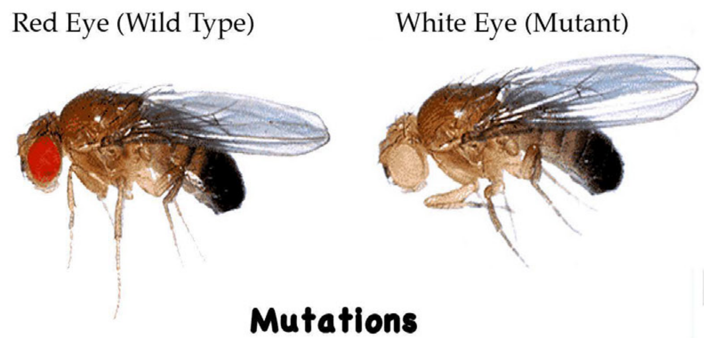
WHAT IS RADIOBIOLOGY?

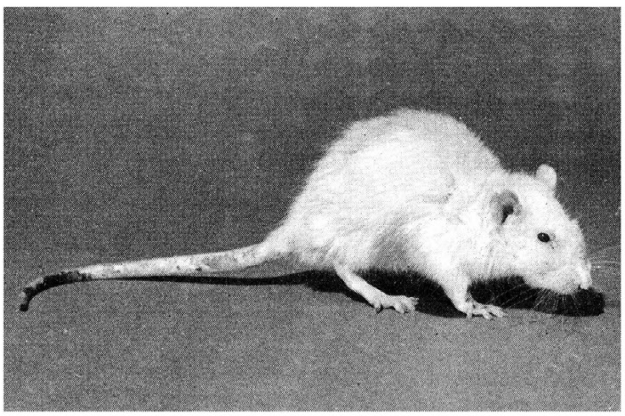
"THE STUDY OF THE EFFECTS OF ELECTROMAGNETIC RADIATION ON BIOLOGICAL SYSTEMS."

