Normal Tissue and Tumor Radiobiology

when intact tissues and organs are irradiated, the very same principles of the radiobiology of cells apply (i.e., cell killing, division delay, cellular repair, mutation induction, etc.)---however, since tissues and organs have their own unique structure, function and growth pattern, the manifestation of radiation damage to cells may appear different for different tissues

1. The Organization of Tissues, and How It Relates to Radiation Response

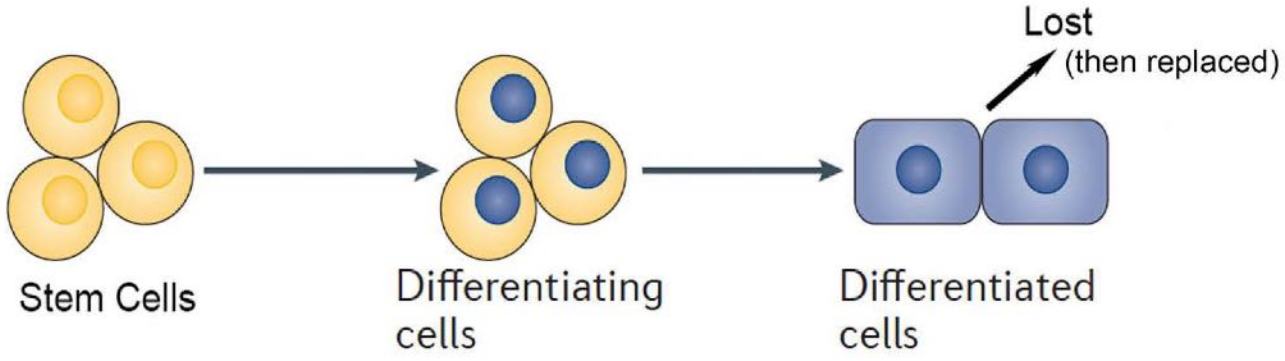
a) **normal tissues are "normal" because they do not grow...*in other words, cell production exactly balances cell loss***

1. for normal tissues , "cell loss" usually means that cells differentiate and thereby lose their reproductive ability, however, for some tissues, the differentiated cells are actually "lost" through wear and tear

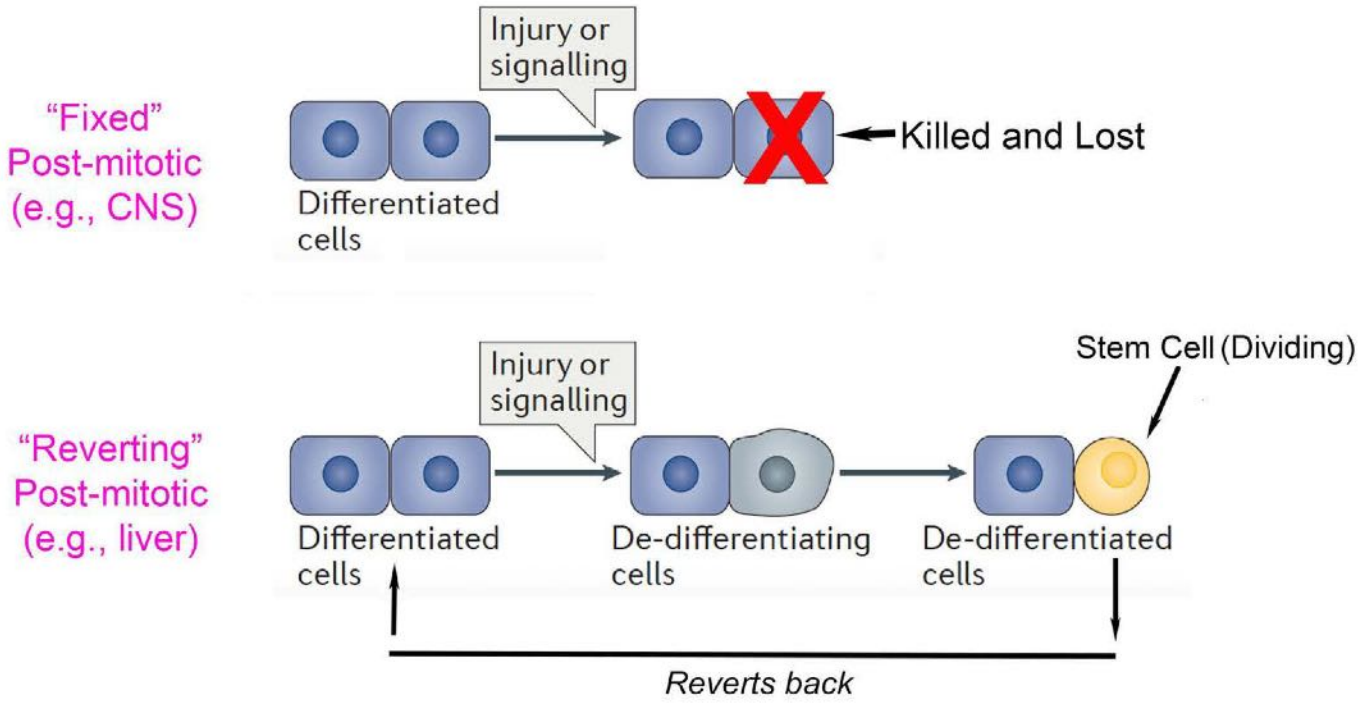
2. it is the differentiated cells that carry out the functions of the tissue, whereas it is the stem cells that carry out the cell production duties (i.e., making new differentiated cells and new stem cells...)

b) there are two general classes of normal tissue organization:

1. **Hierarchical Tissues** (such as skin, GI tract, blood forming bone marrow, testis etc.) - tissues in which the different types of cells are in distinct "compartments" and move sequentially from one compartment to the next (but not backwards)



2. **Flexible Tissues** (such as liver, kidney, brain, spinal cord, muscle etc.) - tissues which appear to only contain differentiated, functioning cells, and which grow slowly if at all; however, if necessary--such as in response to an injury--some of these cells can return to dividing status and replace lost cells



c) how long has it been known that the proliferative organization of tissues has something to do with how they respond to radiation????

Answer: almost 120 years
(although, the details weren't understood *all that well* at the time...)

1. **these ideas were formulated in the so-called "Laws of Bergonié and Tribondeau" in 1906; these French radiobiologists concluded that a tissue was likely to be "radiosensitive" if the cells making up that tissue:**

a) **had a high mitotic rate (i.e., rapidly dividing)**

b) **had a long mitotic future (i.e., that under normal circumstances, the cells would be capable of dividing indefinitely)**

c) **were of the primitive, undifferentiated type (like stem cells)**

2. ***even though Bergonié and Tribondeau didn't know a lot of stuff about radiobiology that we do know today, their "laws" are still used as simple rules of thumb for classifying tissues into different categories according to their expected radio-responsiveness***

CHARACTERISTICS AND RADIOSENSITIVITY OF CELL POPULATIONS

CELL TYPE	CHARACTERISTICS	EXAMPLES	RADIOSENSITIVITY
VIM	Rapidly dividing; undifferentiated; do not differentiate between divisions	Type A spermatogonia Erythroblasts Crypt cells of intestines Basal cells of epidermis	Most radiosensitive
DIM	Actively dividing; more differentiated than VIMs; differentiate between divisions	Intermediate spermatogonia Myelocytes	Relatively radiosensitive
RPM	Do not normally divide but retain capability of division; differentiated	Parenchymal cells of liver Lymphocytes*	Relatively radioresistant
FPM	Do not divide; differentiated	Some nerve cells Muscle cells Erythrocytes (RBCs) Spermatozoa	Most radioresistant

*Lymphocytes, although classified as relatively radioresistant by their characteristics, are very radiosensitive.

