Radiation Chemistry

A. Why do we even care about radiation chemistry?

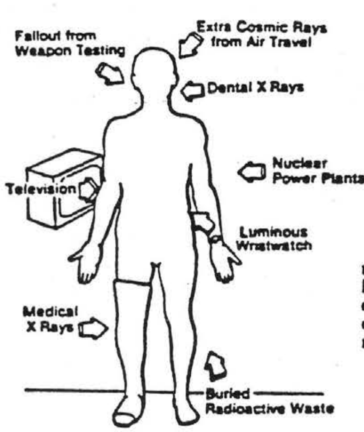
1. ...because we exist in an environment that is, and always has been, bathed in radiation; **given this fact, it would certainly be of interest to understand how radiation interacts with us, and what can happen--good or bad--as a result of this interaction**

2. sources of radiation exposure to the human population:

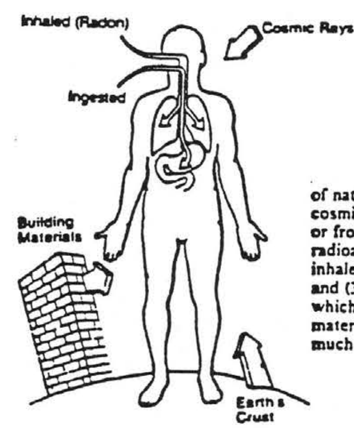
a] Natural Sources - *cosmic radiation* left over from "The Big Bang" plus "solar wind", *terrestrial radiation* from naturally-occurring radioactive materials in soil or rocks, and (for lack of a better term) *bodily radioactivity* from naturally-occurring radionuclides that have been ingested, inhaled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

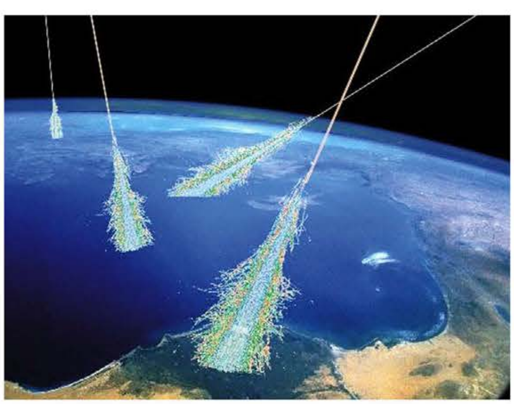
c] Man-Made Sources - *medical procedures* (diagnostic imaging), *global fallout* from nuclear weapons testing, *consumer products* containing radioactive materials or emitting radiation, "association" (deliberate or not) with the *nuclear power industry* etc.



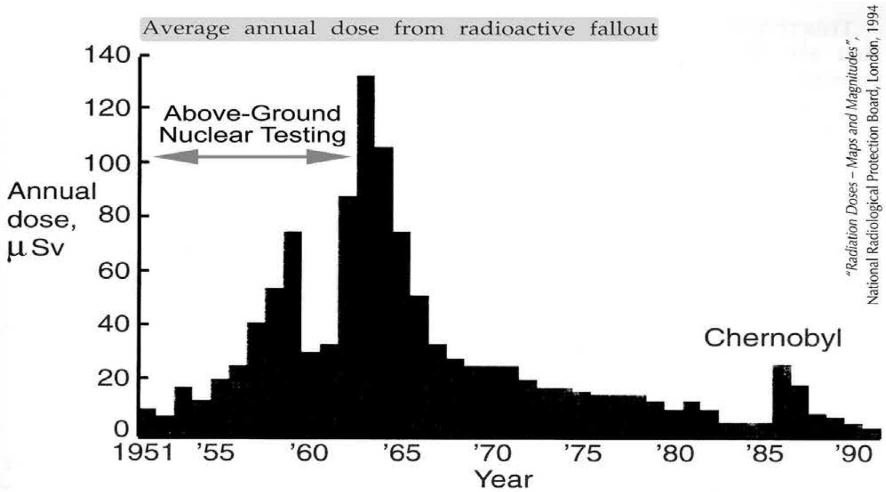
The various sources of man-made radiation to which the human population is exposed. In developed countries the dose equivalent is dominated by medical radiation.



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.