EFFECTS

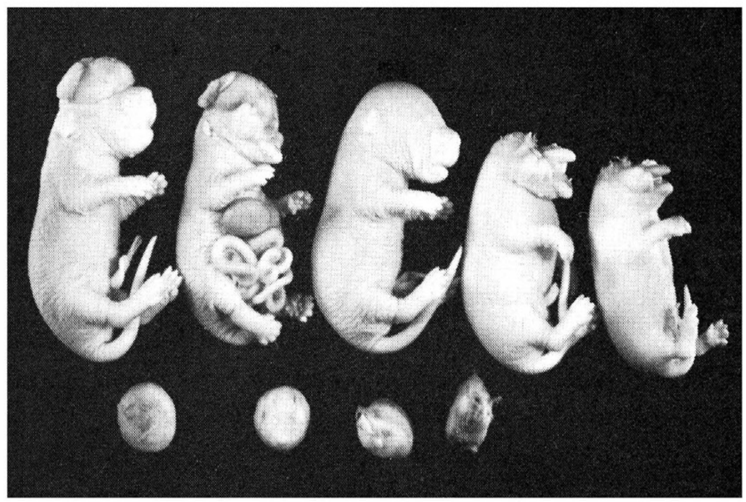


Mutations

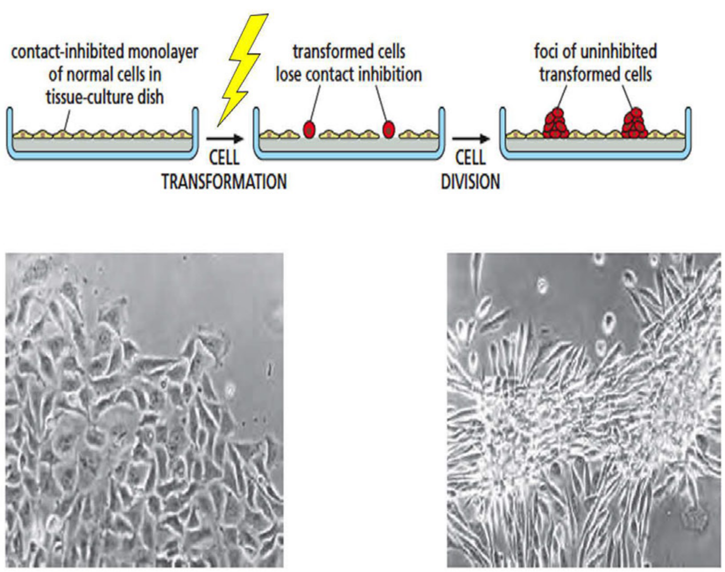
Growth Delay/Disturbance



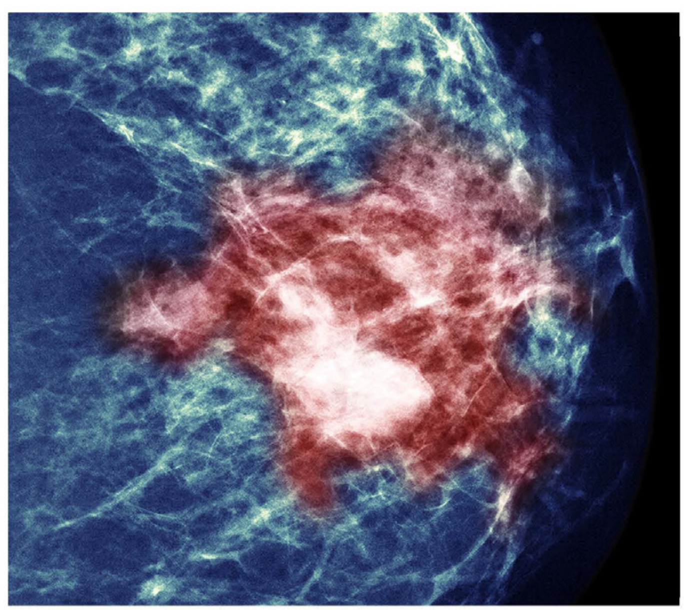
Whole-Body Radiation Syndromes



Teratogenesis

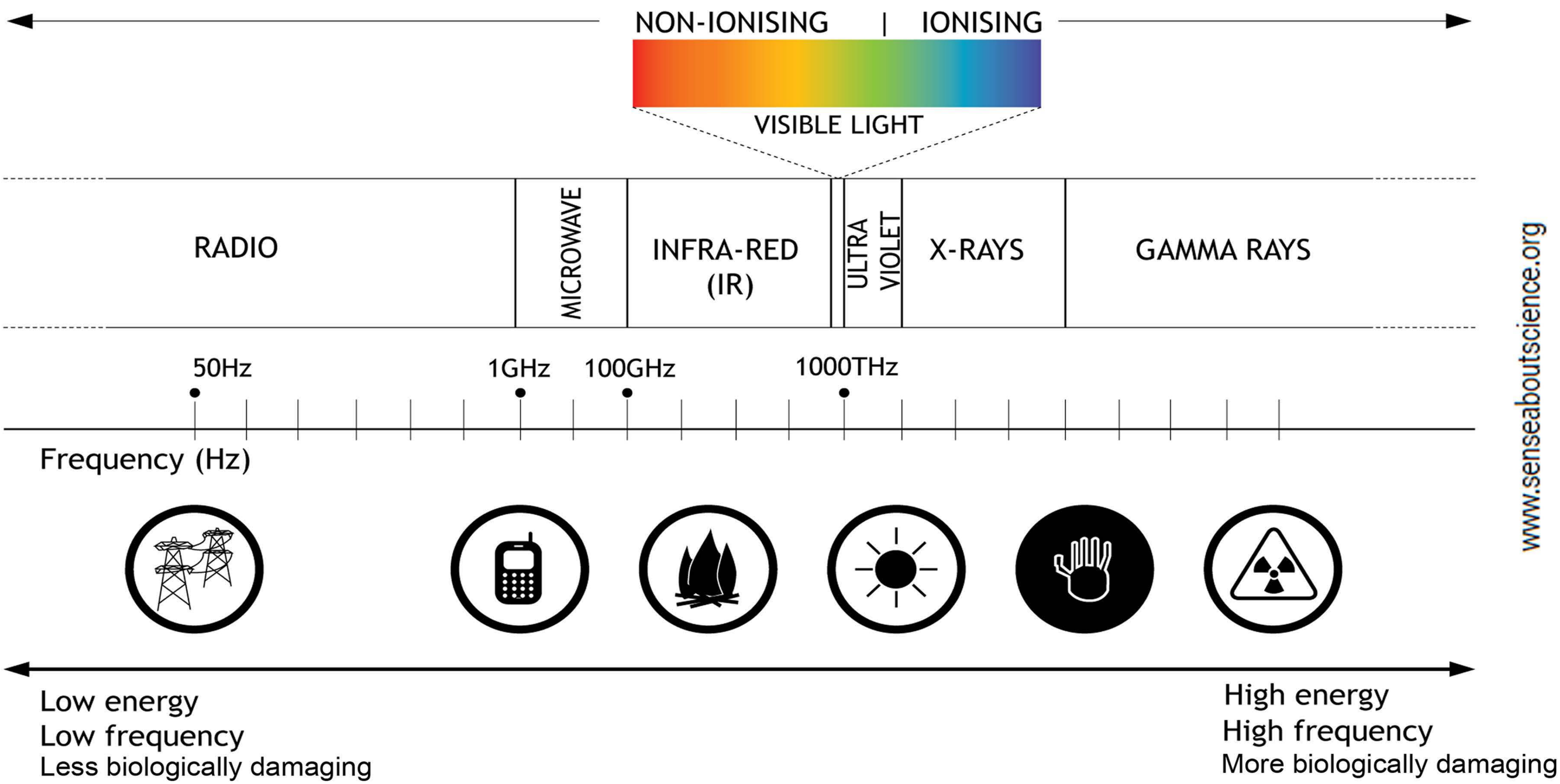


Neoplastic Transformation

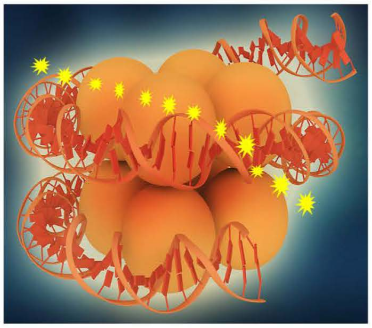


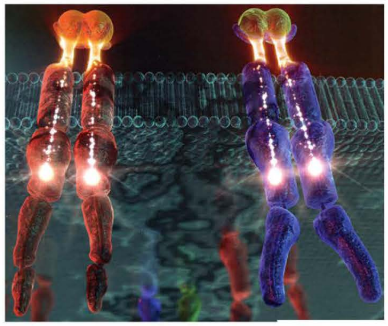
Carcinogenesis

ELECTROMAGNETIC RADIATION

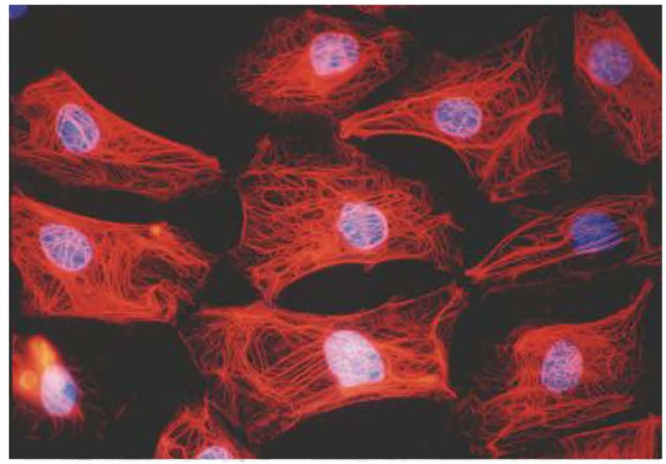


BIOLOGICAL SYSTEMS





Subcellular
(e.g., DNA damage and repair, signal transduction, etc.)

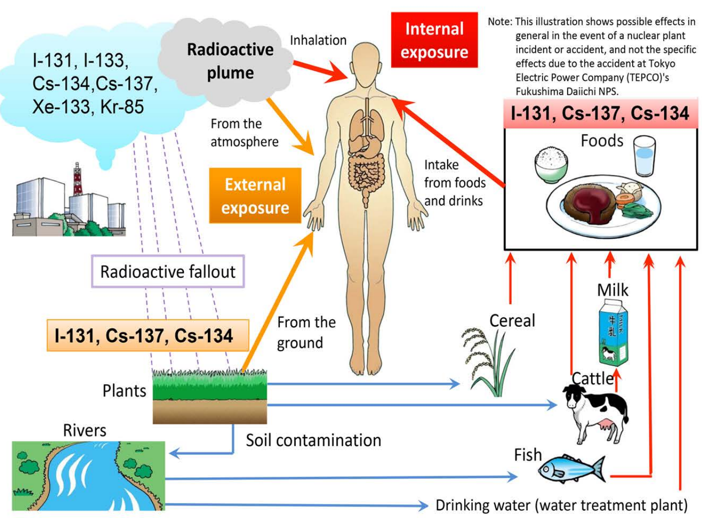


Cells in Culture

Fruit Flies

Laboratory Rodents

Us
(Japanese A-Bomb Survivors)



Ecosystems

What does Radiobiology have to do with Radiation Therapy? (Answer: EVERYTHING!)

Radiobiology provides the tools for evaluating both the risks and benefits of radiation exposure, and can help address the following public health-related questions:

1. How does radiation kill cells?

    a) Why are some cells more radiosensitive than others?

    b) What are the occupational risks associated with the killing effects of radiation exposure?

    c) Can we deliberately alter the radiosensitivity of cells to our advantage, that is, to:

        1] make tumors more radiosensitive?
        2] make normal tissues more resistant?

2. How does radiation cause mutations (and transformation) in cells?

    a) What types of mutations are produced by radiation, and which are most associated with transformation/carcinogenesis?

    b) How long does the process take from transformation of a cell to the gross appearance of a radiation-induced tumor?

    c) How well can we determine whether a particular tumor was radiation-induced?

    d) Why are some cell types more prone to radiation carcinogenesis than others?

    e) What are the occupational risks associated with the mutagenic effects of radiation exposure, and can we intervene in any way to reduce these risks?

3. Why are some types of ionizing radiation more biologically effective than others?

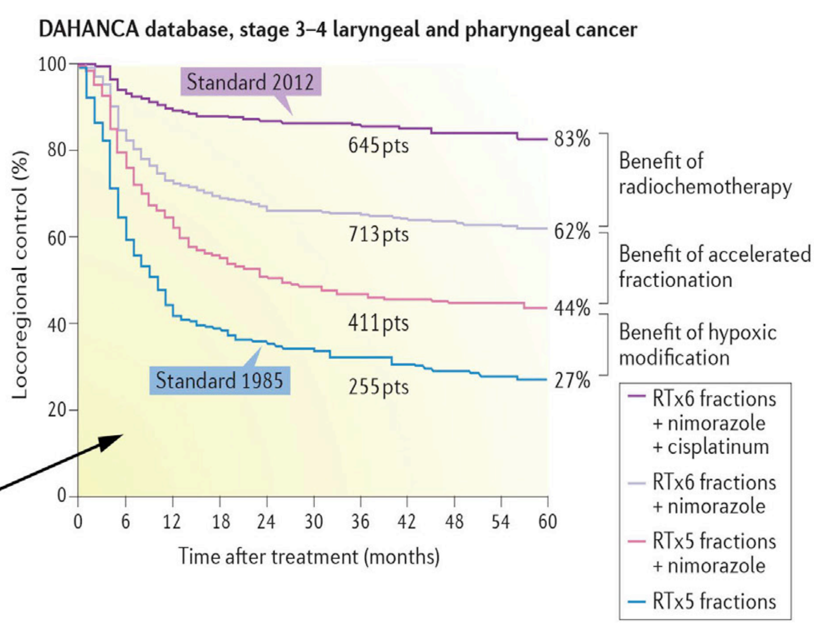
4. Why does the biological effectiveness of radiation—both in terms of cell killing and mutation induction—decrease as the total dose is fractionated and/or protracted?

5. ***Does the application of radiobiological knowledge actually improve patient outcomes?***

a) some might argue "no" in that most of our clinical know-how has been worked out by trial and error (over 120+ years), without having to understand anything about radiation or cancer biology

1. this is somewhat true historically, however since the mid-1980's, more and more clinical practice *is* based on biology

b) the rest of us would argue "yes", for example, how much improvement there's been in outcomes for advanced larynx and pharynx cancer over the last 30-35 years, by making treatment modifications based on radiobiology



A Comparison of Medical Imaging with Radiation Therapy

Nuclear Medicine and Diagnostic Radiology	**Radiation Therapy**
Types of Radiation Used	
External beam (x-rays)	External beam (x- or γ-rays, electrons, neutrons, protons, etc.)
Internal emitters (^{131}I, ^{99m}Tc, etc.)	Internal emitter (^{32}P)
Dose and Volume Characteristics	
Low doses, but large volumes	High doses, small volumes
For example, a typical chest x-ray might deliver: Bone Marrow 0.006 cGy Lung 0.020 cGy Breast 0.014 cGy	For example, a typical radiotherapy treatment course might consist of: 5,000-7,000 cGy over 6 weeks to the tumor, hopefully within the tolerance of the normal tissue
Biological Effects	
No cell killing, but mutations possible	Cell killing
Public Health Concerns	
Somatic cell mutations leading to cancer? Germ cell mutations leading to heritable genetic defects? Effects on a developing embryo or fetus?	Do we get a therapeutic gain, i.e., do we get more tumor cell killing than normal tissue damage (such as: Sterility, Fibrosis, Necrosis, Pneumonitis, Myelitis, etc.)?