Abbreviations:

VIM or "Class I" cells = "vegetative intermitotic" cells, i.e., undifferentiated stem cells

DIM or "Class II" cells = "differentiating intermitotic" cells, i.e., cells that are on the path to terminal differentiation, but aren't quite there yet and can still divide

RPM or "Class III" cells = "reverting post-mitotic" cells, i.e., cells that are differentiated, but can revert to being stem cell-like in response to tissue injury; thus, they are G_0 cells

FPM or "Class IV" cells = "fixed post-mitotic" cells, i.e., cells that are terminally differentiated and incapable of division

3. Skin, Gut Epithelium, Testis and Bone Marrow: Examples of Hierarchical Tissues

a) for each type of tissue, first, we would like (hopefully) to know what cell type is the **target cell** for that tissue

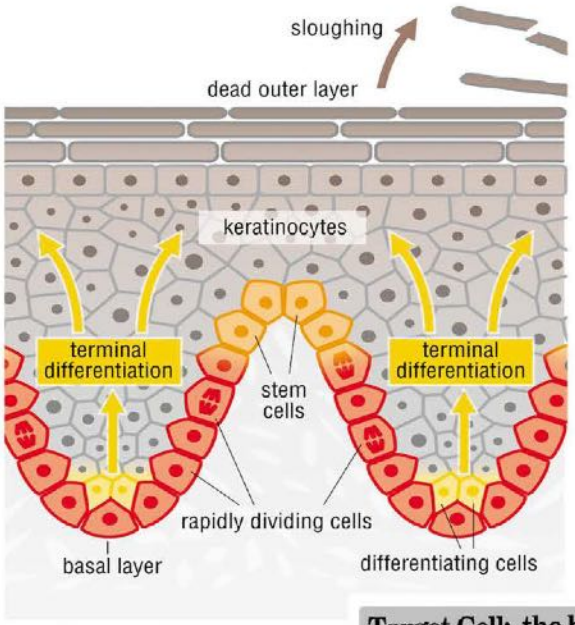
1. definition of "target cell" - *the critical type of cell whose death following irradiation contributes to a reduction in the structure and/or function of the tissue*

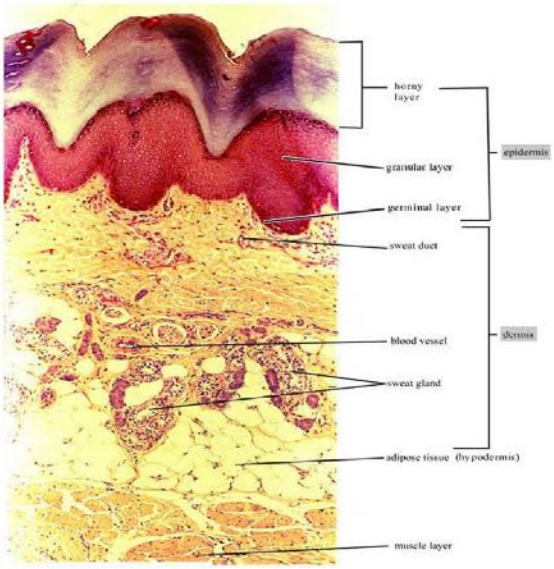
b) second, we would need to know how fast the cells move from one compartment to the next to be able to predict when the killing of target cells is manifest as observable tissue damage

1. **please note that the onset time for the appearance of tissue damage is not so much related to the radiation dose given as to the rate at which cells move through their compartments; however, the ultimate *severity* of the tissue effect is related to the dose, that is, to the inherent radiosensitivity of the target cells themselves**

2. since the target cells of hierarchical tissues tend to proliferate pretty fast (by *in vivo* standards), and because the expression of radiation damage to cells--cell death--occurs during cell division, it follows that the tissue damage will be apparent fairly soon after the radiation exposure; **such tissues are the ones responsible for EARLY EFFECTS in radiotherapy patients**

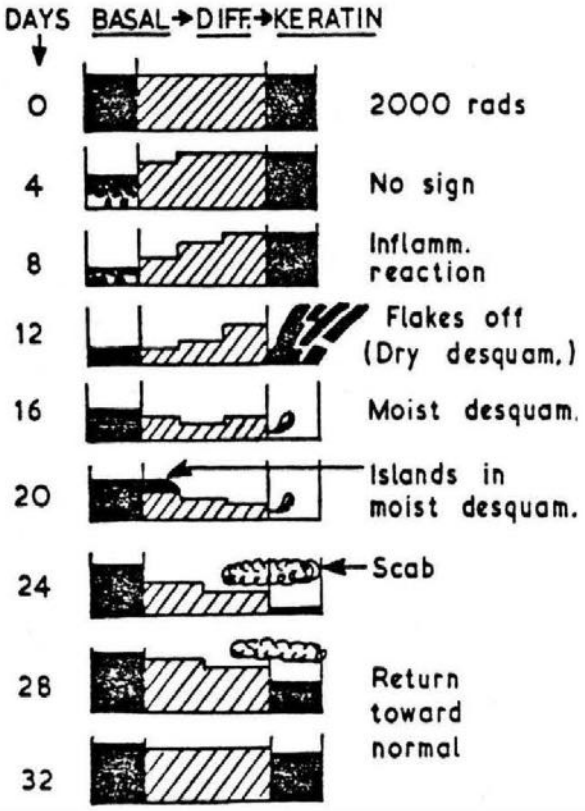
Skin Before Irradiation

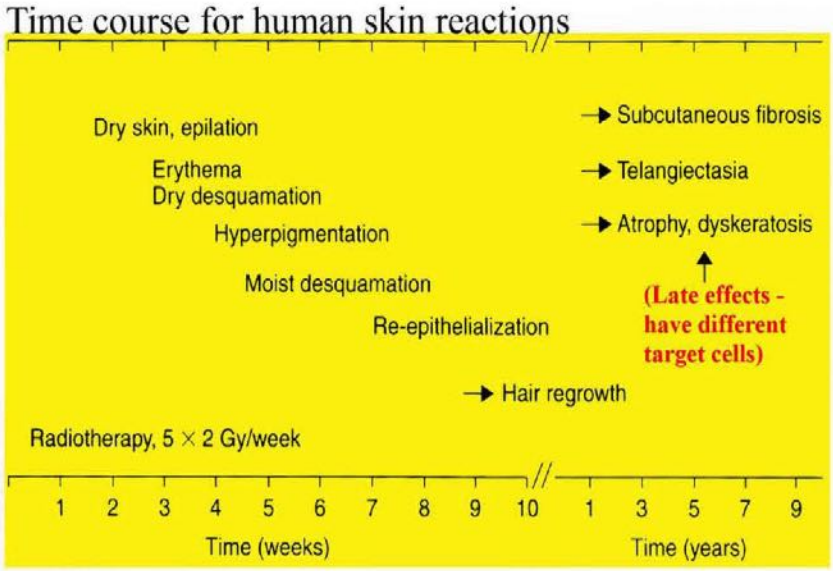




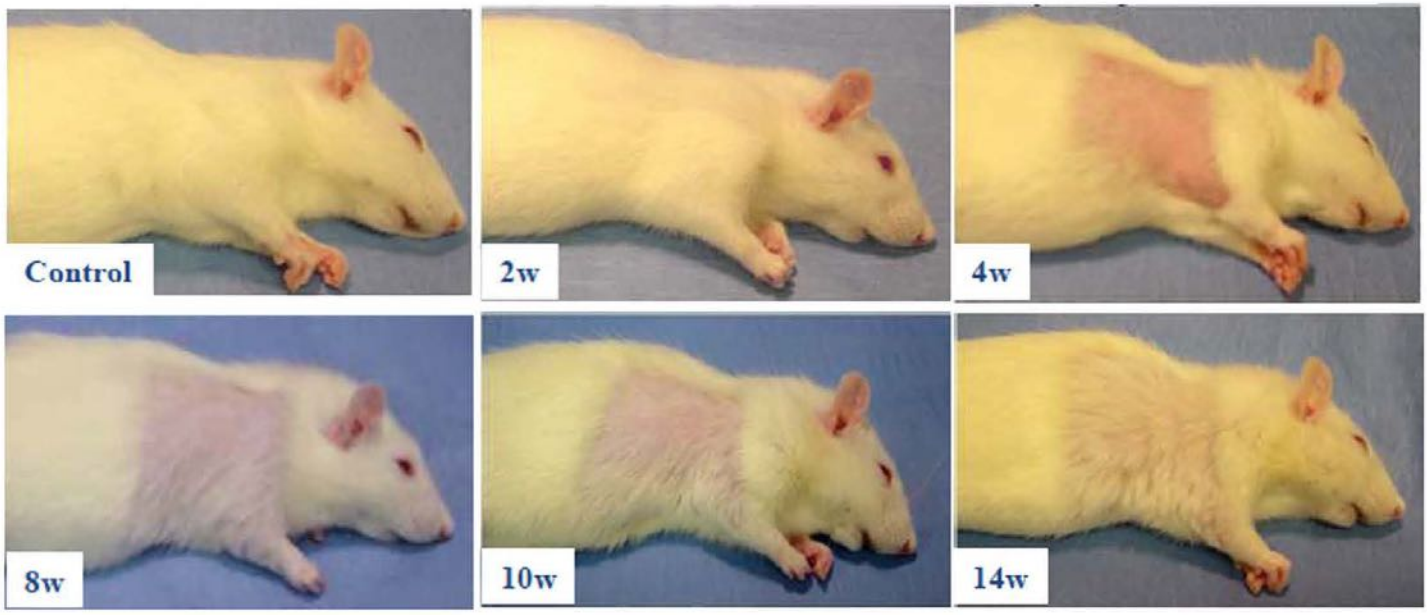
Target Cell: the basal stem cells of the epidermis