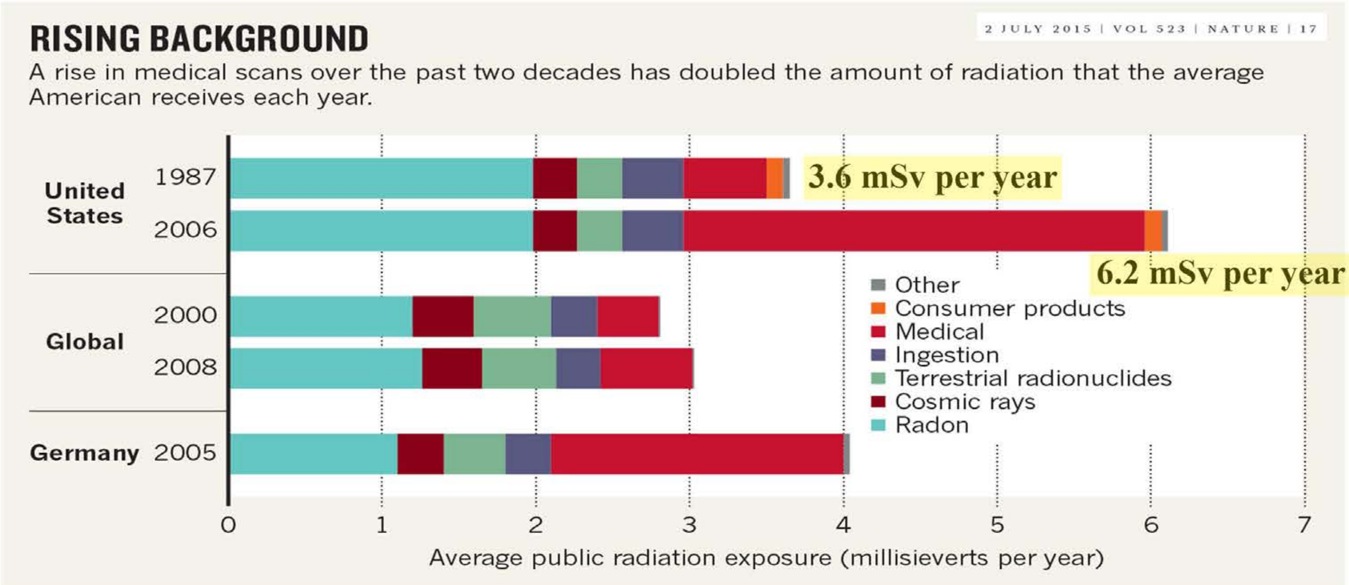


Cosmic rays interacting with the upper atmosphere. (Good thing too, or else we wouldn't be here.)



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

Background Radiation

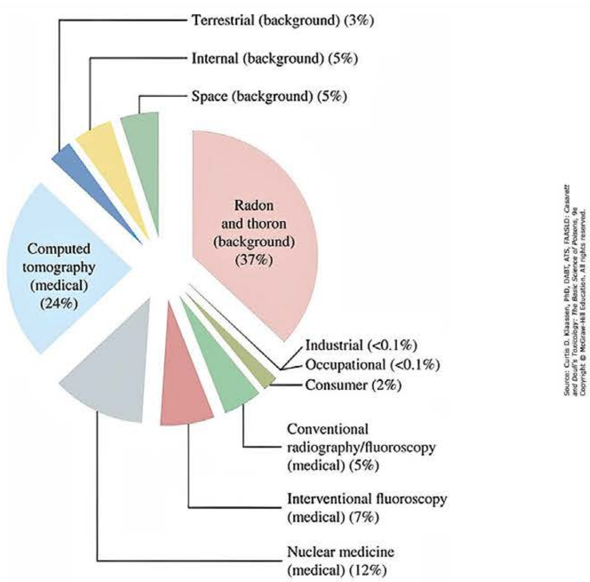


(Ratio of Natural:Man-made ≈ 1:1)

The big change in the annual background radiation exposure in the US between 1987 and 2006 is due almost completely to the increase in the number of CT scans performed per year - they deliver the highest dose of all the medical imaging procedures!

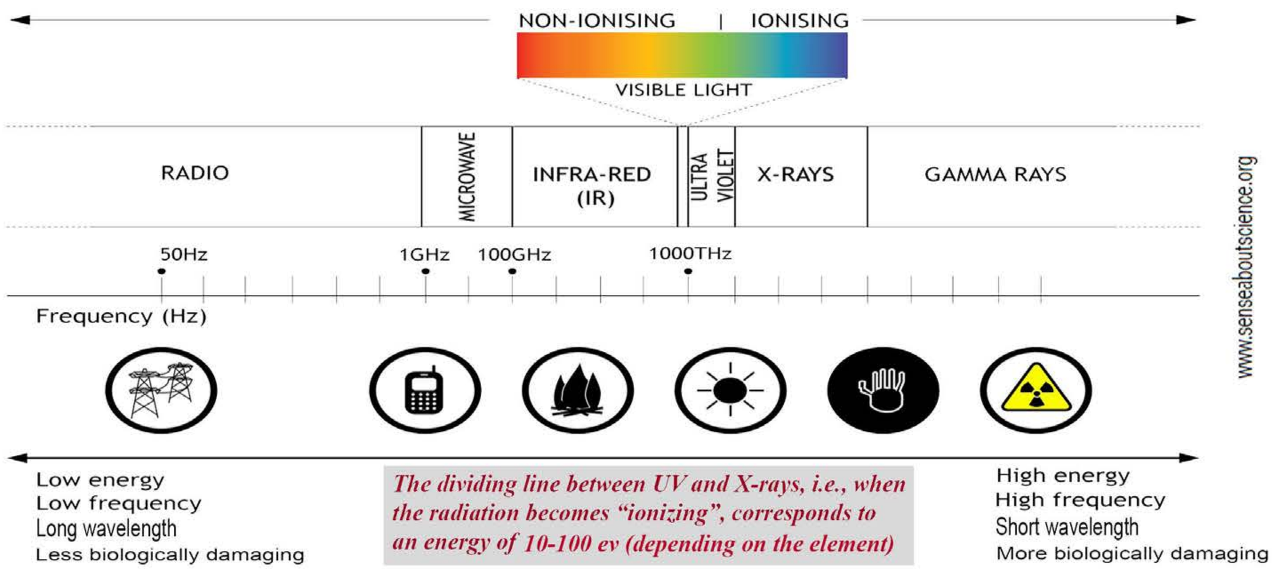
Biggest contributor to ***natural*** background radiation exposure:
<u>Radon</u> (~37% of *all* background radiation)