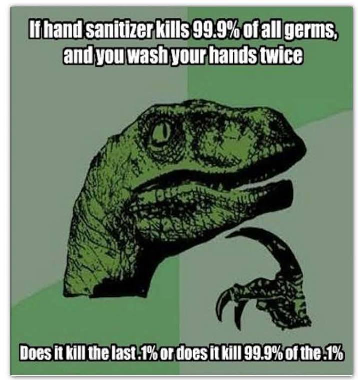
Finally, never forget that radiobiology (and radiation oncology) involve measurements and effects that can span orders of magnitude

That's why it's important to keep all those pesky units straight!

Scientific/Mathematical Units

("Powers of Ten" or "Logs" or "Orders of Magnitude")

Decimal	Percent	Scientific Notation
10,000		10^{4}
1,000		10^{3}
100		10^{2}
50		5 x 10^{1}
20		2 x 10^{1}
10		10^{1}
1.0	100%	10^{0}
0.5	50%	5 x 10^{-1}
0.2	20%	2 x 10^{-1}
0.1	10%	10^{-1}
0.05	5%	5 x 10^{-2}
0.02	2%	2 x 10^{-2}
0.01	1%	10^{-2}
0.005	0.5%	5 x 10^{-3}
0.002	0.2%	2 x 10^{-3}
0.001	0.1%	10^{-3}
0.0001	0.01%	10^{-4}
0.00001	0.001%	10^{-5}



Conversion of Absorbed Dose Units

SI Units (mostly used in physics and medicine)	Old Units (still used in the nuclear and radiation safety industries)
100 Gy	10,000 rad
10 Gy	1,000 rad
1 Gy	100 rad
1 cGy*	1 rad
1 mGy^	0.1 rad

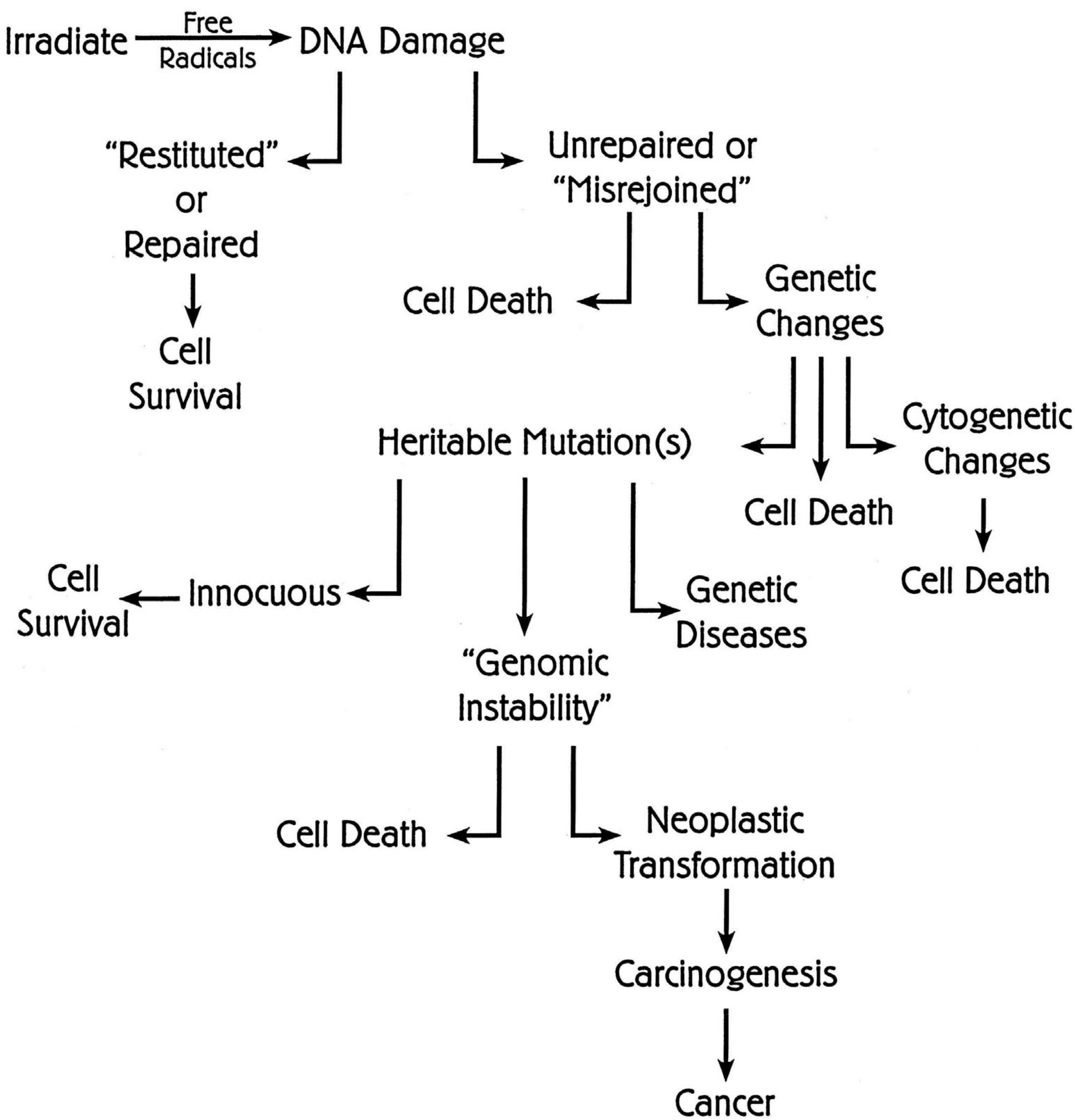
* unit most commonly used in radiation therapy
^ sometimes used for equivalence with mSv (for X-rays)

Conversion of Equivalent Dose Units

SI Units (mostly used in physics and medicine)	Old Units (still used in the nuclear and radiation safety industries)
100 Sv	10,000 rem
10 Sv	1,000 rem
1 Sv	100 rem
100 mSv	10 rem
50 mSv*	5 rem
10 mSv	1 rem
1 mSv^	0.1 rem (100 mrem)

* annual (continuous) exposure limit for radiation workers
^ annual (continuous) exposure limit for the general public

The Flow Chart of Radiobiology



Radiation Chemistry

A. Why do we even care about radiation chemistry?

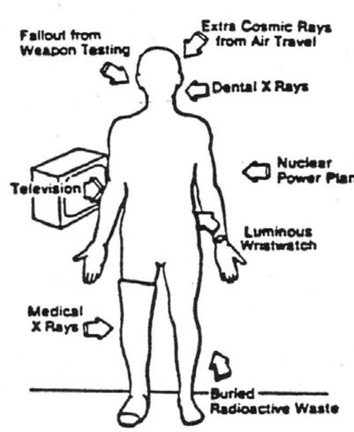
1. ...because we exist in an environment that is, and always has been, bathed in radiation; **given this fact, it would certainly be of interest to understand how radiation interacts with us, and what can happen--good or bad--as a result of this interaction**

2. sources of radiation exposure to the human population:

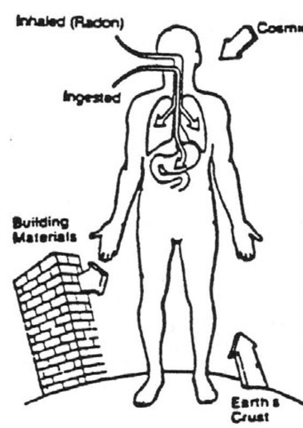
a] Natural Sources - *cosmic radiation* left over from "The Big Bang" plus "solar wind", *terrestrial radiation* from naturally-occurring radioactive materials in soil or rocks, and (for lack of a better term) *bodily radioactivity* from naturally-occurring radionuclides that have been ingested, inhaled or "inherited"

b] Enhanced Natural Sources - sources of radiation that are naturally present, but as a result of human intervention, our exposure to such sources is increased; for example, *air travel* at high altitude (increased exposure to cosmic radiation), living in an energy-efficient, poorly-ventilated, home in certain parts of the country (*radon in your basement*), building your home on top of a pile of *strip mine tailings* etc. etc.