Skin After Irradiation (Mouse)

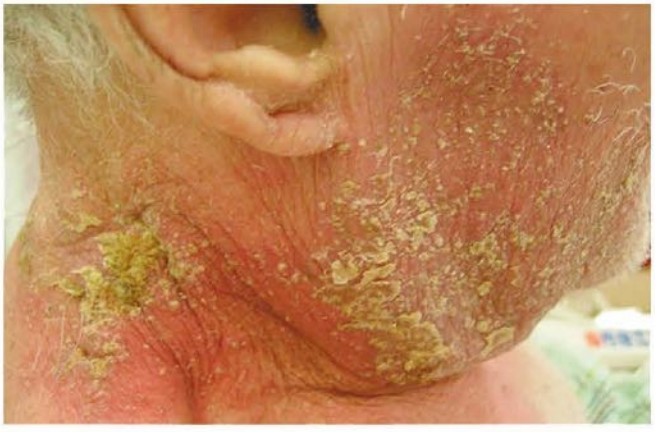




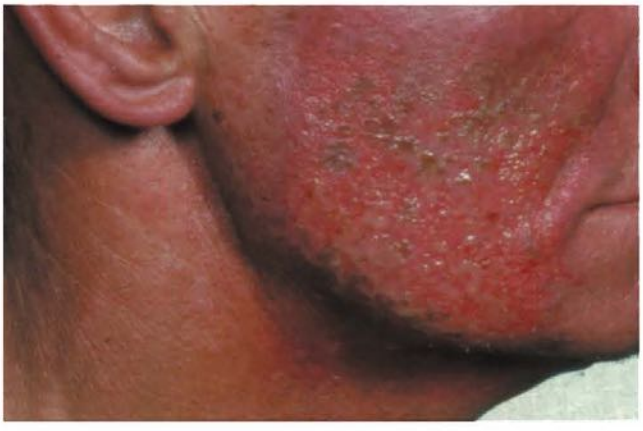
Time course for skin reactions in the rat (large, single dose)



Time course for skin reactions in humans (conventional fractionation)



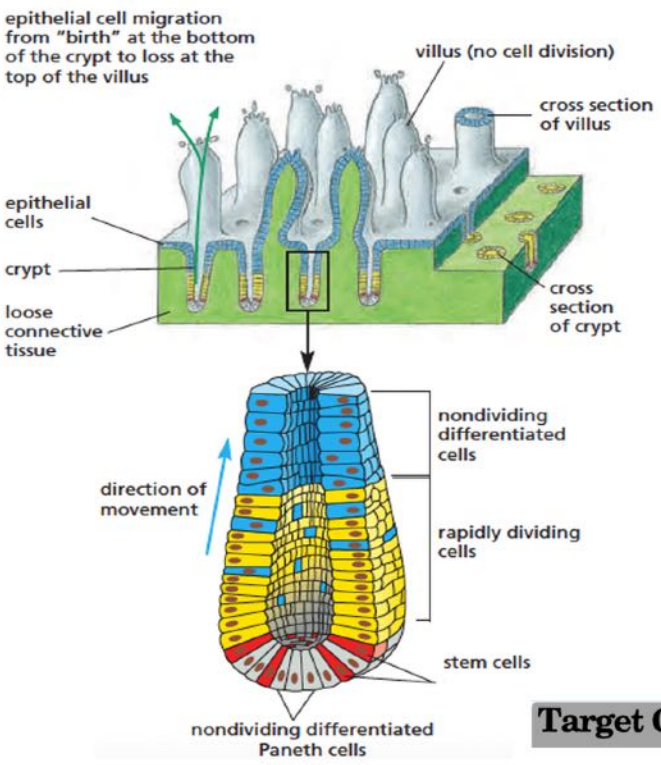
Dry Desquamation (~3.5 weeks)

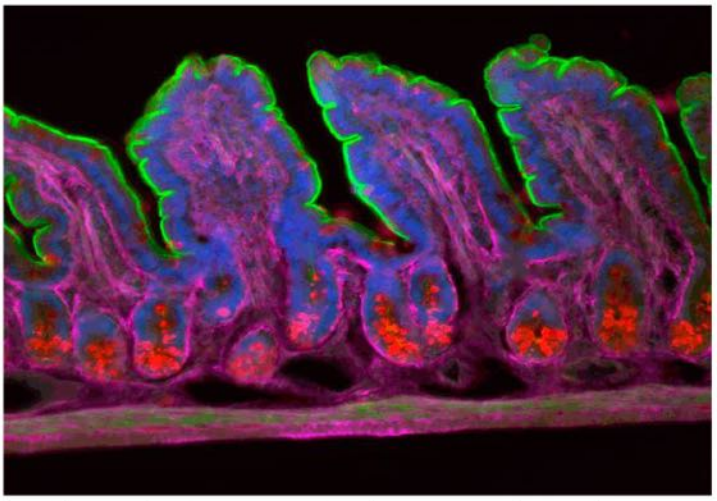


Moist Desquamation (~4.5 weeks)

Intestinal Villi Before Irradiation

Cell division at the bottom of a crypt in the small intestine continually renews the epithelium of the villus. Surface cells, migrating upward, stop dividing and differentiate to perform specific functions





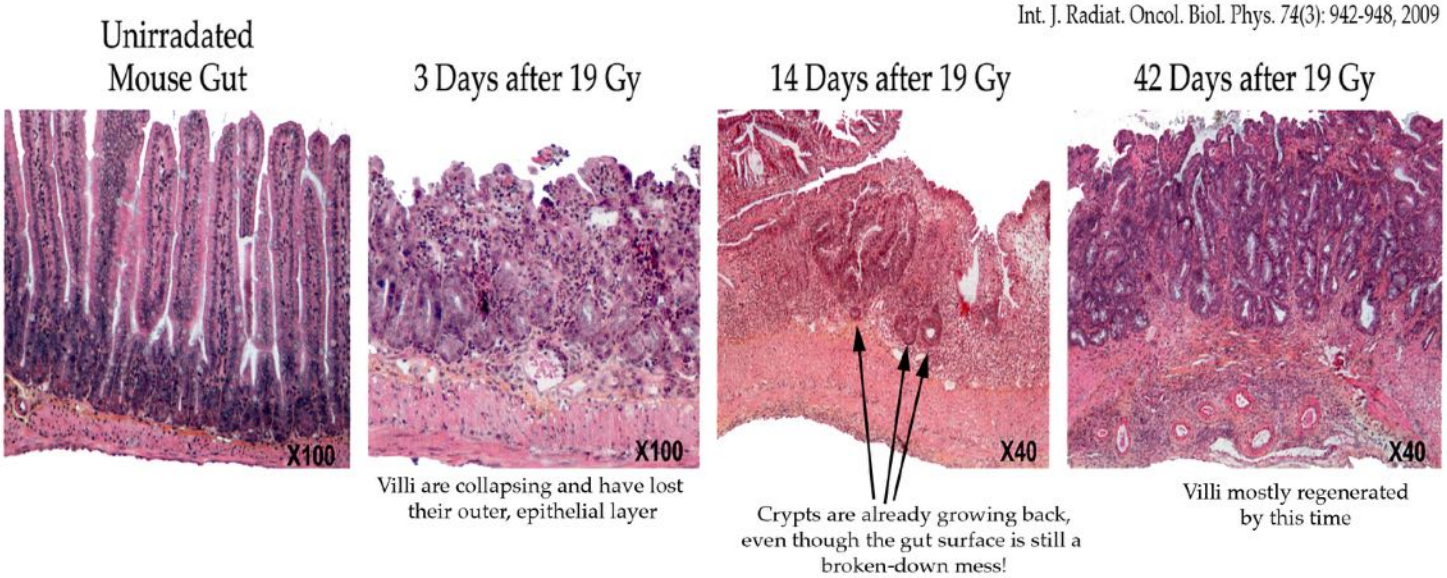
Low-ish magnification cross section of a mouse gut showing fluorescently stained villi.