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

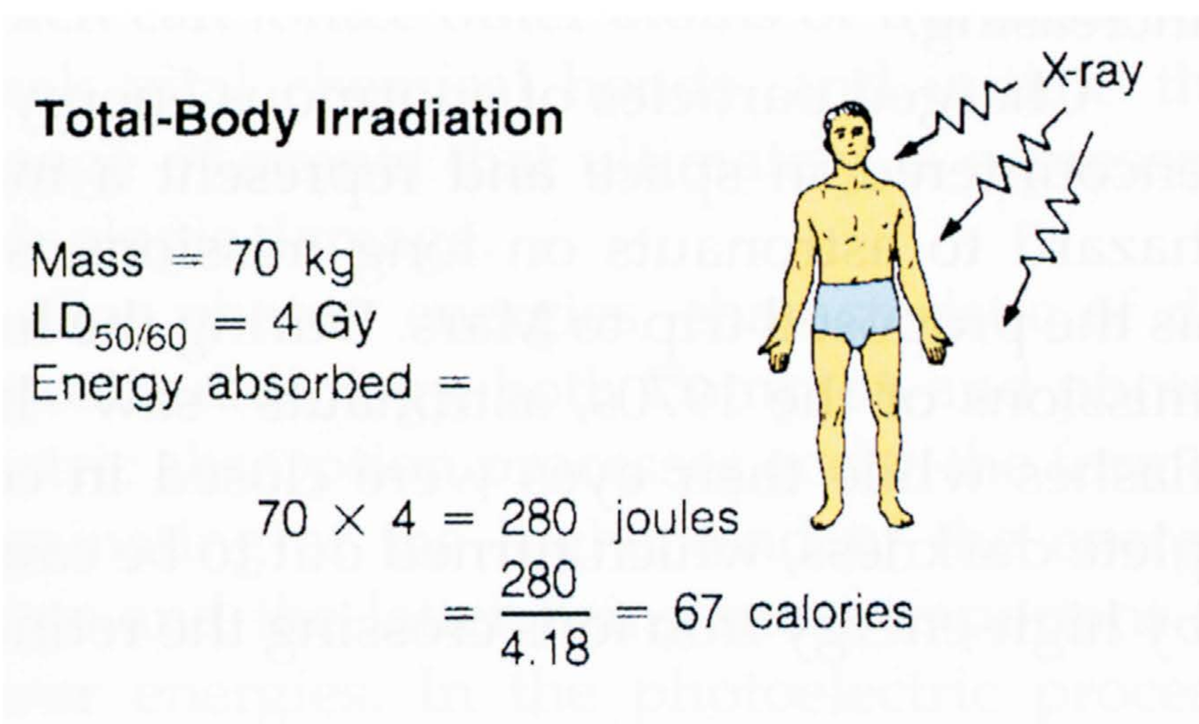


B] A (Thankfully) Brief Review of Radiation Physics

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*)

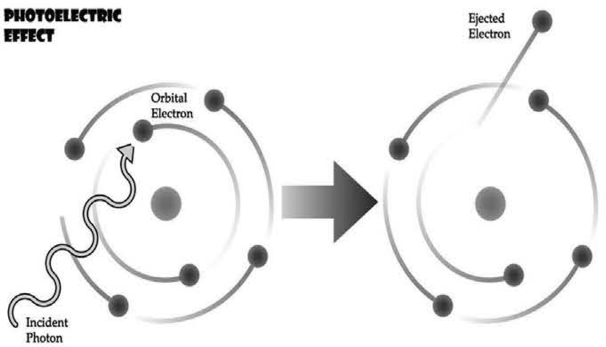


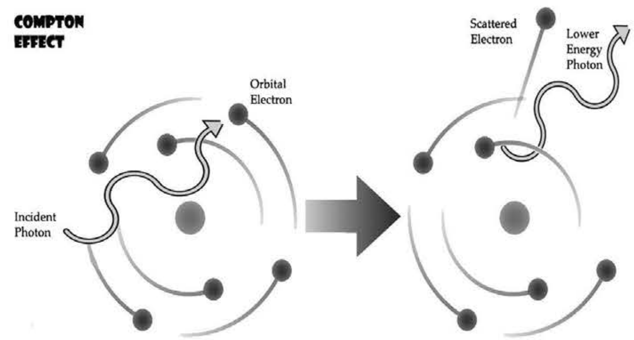
a) probably **the most important characteristic of ionizing radiation from a biological perspective is the random and discrete nature of the energy deposition**, that is, that while the average energy deposited in a macroscopic volume of tissue might seem rather small, the distribution of this energy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