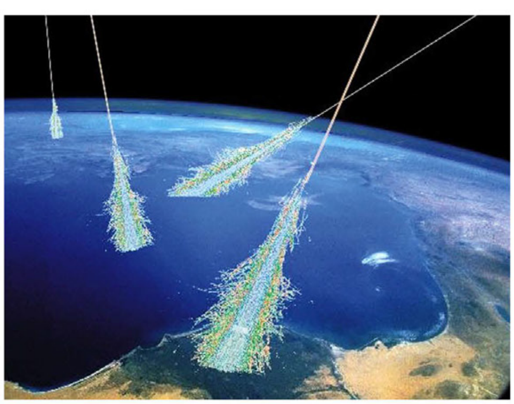
c] Man-Made Sources - *medical procedures* (diagnostic imaging), *global fallout* from nuclear weapons testing, *consumer products* containing radioactive materials or emitting radiation, "association" (deliberate or not) with the *nuclear power industry* etc.



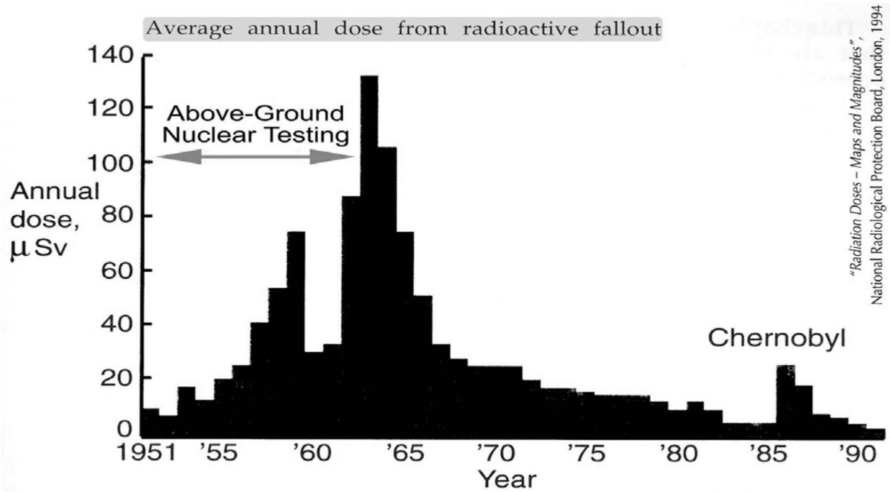
The various sources of man-made radiation to which the human population is exposed. In developed countries the dose equivalent is dominated by medical radiation.



Three principal components of natural background radiation: (1) cosmic rays from solar flares in the sun or from outer space; (2) Ingested radioactivity, principally ^{40}K in food and inhaled radioactivity, principally radon, and (3) radiation from the earth's crust, which in practice means from building materials, since most individuals spend much of their lives indoors.

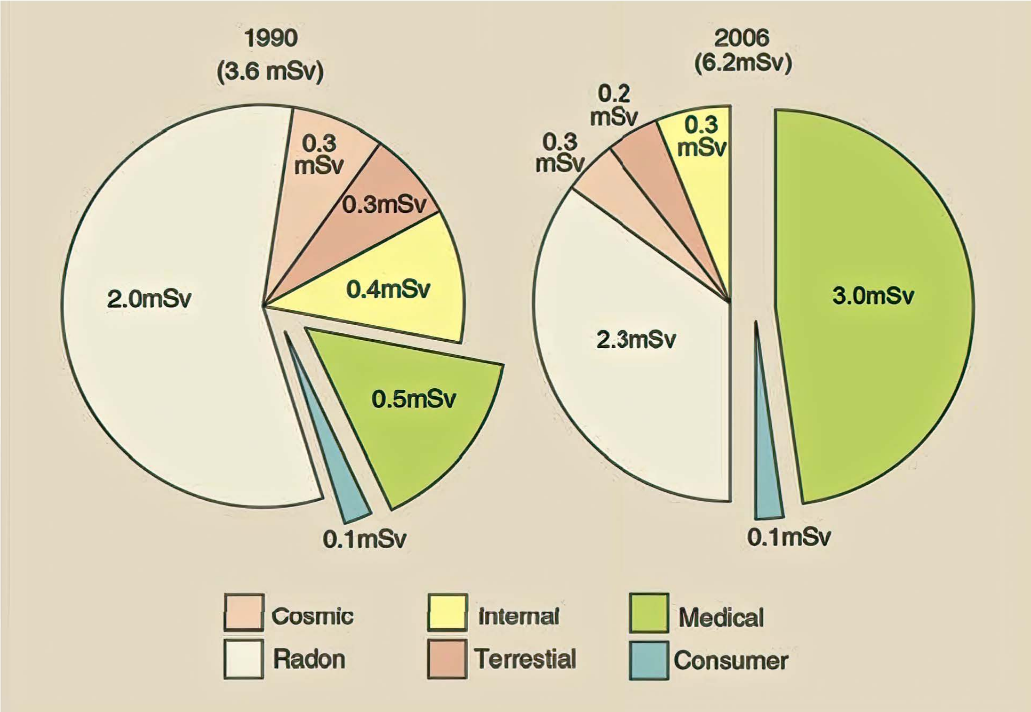


Cosmic rays interacting with the upper atmosphere. (Good thing too, or else we wouldn't be here.)



"Radiation Doses – Maps and Magnitudes", National Radiological Protection Board, London, 1994

Background Radiation



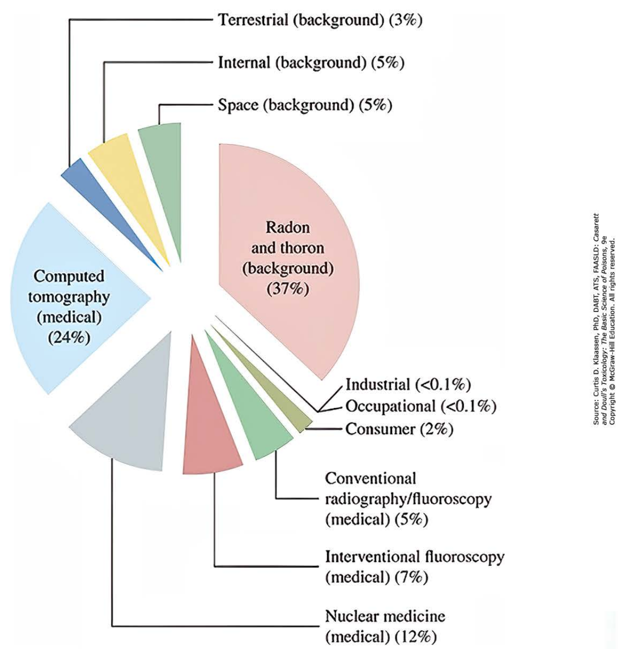
The big change in the annual background radiation exposure in the US between 1990 and 2006 is due almost exclusively to the large increase in the number of CT scans performed per year - they deliver the highest dose of all the medical imaging procedures.

Today, the ratio of natural to man-made background radiation is 1:1.

The contribution of various sources to the average US population radiation dose, 1990 and 2006.

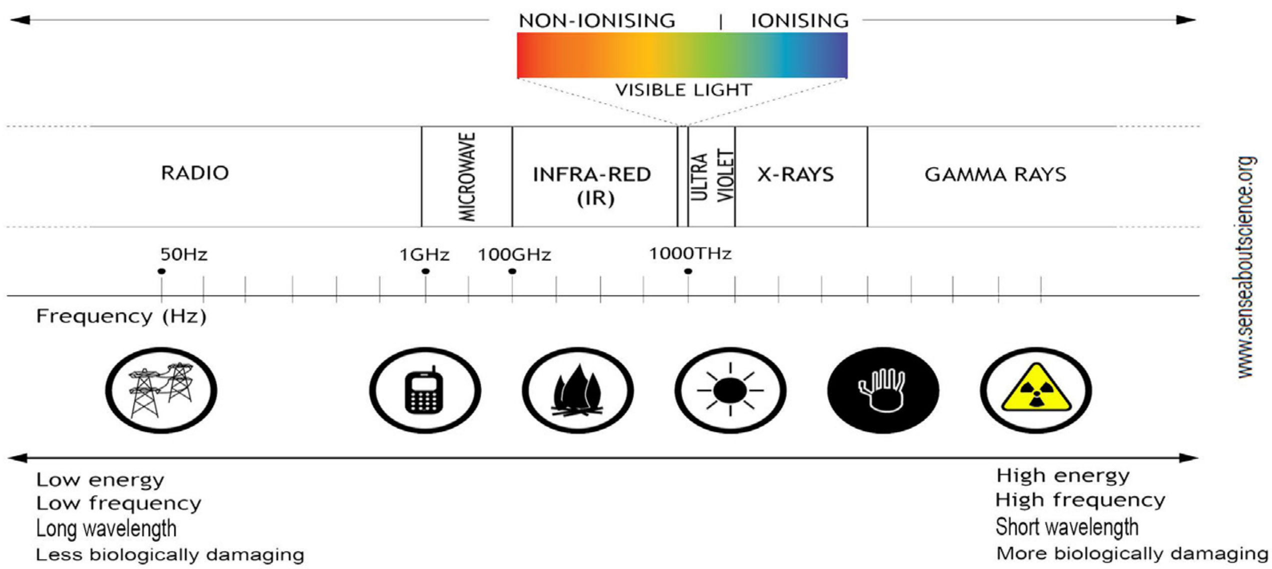
Biggest contributor to ***natural*** background radiation exposure: <u>Radon</u> (~37% of *all* background radiation)