Surface epithelial cells = neon green
Supporting cells and blood vessels = blue/purple
Crypt cells = neon red

Target Cell: the "crypt" cells at the bottom of the villus

Intestinal Villi after Irradiation

Int. J. Radiat. Oncol. Biol. Phys. 74(3): 942-948, 2009



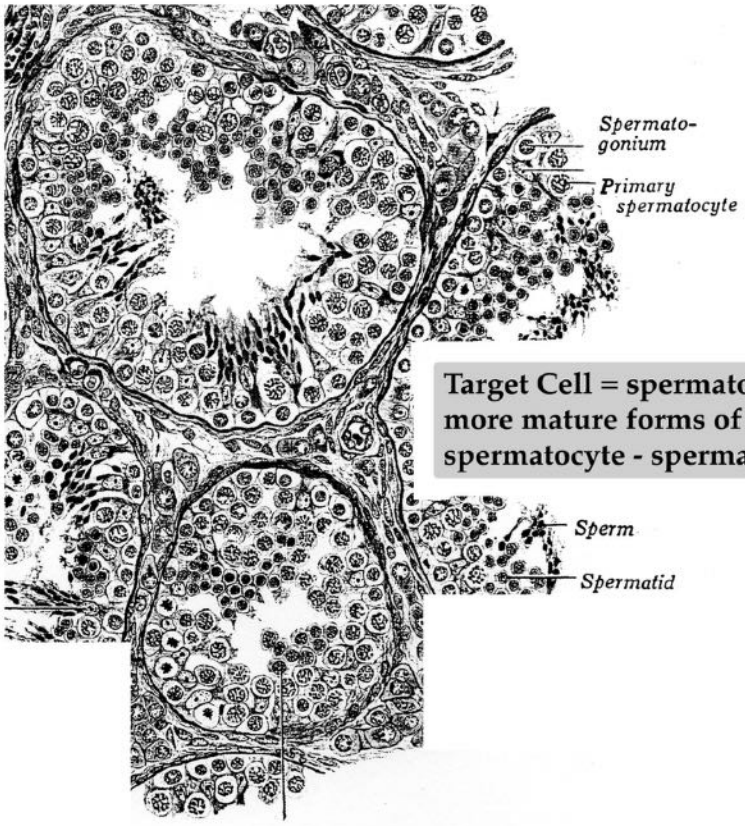
Villi are collapsing and have lost their outer, epithelial layer

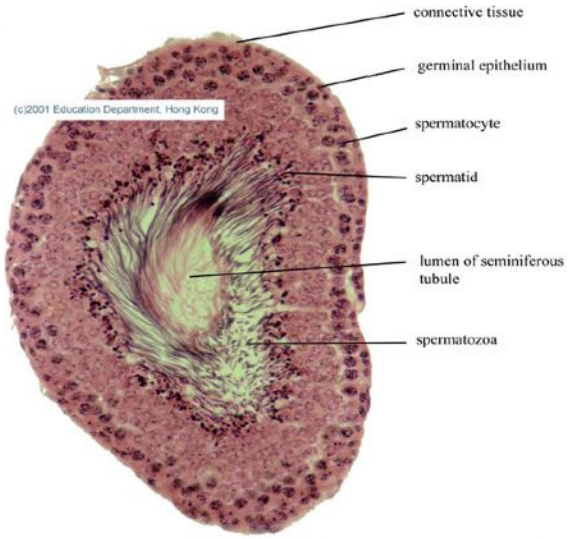
Crypts are already growing back, even though the gut surface is still a broken-down mess!

Villi mostly regenerated by this time

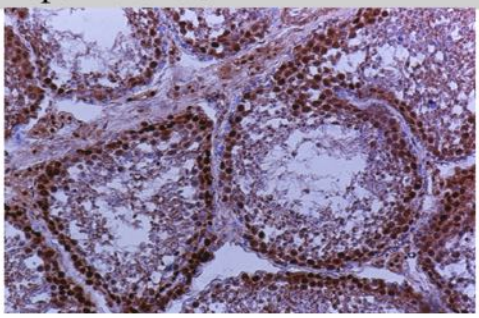
Transit time through compartments = 7-10 days

Seminiferous Tubules of the Testis Before Irradiation



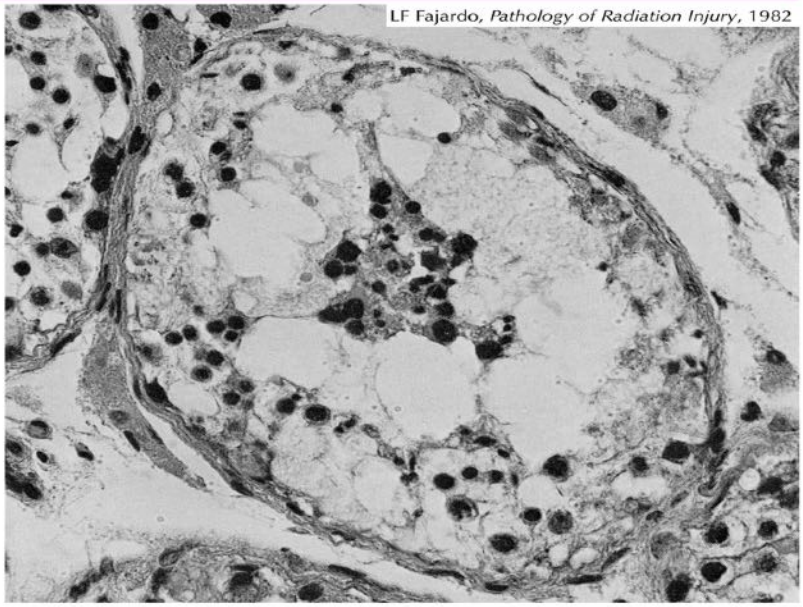


Target Cell = spermatogonium, the undifferentiated precursor of more mature forms of the sperm lineage (i.e., spermatogonium - spermatocyte - spermatid - spermatozoa)



Cross-section of canine testis, showing seminiferous tubules. Spermatogonium stain darkest, and are located along the outer edge of each of the tubules

Cross-Section of Seminifeous Tubule After Irradiation

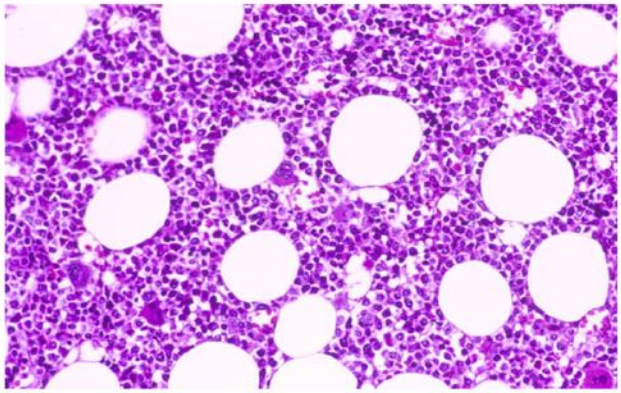


Transit time through compartments ≈ 90 days

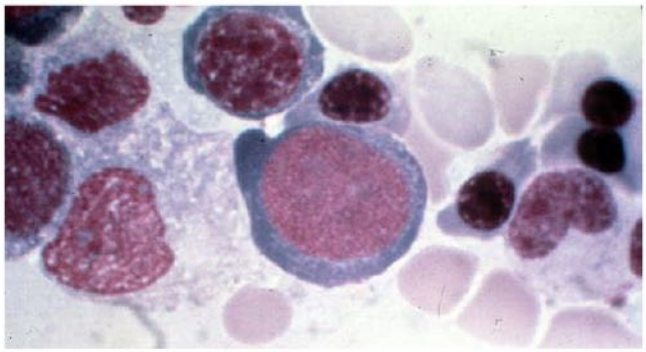
Cross section of a seminiferous tubule of a nuclear worker involved in a fatal radiation accident at a nuclear fuel reprocessing plant. He received in excess of 60 Gy of γ-rays and 20 Gy of neutrons, and lived for less than 3 days.

Note the massive damage to all types of sperm precursors, but especially the spermatogonium at the outer rim of the tubule.