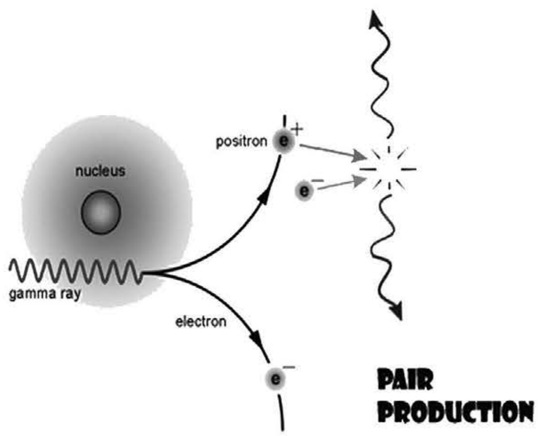


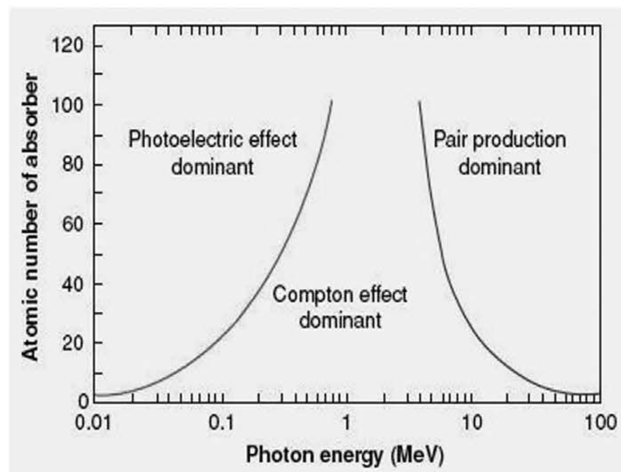
2. Ionizing radiations can loosely be characterized as **electromagnetic waves/photons** (such as x-rays or γ-rays) or **particles** (electrons, neutrons, protons, α–particles etc.--these can be charged or uncharged).

(a) <u>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</u>, 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**

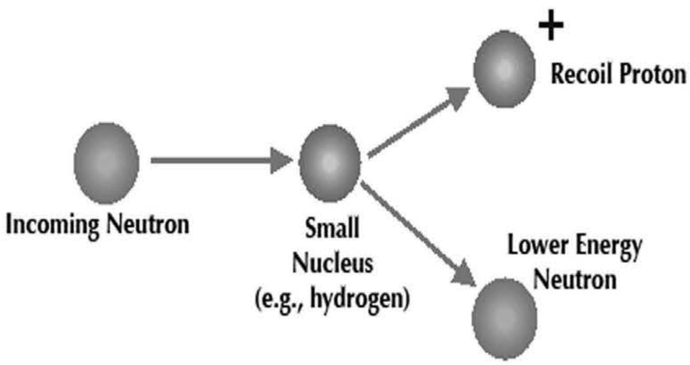


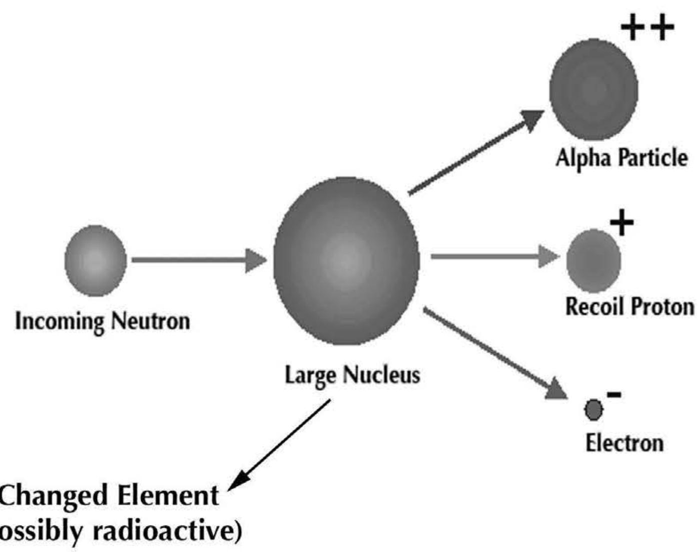






(b) <u>for neutrons, the interaction is between the particle and the nuclei of the atoms in the absorbing material</u> (predominantly, with hydrogen atoms), which results in the ejection of recoil protons (and lower energy neutrons)