Biggest contributor to ***man-made*** background radiation exposure: <u>CT scans</u> (~24% of *all* background radiation)

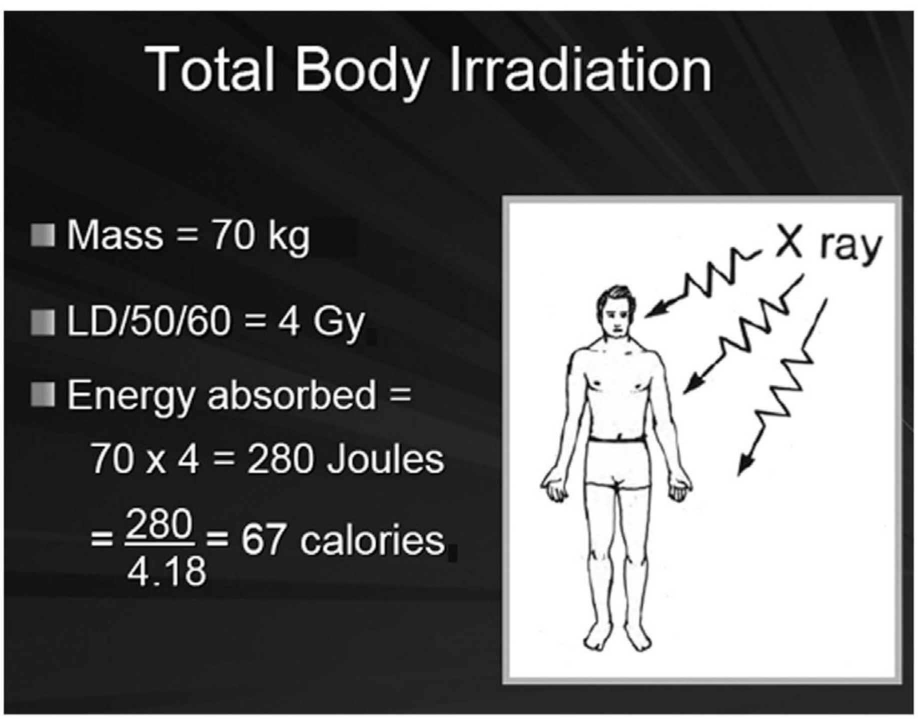


B] A (Thankfully) Brief Review of Radiation Physics

1. The absorption of energy from radiation in biological material can lead to **excitation** (the "jumping" of an electron in an atom or molecule to a higher energy level than normal—more typical of electromagnetic radiations with wavelengths *greater than about 125 nm*) or to **ionization** (the "ejection" of an electron completely out of its atomic or molecular orbital--more typical of electromagnetic radiations with wavelengths *less than about 125 nm*)

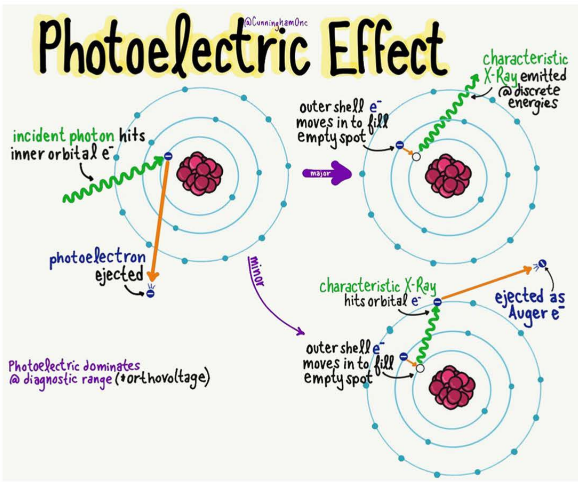


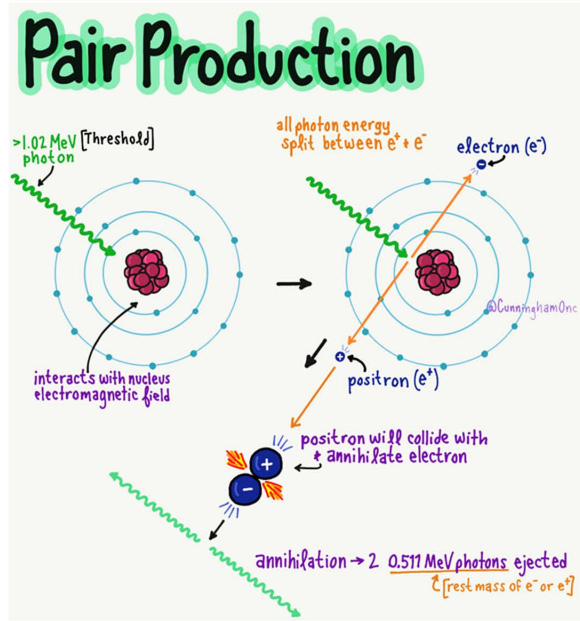
a) probably **the most important characteristic of ionizing radiation from a biological perspective is the random and discrete nature of the energy deposition**, that is, that while the average energy deposited in a macroscopic volume of tissue might seem rather small, the distribution of this energy on a microscopic, or "micro-dosimetric", scale can be quite large...

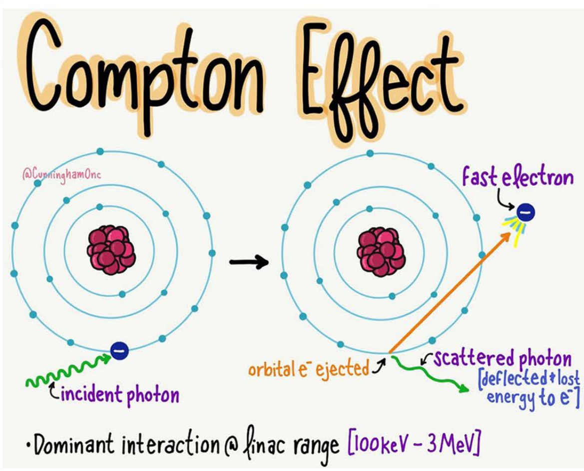


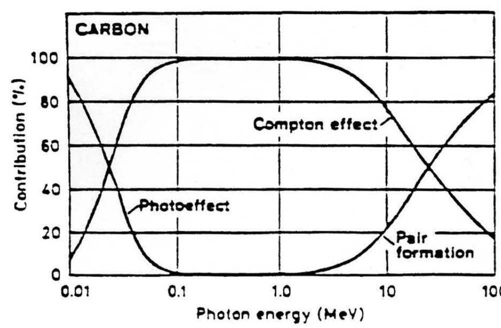
2. Ionizing radiations can loosely be characterized as **electromagnetic waves/photons** (such as x-rays or γ-rays) or **particles** (electrons, neutrons, protons, α–particles etc.--these can be <u>charged</u> or <u>uncharged</u>).