Bone Marrow Prior to Irradiation



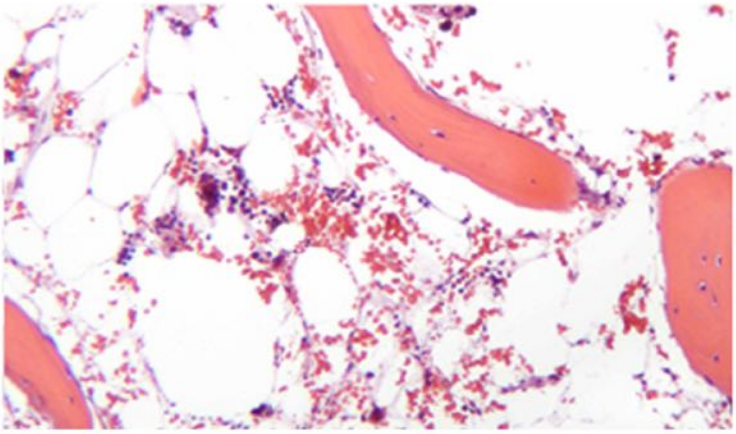
Low Magnification



High Magnification

Target Cell = all bone marrow cell types are the precursors of the mature red and white blood cells and platelets

Bone Marrow after Irradiation with ~6 Gy of Mixed γ-rays and Neutrons



Bone marrow specimen obtained at autopsy from a 26 year old nuclear scientist involved in a criticality accident at Los Alamos National Laboratory in the late 1940's. The subject lived 24 days.

The bone marrow contains many fewer cells than normal, and many of those that are present are in various stages of dying.

Transit time through compartments ≈ 60 days

4. Liver, Kidney and Lung: Examples of Flexible Tissues

a) other tissues in the body have **parenchymal cells** (**another term for differentiated, functioning cells**), but don't seem to have stem cells, or at least not in any easy-to-identify compartment

b) *often, these parenchymal cells divide very slowly* (kidney, liver) *or not at all* (muscle, spinal cord, brain)

1. for the tissues whose cell divide slowly, an injury to the tissue can stimulate a short burst of proliferation in the area of the injury in order to replace the cells that were lost or damaged; after the damaged cells are replaced, proliferation returns to its normal, very slow rate

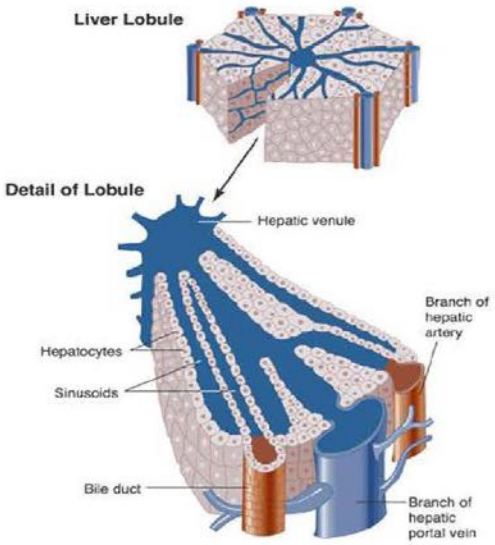
2. for the tissues whose parenchymal cells don't divide at all, an injury to the tissue will not be reversible, and dead or damaged cells will be lost permanently, and *if anything, the areas where the cells were lost will be filled in with non-functioning fibrous tissue*

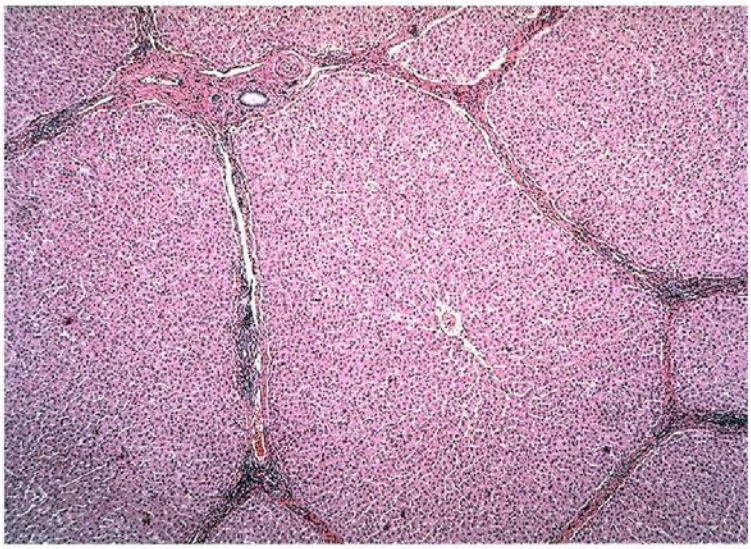
c) because the death of cells from radiation is usually linked to the cell division process, it follows that tissues that only contain slowly or non-cycling cells won't *seem* to be very radiosensitive, or at least, won't express damage caused by the radiation until (very) long times after the radiation exposure ---> such tissues are the ones responsible for LATE EFFECTS in radiotherapy patients

d) in fact, sometimes, the parenchymal cells of a tissue proliferate so slowly, even when stimulated by an injury, that it ends up being radiation damage to the vasculature (cells making up the blood vessels) and/or the stroma (cells which provide nutritional or structural support to the parenchymal cells of the tissue) which ultimately causes the tissue to stop working!

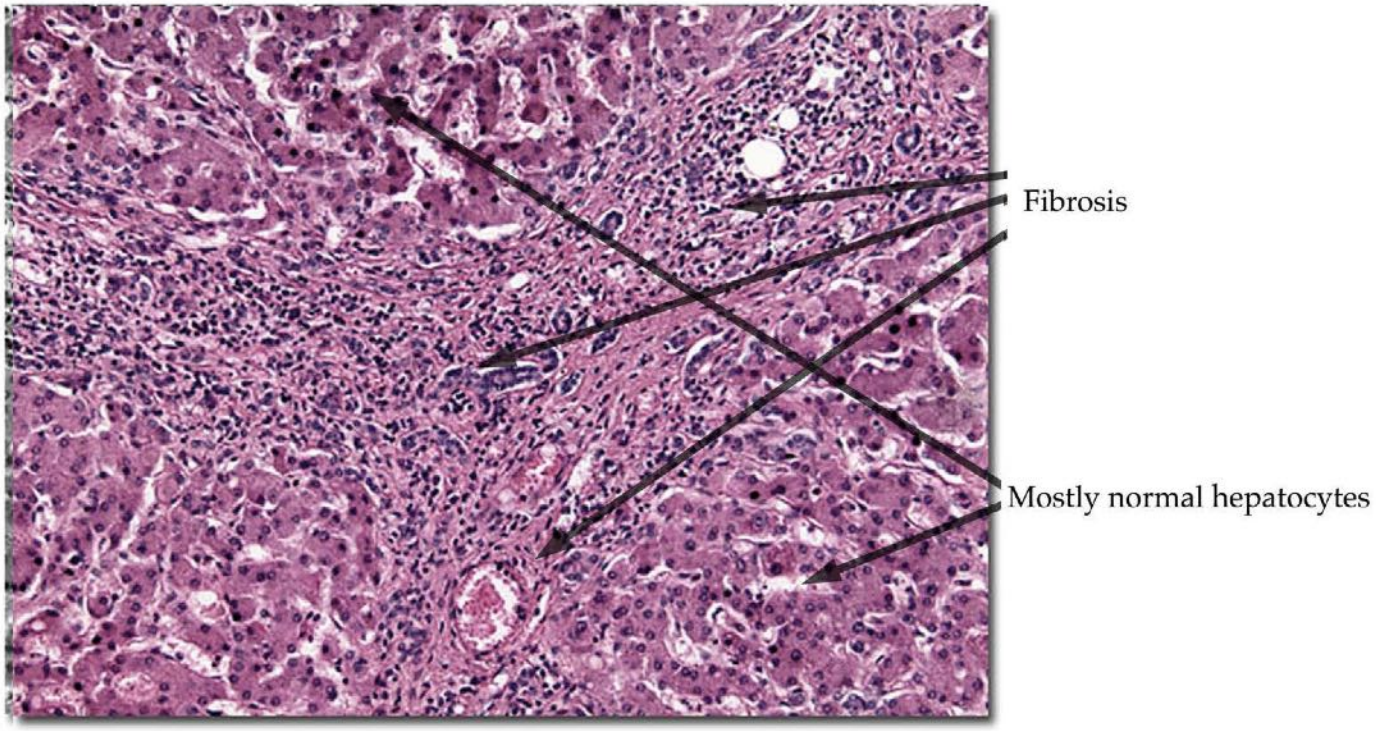
Liver Prior to Irradiation

Target Cell: the hepatocytes (mature liver cells) or the blood vessel cells or ????