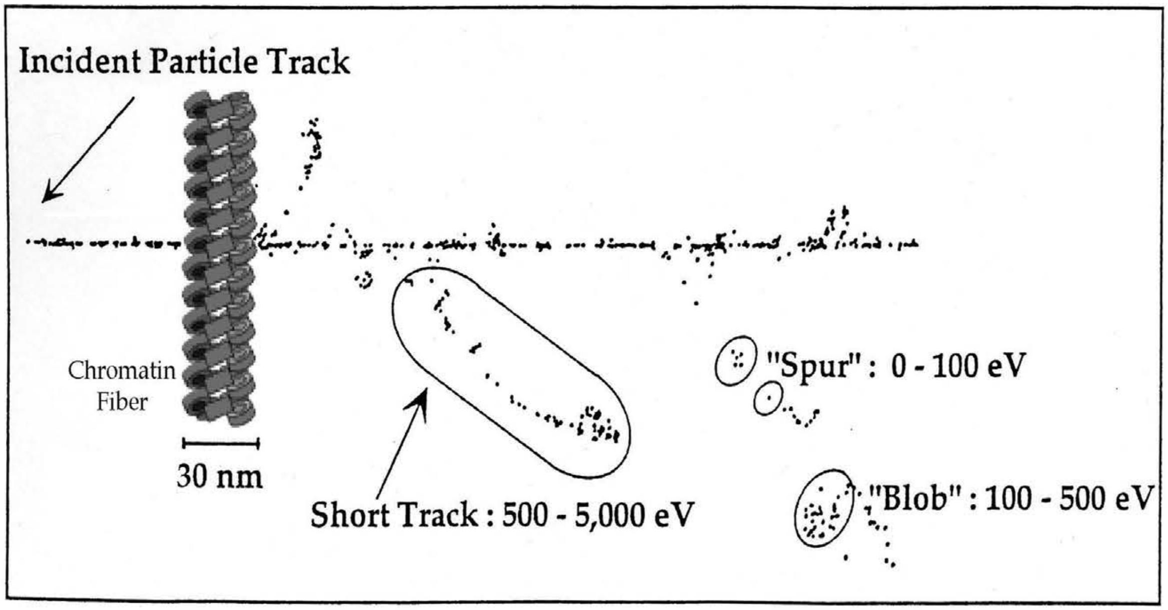




Regardless of the type of ionizing radiation – photon or particle – and the type of atomic interaction, the net effect is more charged particles being set in motion, and "damaged" atoms left in their wake

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

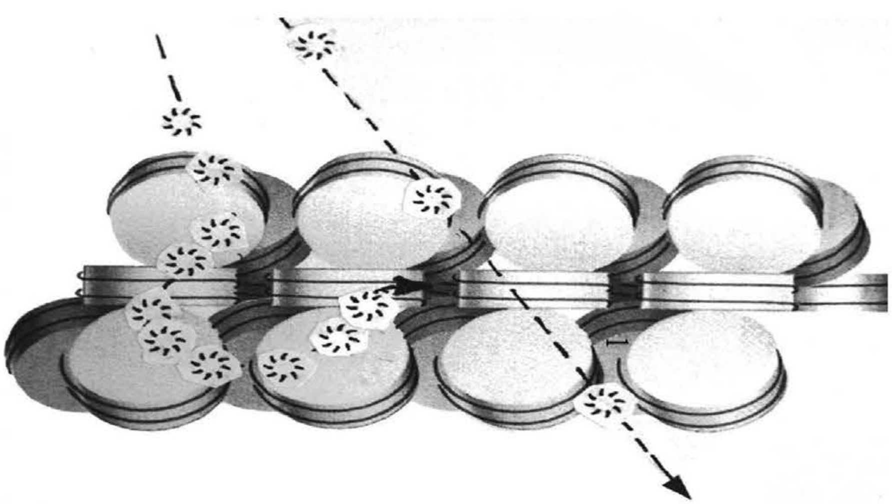
(a) the energy is deposited in the absorbing medium in little packets of variable size and shape, which depend on how much energy is actually expended; these have cute names like **"spurs", "blobs", "short tracks"** etc.



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

2) 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).

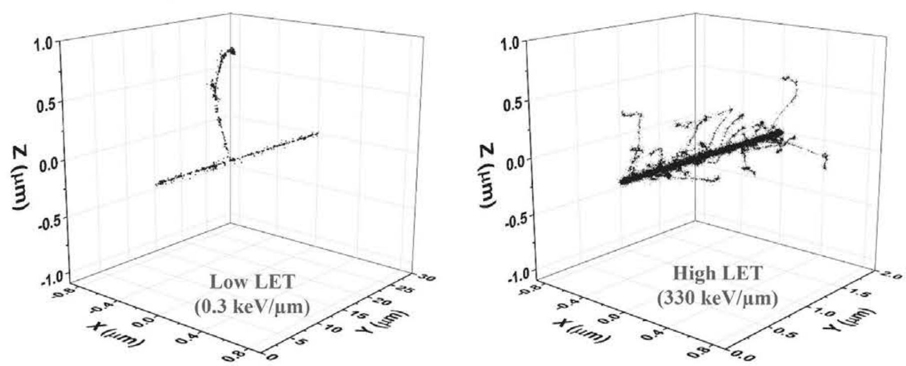
a] *the "clustered" nature of DNA damage caused by ionizing radiation explains why radiation is so efficient at killing cells per number of damages produced*

d) Does 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



3D simulations of primary and secondary track structures and density of ionizations for low (left) versus high (right) LET beams

