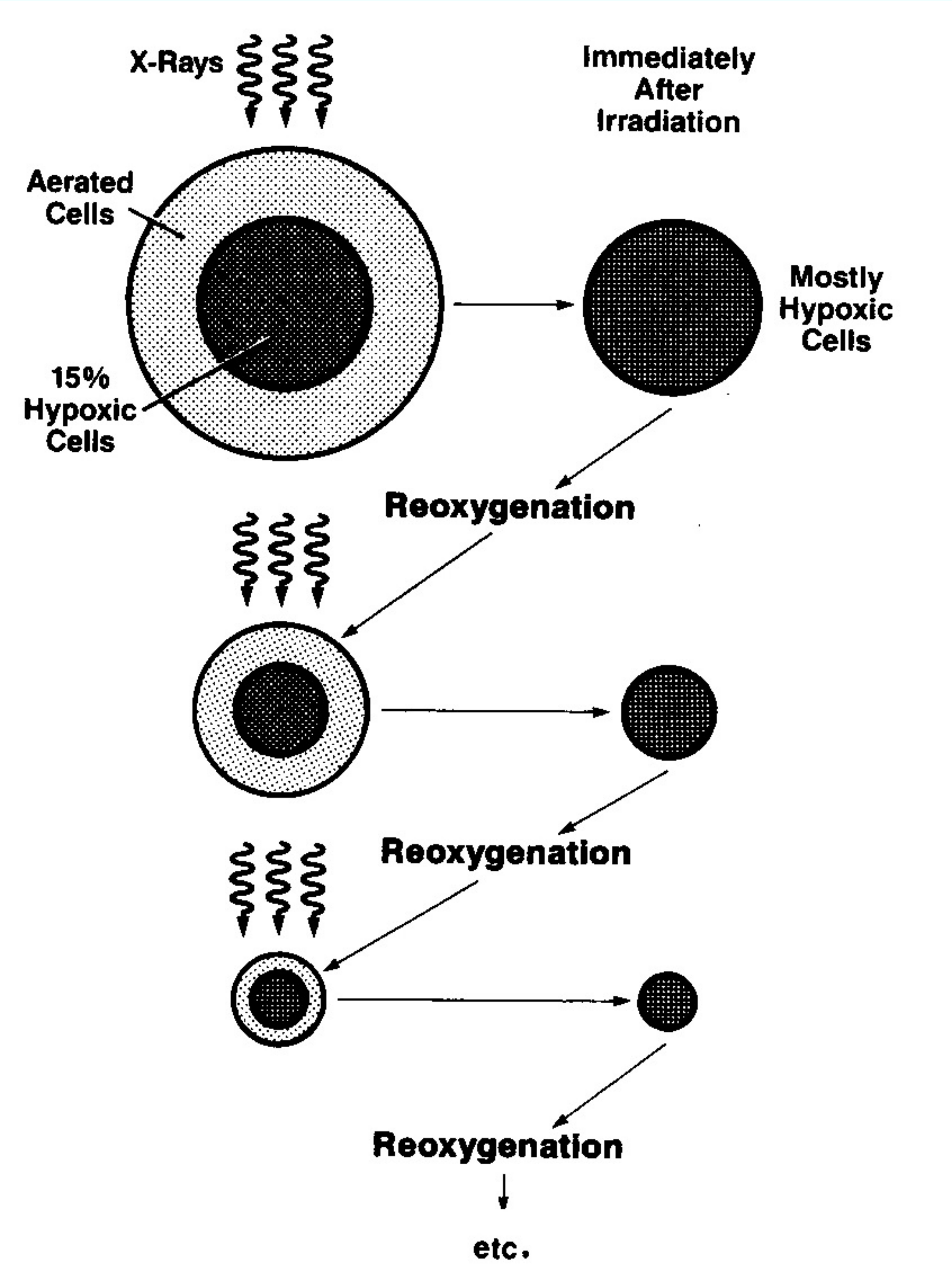
Hypoxia in a tumor. Close to the blood vessels, the cells receive relevant oxygen, at increasing distance the oxygen supply decreases, and the cells become more radiation resistant.