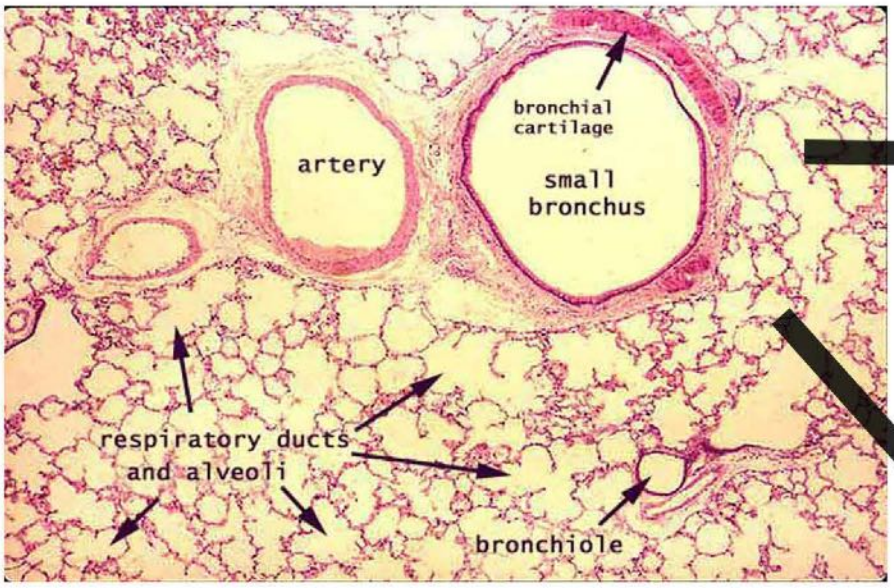
Liver after Irradiation

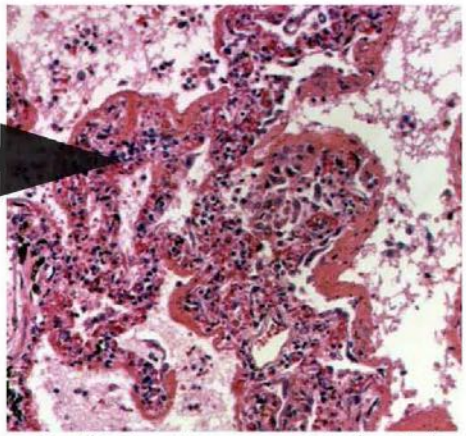


Lung Prior to Irradiation

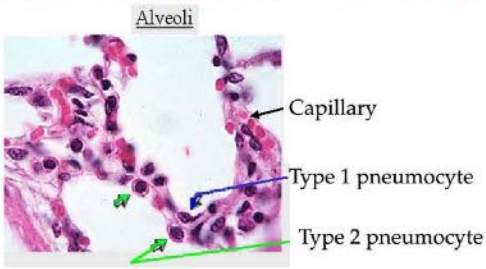
Lung after Irradiation

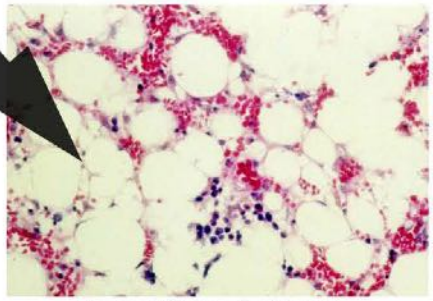
Target Cell = Type 1 or 2 pneumocytes or lung capillaries or ?





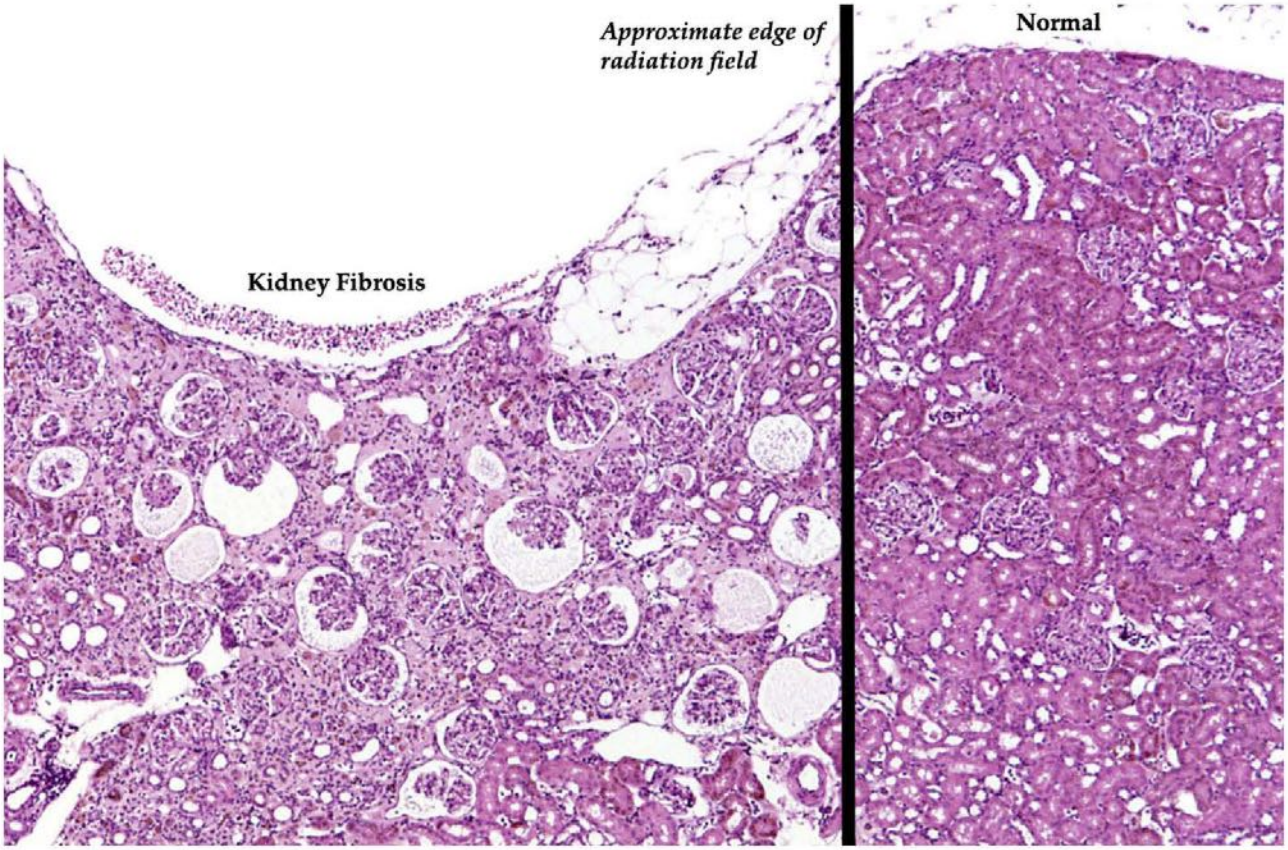
Radiation Pneumonitis (early)





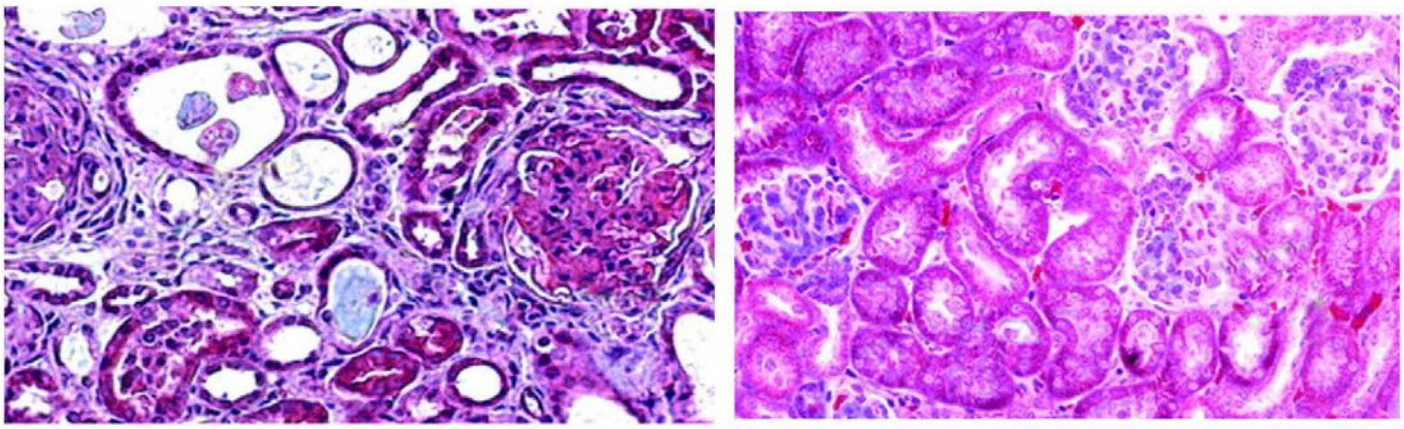
Lung Fibrosis (late)