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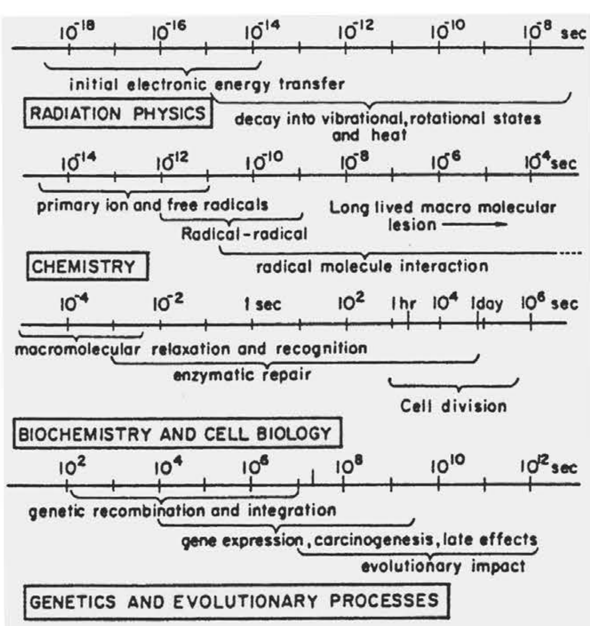
3} What is the time scale for energy deposition events, and all of the consequences that follow?

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???

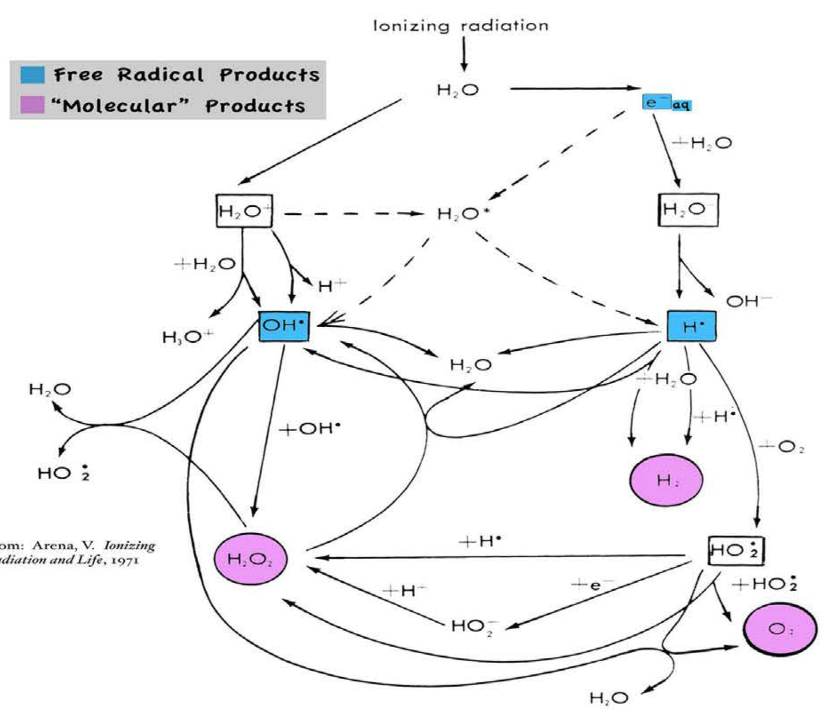
1. molecules unfortunate enough to receive a "direct hit" from a spur or blob experience, relatively speaking, a huge deposition of energy in a very small volume (hence, the terms "random and discrete") causes the atoms to lose electrons

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

a FREE RADICAL is an atom or molecule that contains an unpaired electron (these may be charged or uncharged); 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

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?**

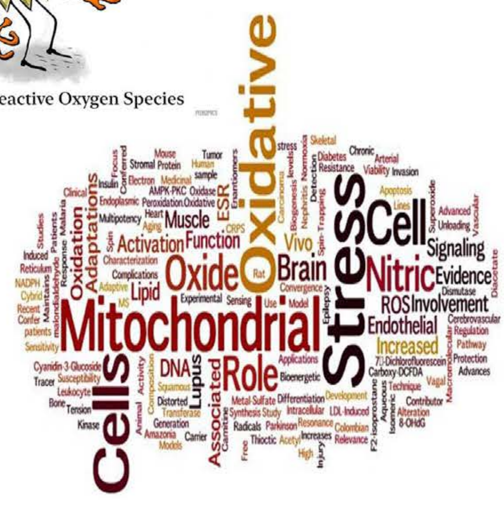
a) Answer: the most abundant molecule in the cell, namely **WATER, which comprises some 80-90% of the cell on a per weight basis**



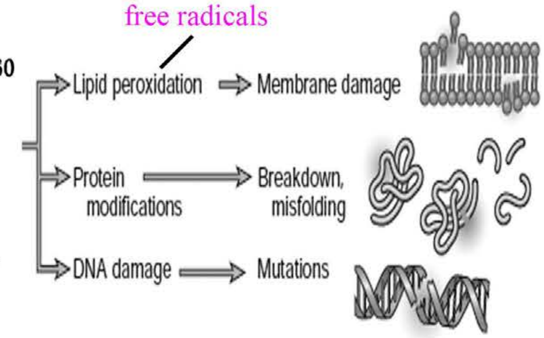
From: Arena, V. *Ionizing Radiation and Life*, 1971

Radiolysis of water.