Oxygen effect in a tumor

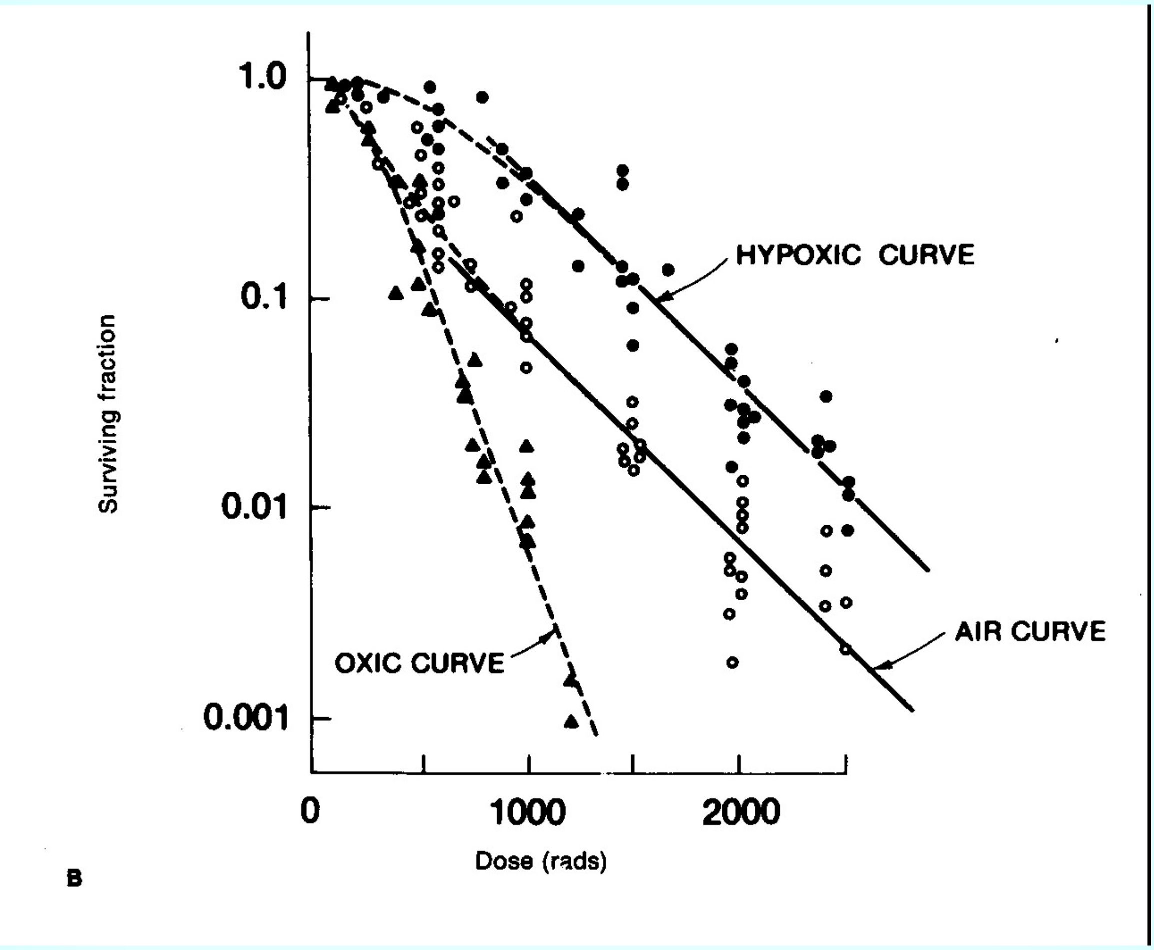


Killing of the hypoxic fraction requires higher radiation doses.