Cross-Section Through an Irradiated Kidney Showing Late Fibrosis Next to Normal Parenchyma



Thickening of glomeruli, thining of the linings of the renal tubules, and massive bleeding and fibrosis are seen in a heavily irradiated mouse kidney

Higher Magnification



Target Cell = epithelial cells lining renal tubules (probably)

Tumor Biology

Growth Characteristics of (Already Well-Established) Tumors – *because of all the abnormalities characteristic of tumor cells, it is much harder to understand the growth patterns of tumors as a whole, especially compared to normal tissues that are much more predictable in their behavior*

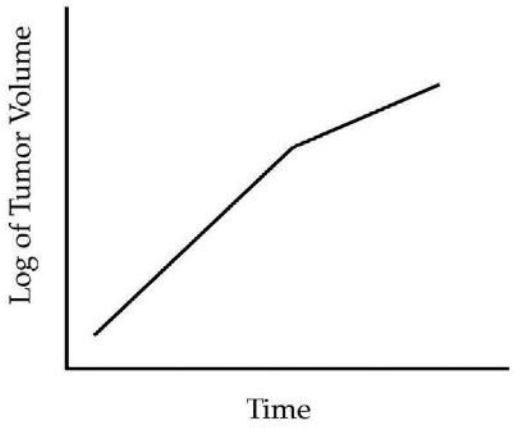
1. ***one thing that is clear about tumors, and that distinguishes them from normal tissues, is that cell production exceeds cell loss*** (in normal tissues, new cell production, if any, exactly balances cell loss)

a) however, **even though tumors continue to grow due to a net production of new cells, this does NOT necessarily mean that the tumor as a whole grows fast, uncontrollably, or even that every cell in the tumor is actively growing**; in fact, **all things considered, most (with some exceptions) human tumors grow relatively slowly**

2. tumor growth as a whole is best described by changes in its size or volume over time, i.e., the **Volume Doubling Time** (T_D)

a) most common growth pattern for human *solid* tumors:

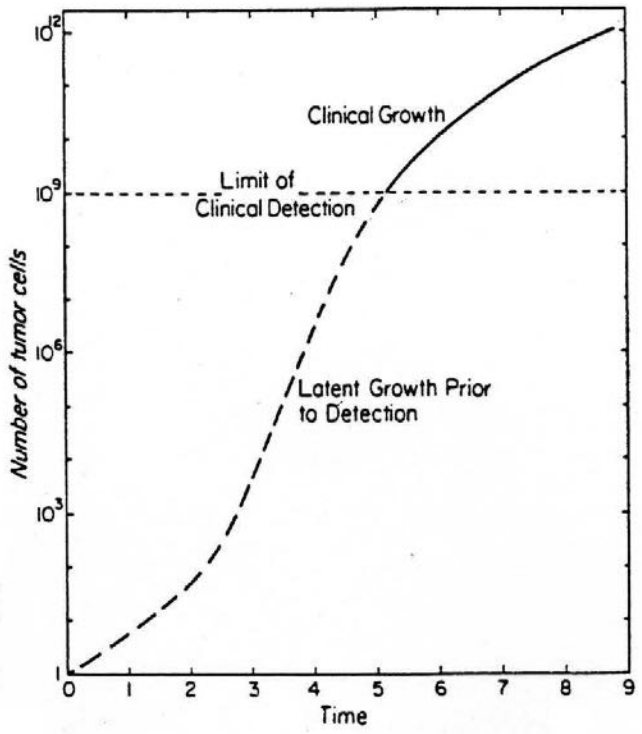
Gompertzian Growth: growth starts out roughly exponential, but progressively slows as the tumor gets bigger



1. however, this can be somewhat deceiving in terms of what's going on with individual tumor cells, compared to the tumor as a whole

2. also, things get even more confusing when you realized that **most of the growth of tumors from a single cell to a clinically measurable tumor mass occurs prior to clinical detection** (*the clinically observable range of tumor growth is from about 10^9 cells to about 10^{12} cells, or about 30-40 cell divisions, and this is thought to represent only about 25% of the tumor's growth history*)!

a) the only growth characteristics of the tumor that we can measure are in the tumor's "old age", and when it is a serious threat to the life of the host



Hypothetical growth curve for a human tumor, showing the long latent period prior to detection. Tumors may show an early lag phase, and progressive slowing of growth at large size.

3. What factors contribute to the shape of the tumor's growth curve, and the relatively long time it takes for most solid tumors to double their volume (***on average, 90-100 days for human tumors***)?

- *what rate the growing cells are going through the cell cycle* (the **cell cycle time**)
- *what fraction of cells in the tumor are actually growing* (the **growth fraction**)
- *how many cells are normally "lost" from the tumor as it grows* (the **cell loss factor**)

usually, the main reason why human tumors grow slowly overall...high cell loss factor!

Early and Late Effects in Normal Tissues

A. What makes a normal tissue reaction during and after radiation therapy "early" versus "late"?

1) Answer: early effects are early and late effects are late because of the **turnover kinetics** of the particular cells at risk, and the proliferative behavior of the tissue as a whole

a] *"turnover kinetics" refers to how, and at what rate, a tissue responds to damage, and the way in which it replaces lost cells (if at all)*

b] tissues that replace lost cells quickly exhibit early reactions, and those that replace lost cells more slowly, or barely at all, show late reactions

B. OK, so which effects are considered "early" and which are considered "late"?

1) the definitions of these terms are somewhat arbitrary, but in general:

EARLY EFFECTS: develop (and resolve, if they're going to) during irradiation, or within the first 3-4 months following irradiation (examples: skin and gut reactions, bone marrow depletion, reduction in fertility, etc.)

LATE EFFECTS: develop anywhere from about 6 months up to years following irradiation (examples: fibrosis in a variety of tissues, nervous system injuries, damage to blood vessels, cataracts, second malignancies, genetic effects that occur in subsequent generations, etc.)

2) please note that because these definitions are a little vague, a few radiation effects don't neatly fit into either category, but are sort of "in between", such as some types of lung damage (radiation pneumonitis), and also, effects on the developing embryo and fetus (teratogenesis)

3) another complicating factor is that *some tissues can show both early and late effects,* most likely due to the killing of different types of cells within the same tissue, each of which dies according to its own unique radiosensitivity and turnover kinetics

a] skin is a perfect example of this, because it can show not only more than one early effect but also, more than one late effect!

Early effects = erythema (reddening), edema (swelling), desquamation (skin surface breakdown)

Late effects = fibrosis, pigmentation changes, edema (of a different type), telangiectasia (abnormal proliferation of small blood vessels, i.e., "spider veins")

C. Does "early and late" mean the same thing as "radiosensitive and radioresistant"?

1) short answer: **NO!** **("timing" should not be confused with "sensitivity")**

2) for example, *the cells responsible for a certain type of late effect may be killed at relatively low doses, even though the tissue reaction itself doesn't happen for months…*

in other words, the cells are radiosensitive, but react slowly; conversely, there are also cell types that take high doses to kill, yet they react relatively quickly

Acute, Whole-Body Radiation Syndromes - Good news: *very* infrequent; Bad news: bad stuff

following total body irradiation to doses greater than approximately 2.5 Gy, all organ systems of the body are damaged (and would, with sufficient survival time, show moderate-to-severe tissue responses), but it is usually one of three main syndromes that leads to death:

- the neurovascular syndrome
- the gastrointestinal syndrome
- the hematopoeitic (bone marrow) syndrome

in the less than 1-2 Gy dose range (not enough to cause death, or to *severely* manifest any of the other syndromes), the major risk to the irradiated individual is ***carcinogenesis***

A. **The whole-body radiation syndromes ONLY occur in their life-threatening form when most, or all, of the body is exposed to large, single radiation doses**, such as might occur during and after nuclear bombings, or in nuclear reactor or experimental physics accidents...however, ***some*** *of the signs and symptoms of the whole-body syndromes do occur in radiation therapy patients (depending on what's being irradiated), yet the full-blown syndromes do not occur*

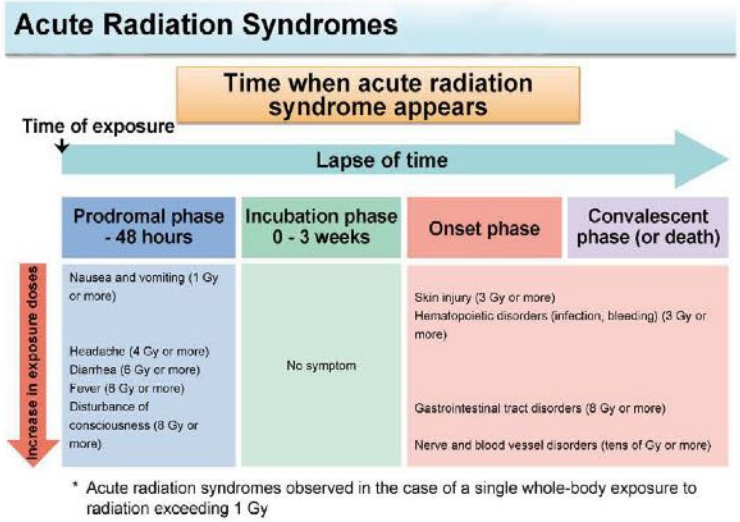
1) in an accident situation though, how do you know exactly what dose the victim received?

a] Answer: YOU DON'T (especially because any film badge the person might be wearing - which they usually aren't - would be completely overexposed even for moderate doses)

b] then, how do you even have a clue as to how to treat them when and if they show up at the hospital?