Overreactive Oxygen Species



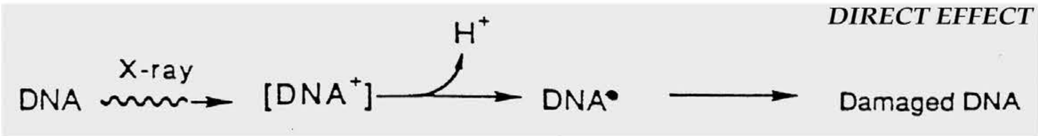
This process can generate even more free radicals



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**

DNA's particular vulnerabilities are that it's a large molecule (big target), has a low copy number, and is critically important to the continued functioning of the cell

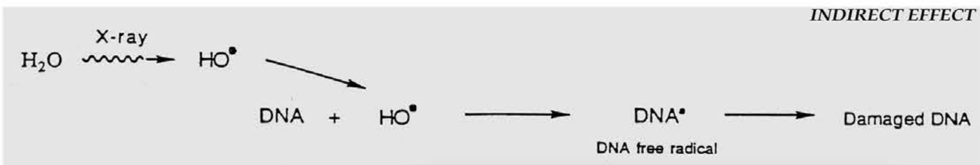
☞ Should a spur or blob land right in the middle of a DNA strand, there is little question that the DNA will be ionized, and some sort of chemical damage will result. **This process is termed "the direct effect of ionizing radiation".**



30% of damage

For Low LET

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

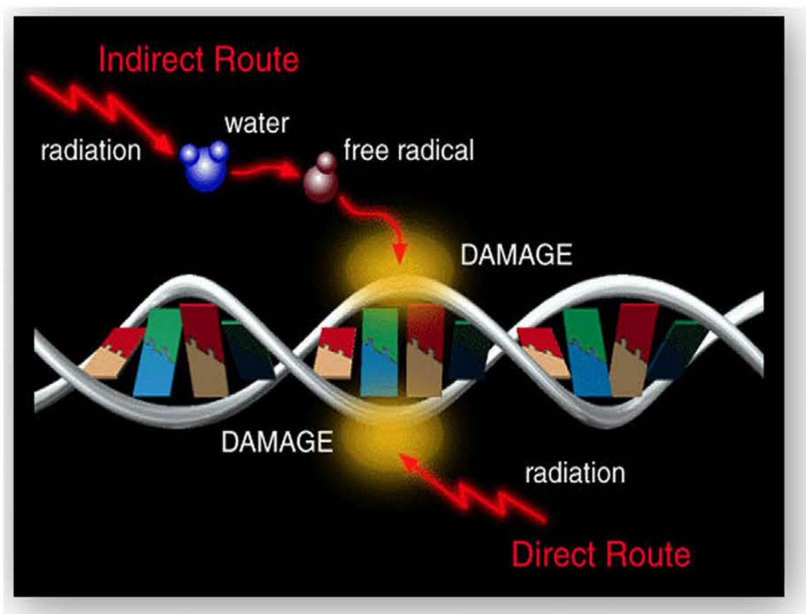


70% of damage

For High LET

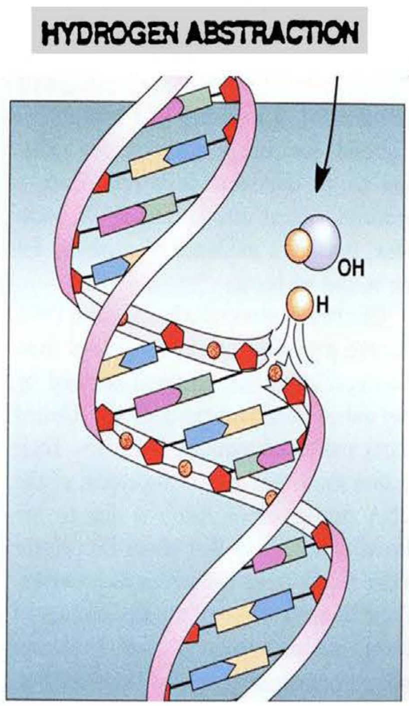
Most, if not all, of the damage is caused by the direct effect

More colorful, sexier graphic illustrating the direct versus indirect effect of ionizing radiation

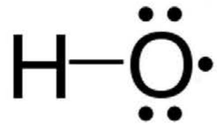


5. **Which free radical is the meanest and nastiest of them all????** The Hydroxyl Radical (**•OH**), formed from the radiolysis of water...