Reoxygenation

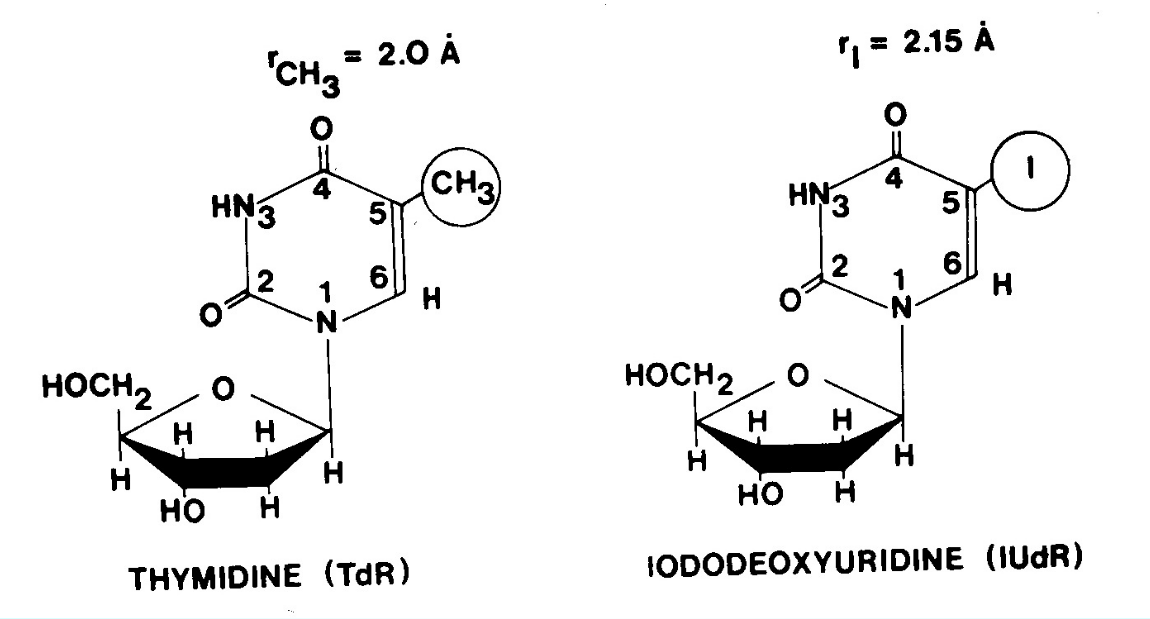


Oxygen effect



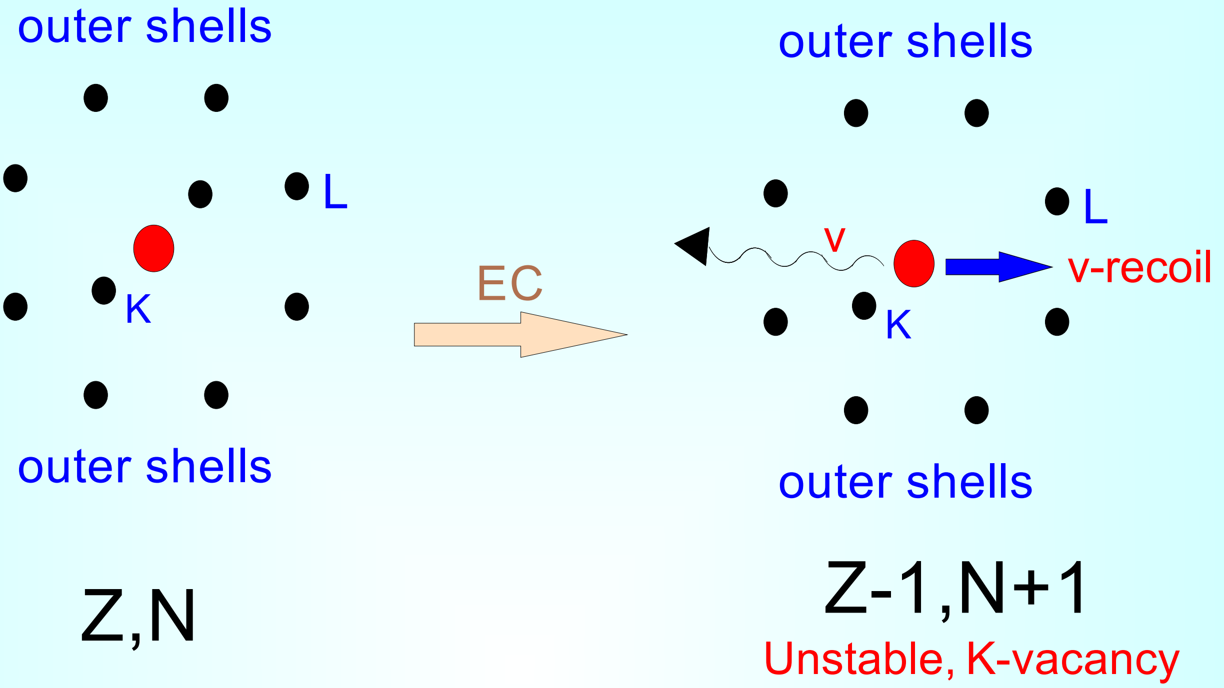
Clear differences in radiosensitivity for cells in pure oxygen, air or in the absence of oxygen