(a) the process by which x- or γ–rays convert their energy into charged particles involves an interaction with the orbital electrons of the atoms of the absorbing material, and depends both on the energy of the radiation and the composition of the absorbing material...this can occur via the **Photoelectric Effect**, the **Compton Effect**, or **Pair Production**

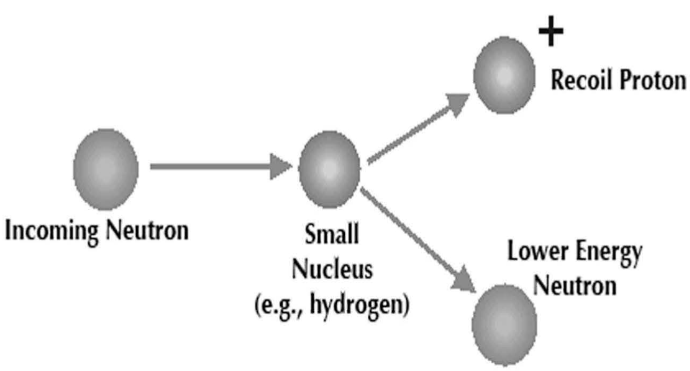


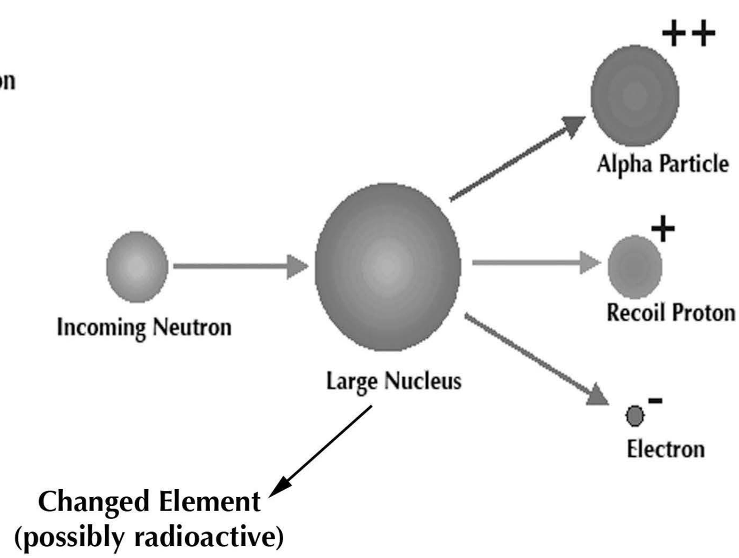






(b) for neutrons, the interaction is between the particle and the nuclei of the atoms in the absorbing material (predominantly, with hydrogen atoms), which results in the ejection of recoil protons (and lower energy neutrons)

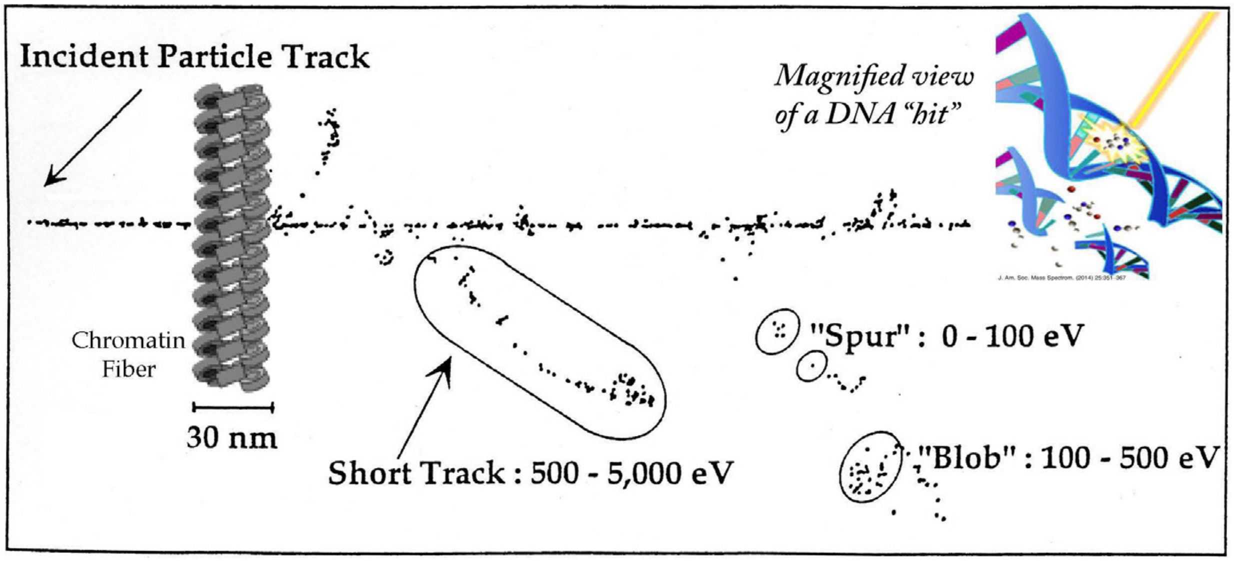




3. Regardless of their mechanism of production, once these charged particles are put into motion, they also deposit energy into the absorbing medium, eject more charged particles, produce chemical damage, and the cycle of ionization continues...

1} **What do these energy deposition events "look" like?**

(a) the energy is deposited in the absorbing medium in little packets of variable size and shape, which depend on how much energy is actually expended; these have cute names like **"spurs", "blobs", "short tracks"** etc.



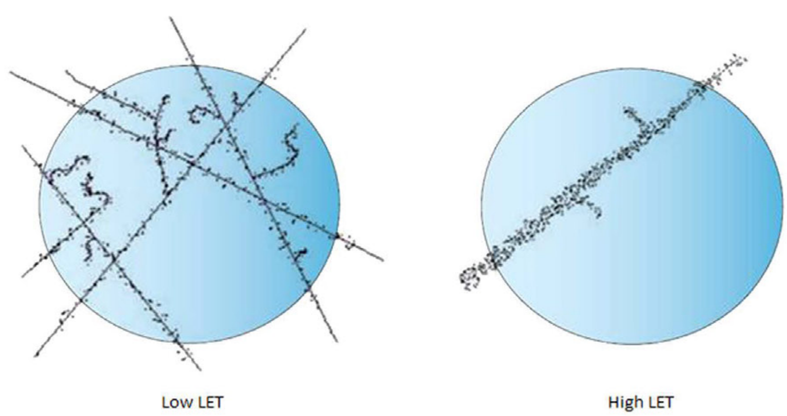
Several types of energy deposition are associated with the passage of a primary energetic electron through a condensed medium. Only positive ions are indicated by the dots; neither the associated (geminate) electrons nor possible (associated) excited species present in spurs, blobs, and tracks are shown

d) **Do the density and distribution of these events vary with different types of ionizing radiation?**

1] yes—*for certain types of ionizing radiation, the density per unit track length of energy deposition events is much higher than for other radiation types; such radiations are said to have a high linear energy transfer or LET*

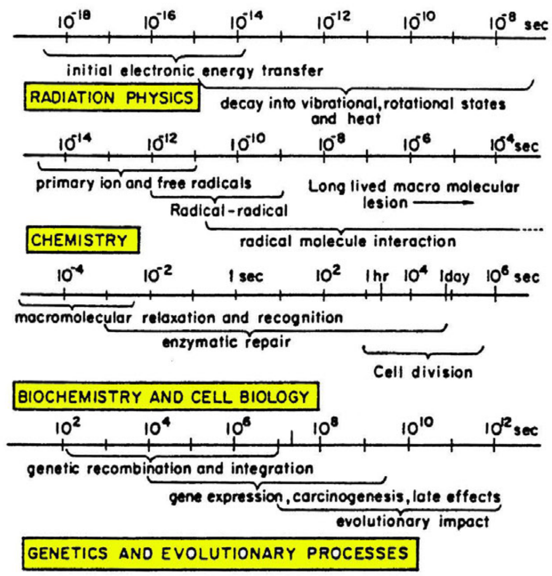
2] in addition, the distribution of spurs, blobs and short tracks is different for high versus low LET radiation—*there tend to be more blobs and short tracks for high LET, whereas there tend to be more spurs for low LET radiation*

3] **taken together, these microdosimetric differences translate into much more potent biological effects (killing, mutations, carcinogenesis, etc.) for high LET radiation compared to low LET**



3} **What is the time scale for energy deposition events, and all of the consequences that follow?**

(a) Answer: <u>a *really, really* short time for the physical and chemical events, although the biological consequences may not appear for years!</u>



Time sequence of the radiobiological events found with cell irradiation, from the initial electronic energy transfer through the late genetic effects. The physics events include time for heat transport.

C] The Chemistry of Free Radicals: What Happens After the First Picosecond or So???

1. molecules unfortunate enough to receive a "direct hit" from a spur or blob experience, relatively speaking, a huge deposition of energy in a very small volume (hence, the terms "random and discrete")

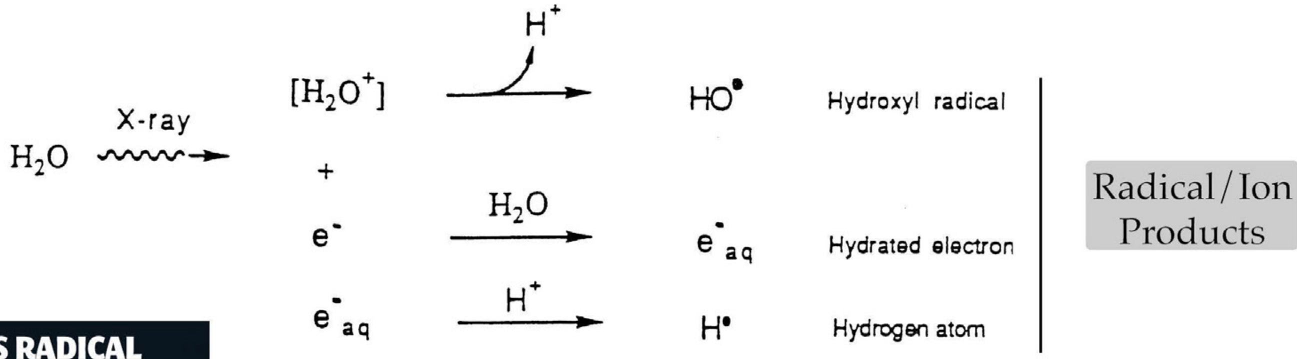
2. this causes the atoms to lose electrons and then...all hell breaks loose!