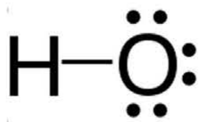
   a) hydroxyl radicals are highly energetic and reactive, and readily attack other molecules, including DNA, via two different mechanisms: **hydrogen abstraction** or **hydroxyl addition**

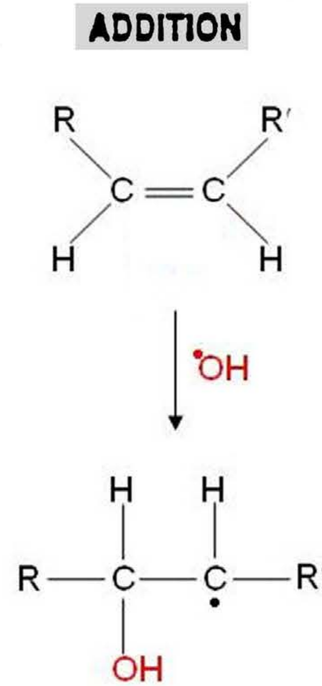


Hydroxyl radical looks like this:

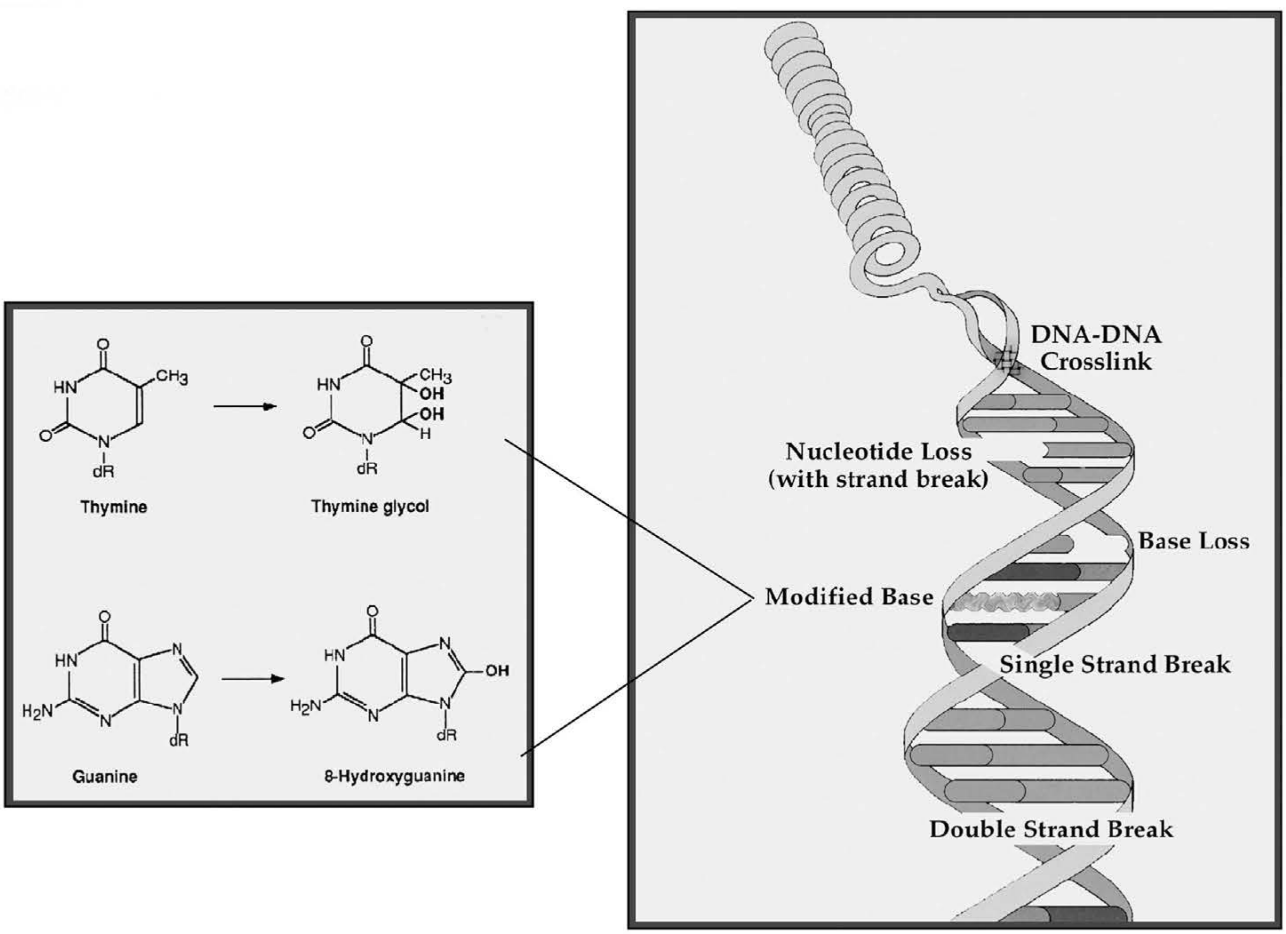


But it wants to look like this:





b) some real, live, measurable, consequences of direct and indirect damage to DNA: base alteration or loss, strand breaks and crosslinks



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 have a certain probability of reacting with:

1. cellular macromolecules like DNA, ultimately forming a DNA radical

2. each other, forming "molecular products"

3. other, naturally-occurring, reactive molecules in the cell, like oxygen or glutathione, a sulphydryl compound

c) when a DNA radical is formed, the damage can either be...

"Fixed" (made permanent, in the chemical sense)
or
"Restituted" (restored to its original form as if no ionization had occurred)

...and these two processes are in competition with each other

The simple diagram that launched thousands of research grants and clinical trials worldwide over 50+ years...