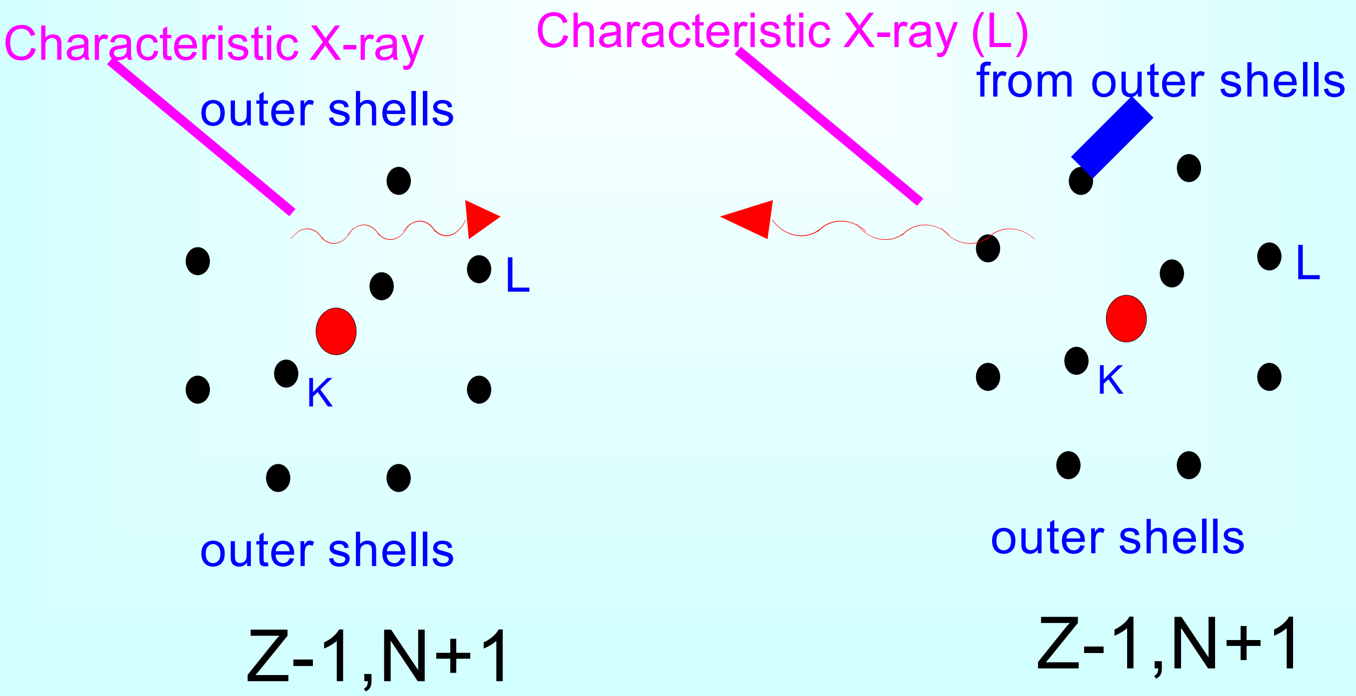
Auger effect



Iodo-deoxyuridine “fools” the DNA synthesis and incorporates the “pretender compound” into the DNA synthesis.