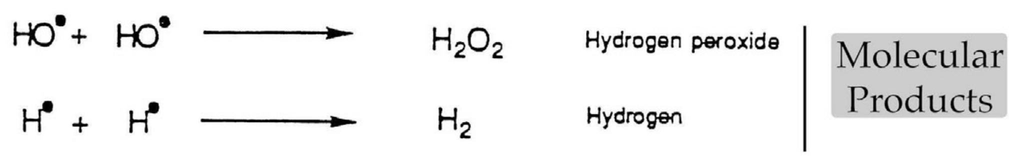
a) <u>a fundamental truth about atoms that lose electrons: they don't like it,</u> especially if the loss results in atoms or molecules left with **unpaired electrons**

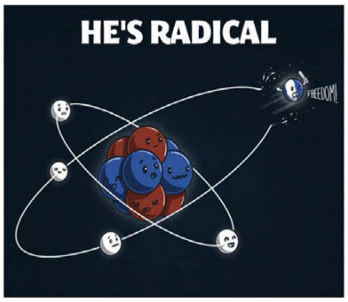
b) a **FREE RADICAL is an atom or molecule that contains an unpaired electron (these may be charged or uncharged)**; <u>free radicals are highly reactive chemically, and would do almost anything to either pick up a new electron or get rid of the remaining unpaired one...up to and including taking part in the breaking or formation of chemical bonds with other molecules in the vicinity</u>

3. **Assuming that the "absorbing medium" is a biological system, a cell for example, what molecule has the highest probability of being hit by a spur or blob?**

a) Answer: the most abundant molecule in the cell, namely **WATER, which comprises some 80-90% of the cell on a per weight basis**







b) **other cellular macromolecules (proteins, lipids, carbohydrates etc.) also have a certain probability of being ionized, but whether this results in a measurable biological effect or not depends on a number of factors** including: how big a "target" the other cellular macromolecule appears from the point of view of the ionizing particle; how "important" the other cellular macromolecule is; how many copies of it are present in the cell, etc.

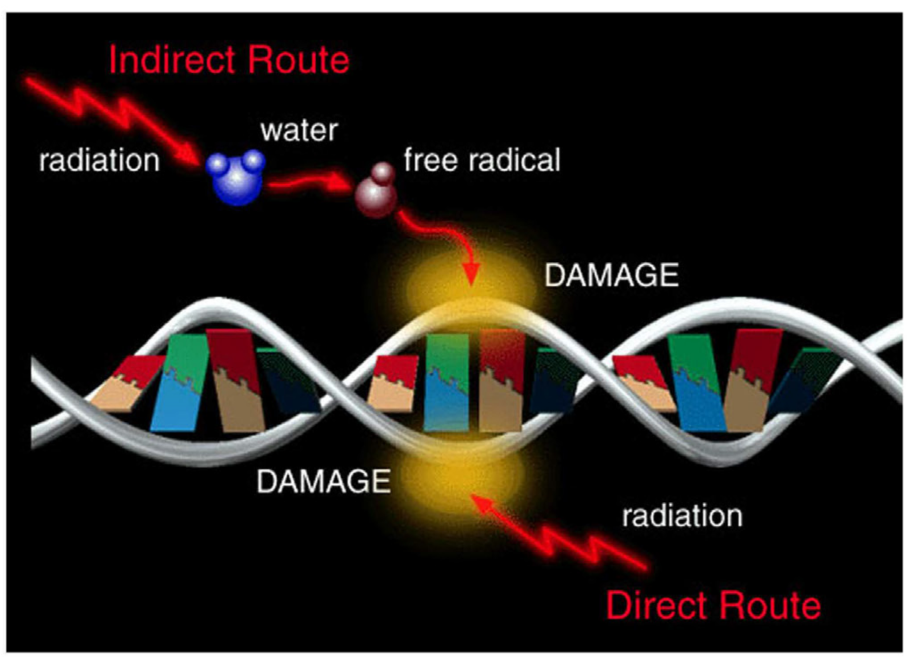
[1] and, as we all know (hopefully), **DNA is a big, important, target present in small copy numbers**

4. **But isn't DNA the only thing we really care about????**

a) <u>Yes and No!</u>

Should a spur or blob land right in the middle of a DNA molecule and damage it, the process is termed the "**direct effect of ionizing radiation**".

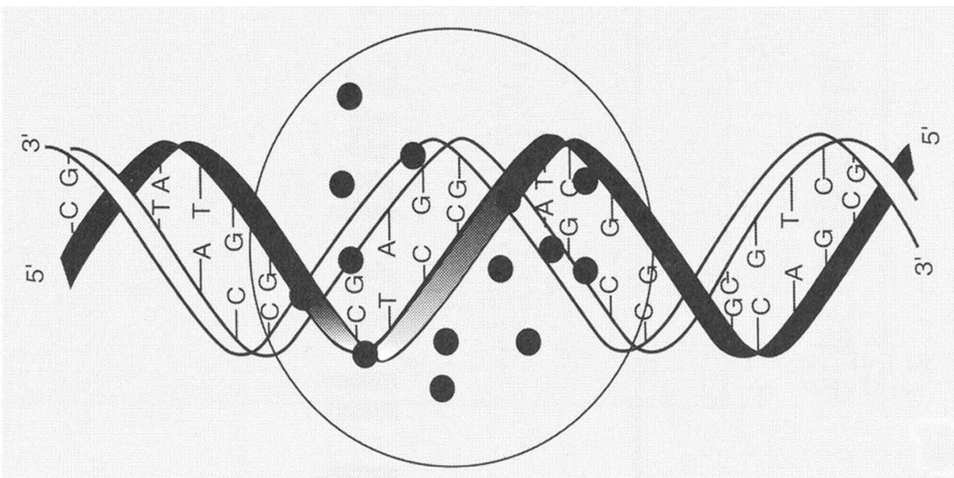
Should a spur or blob instead ionize some water molecules, and the resulting water free radicals drift over to the DNA and damage it, the process is termed the "**indirect effect of ionizing radiation**".



Our best estimates are that about 70% of the total DNA damage is caused by the indirect effect, and about 30% by the direct effect

b) in either case, this "explosion" of free radicals can produce more than one type of DNA damage in a very localized area; this process has been termed the **Locally Multiply Damaged Sites (LMDS) or Cluster Hypothesis**

LOCALLY MULTIPLY DAMAGED SITES (LMDS)

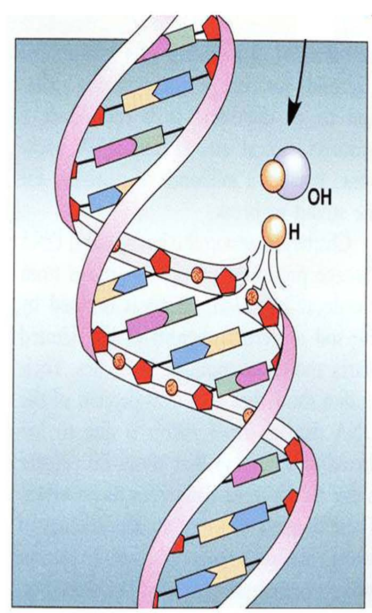


A spur or blob landing directly on top of the DNA causes multiple ionizations in a highly localized area, which in turn can result in several DNA damage sites within a few base pairs of each other. These "clustered" lesions are harder to repair than if the same total amount of damage was spread out further in space (and/or time).

[1] *the "clustered" nature of DNA damage caused by ionizing radiation explains why radiation is so efficient at killing cells per number of damages produced*

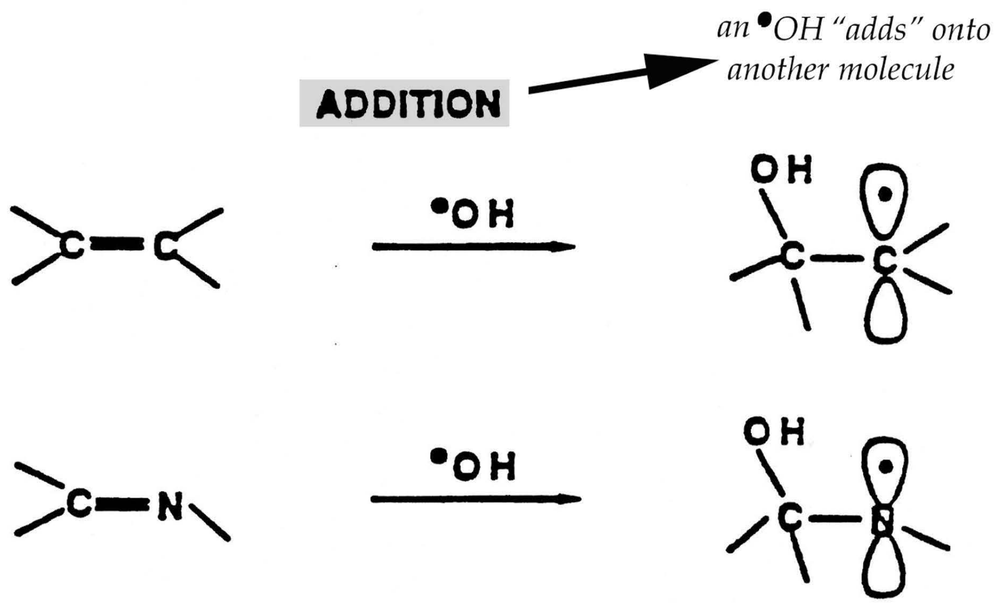
5. **Which free radical is the meanest and nastiest of them all???? The Hydroxyl Radical (•OH)**, formed from the radiolysis of water...

a) hydroxyl radicals are extremely reactive, and "attack" other molecules (like DNA) via two different mechanisms: **hydrogen abstraction** or **hydroxyl addition**

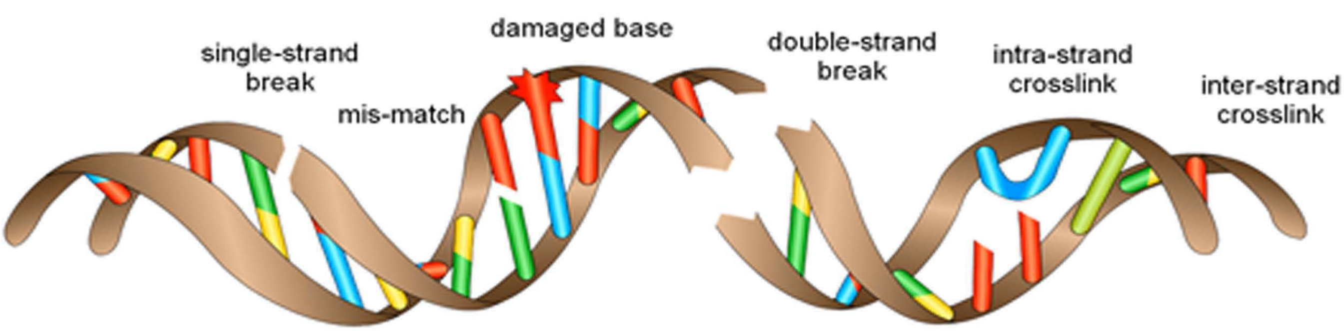


HYDROGEN ABSTRACTION

occurs when a hydrogen atom is "stolen" from a different molecule by the action of •OH



some real, live, measurable, consequences of direct and indirect damage to DNA:



Bottom Line: all this "adding" and "stealing" by free radicals ultimately causes the types of damage normally seen in DNA that has been irradiated, including:

1. damaged or lost bases
2. single strand breaks
3. double strand breaks

Double strand breaks in DNA are the hardest for the cell to repair, and therefore, are most responsible for cell killing

C] The Radiochemistry of the Oxygen Effect--Another Important Role for Free Radicals!

1. *in addition to the role of radiation chemistry in helping us understand how radiation damages DNA and other cellular macromolecules, another important concept in radiation biology and therapy--the oxygen effect--is also governed by free radical reactions*

2. **The Oxygen Fixation or Radical Competition Model**

a) as mentioned above, about 70% of the biological damage caused by x-rays is a result of the indirect effect, and is mediated by water free radicals, particularly •OH

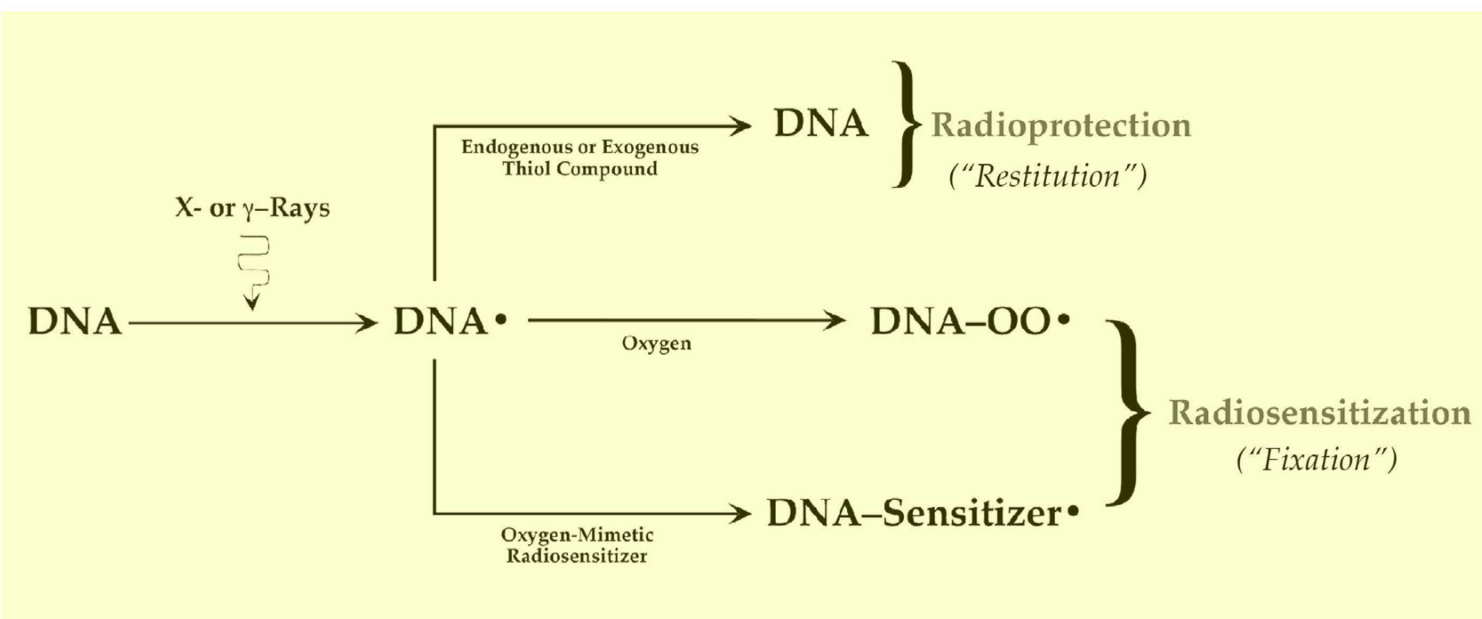
b) when these radicals are formed, they are highly reactive and have a certain probability of reacting with:

1. cellular macromolecules like DNA, ultimately leading to DNA damage
2. each other, forming the so-called "molecular products"
3. other, naturally-occurring, reactive molecules in the cell, like oxygen or radical scavengers such as glutathione, a sulphydryl compound

c) when a DNA radical is formed, in that instantaneous moment during its very short lifetime, the damage can either be…

"Fixed" (made permanent, and possibly irreparable)
or
"Restituted" (restored to its original form as if no ionization had ever occurred)

…and these two processes are constantly in competition with each other



1. **the presence of oxygen tends to tip the scale in favor of fixation,** since oxygen can insert itself into the radical reactions and lead to the formation of a DNA peroxide, which is less reparable

2. **the (relative) absence of oxygen, and/or the presence of a high concentration of free radical scavengers tips the scale in favor of restitution** (for instance, the radical scavengers can add back the electrons abstracted by •OH radicals, or the lack of oxygen prevents peroxide formation)

3. *all this stuff that happens in a fraction of a second may not seem all that important, but in fact, the presence or absence or oxygen, and the presence or absence of radical scavengers (natural or "artificial"), have a large impact on the radiosensitivity of cells, normal tissues and tumors!*

a) in addition, **this relatively simplistic Radical Competition Model has formed the basis for <u>many</u> clinical strategies designed to overcome the radioresistance of tumors caused by hypoxia,** not the least of which include:

1. hypoxic cell radiosensitizers

2. normal tissue radioprotectors