Electron capture sequence





Vacancy is filled by transition of an electron from a higher shell.
Atom still unstable (L-vacancy)

L-vacancy filled from a higher shell. X-rays may be converted to Auger electrons

Auger effect

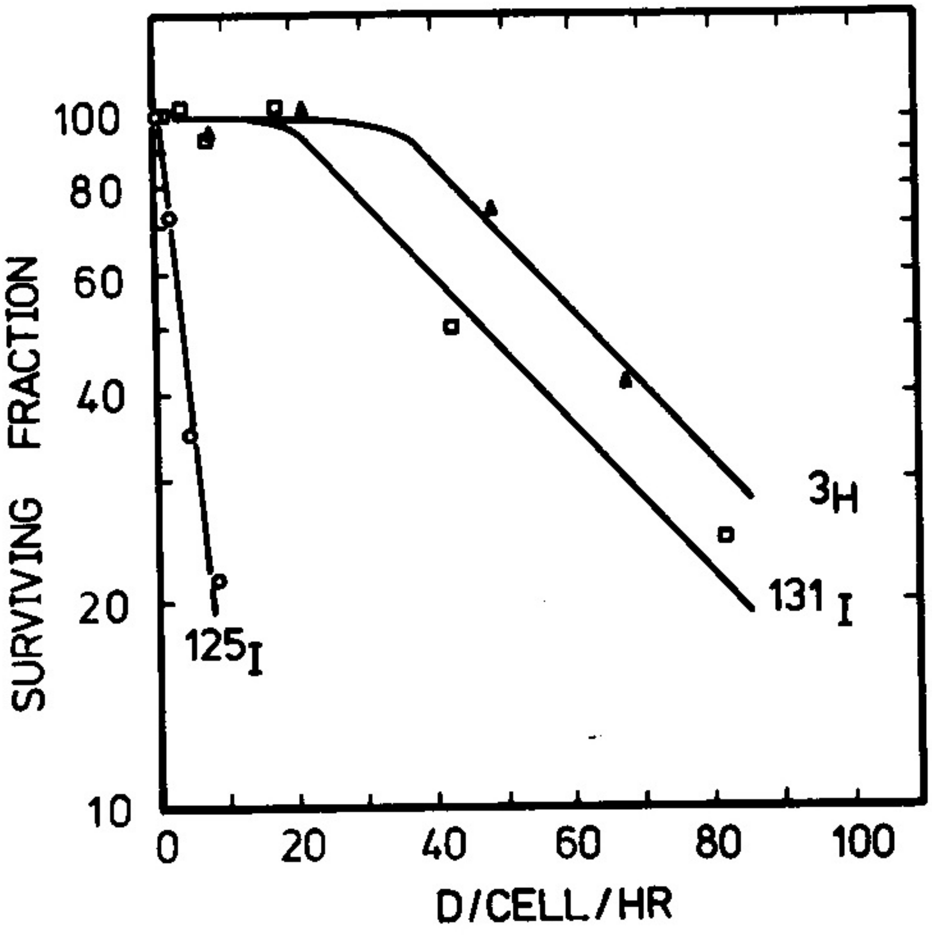


FIG. 4. Dose-survival curves for ^{125}I, ^{131}I and ^{3}H.

The decay of ^{125}I gives shake-off of a large number of electrons (average: 5.1), creating a quasi-high LET effect, only when incorporated into DNA