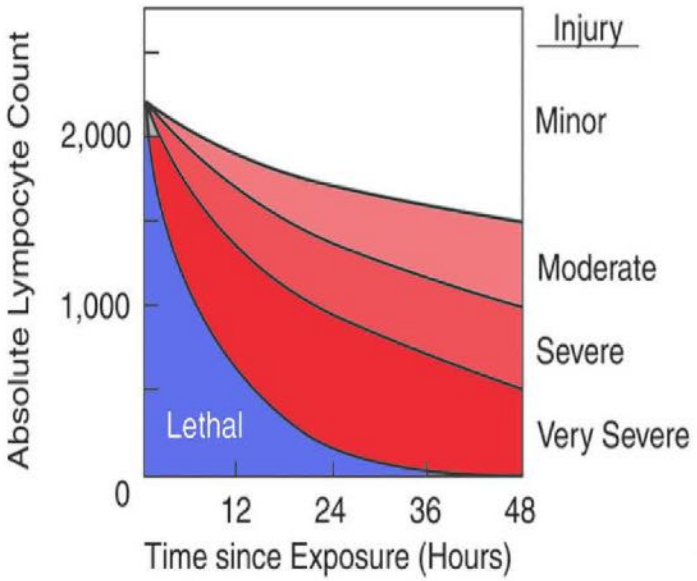
1. again, YOU DON'T...however, there *are* a few signs you can look for that might help you get a rough estimate of the exposure dose

2) The Prodromal Radiation Syndrome - a "going-into-shock"-like reaction that usually occurs soon after irradiation, and consists of both neuromuscular and gastrointestinal symptoms; unless the dose is supra-lethal, symptoms then subside, and later, symptoms of the actual syndrome begin to appear



In general, more pronounced prodromal symptoms, the earlier they occur after irradiation, and the longer they last, indicate that the dose received was higher, and more likely to be lethal, than if the symptoms were less severe and shorter lasting.

This can be used as a (very) rough estimate of the dose received for the purposes of deciding how to manage the patient.



• Effect of whole-body irradiation on absolute lymphocyte count, a useful early biologic dosimeter, particularly in cases of accidental exposure. (From Andrews G, et al: Personnel Dosimetry for Radiation Accidents. Vienna, International Atomic Energy Agency, 1965).

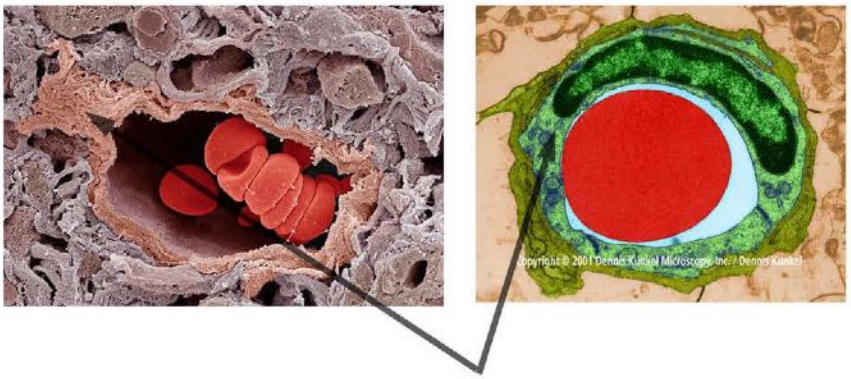
A second type of "symptom" can also be used to give a rough idea of dose: **peripheral blood lymphocyte counts**, which tend to drop very quickly after irradiation (because lymphocytes are pretty much THE most sensitive type of cell, and they die rapidly due to apoptosis)

3] The Neurovascular Syndrome (used to be called either the "cerebrovascular" or "CNS" syndrome)

a] ***this syndrome occurs for acute, whole body doses of 30 Gy or more, and causes death within minutes to a couple of days; the syndrome is caused by massive damage to the central nervous and vascular systems, leading to rapid destruction of neurons and glial cells, and often, circulatory system collapse***

b] however, we now think that these cells are not the original targets of the radiation (because they are quite radioresistant) , but rather that they die secondary to damage to small blood vessels, that start to leak after irradiation, and can then rupture

1. because of this, what usually kills the patient (and why it happens so quickly) is **brain edema**



Vascular Endothelial Cells

So what's the real "target cell"?

Probably, the single layer of cells that line the inside of blood vessels, called **vascular endothelial cells**. Without them to provide insulation, the vessels start to clog and leak and rupture, filling the brain with blood and other fluids, and effectively starving (and drowning) the actual neurons and glial cells.

c] **the neurovascular syndrome is invariably fatal** - thankfully, there are only a handful of documented cases in the medical literature

Cerebrovascular Syndrome: Case Report

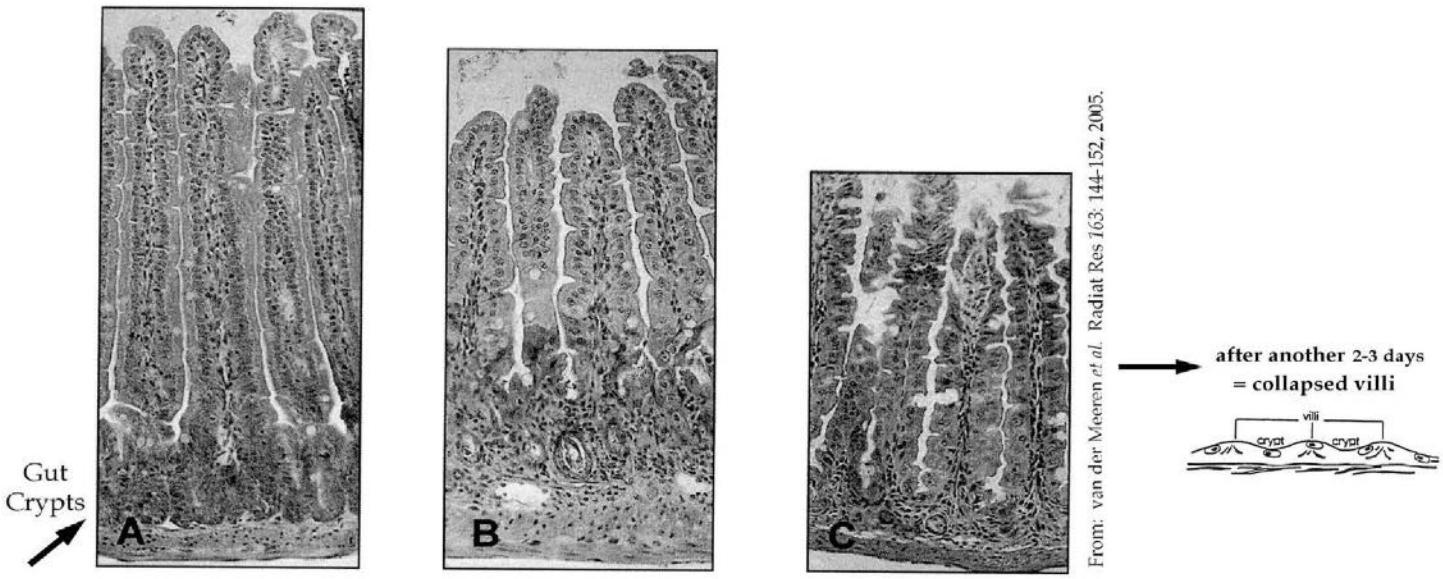
In 1964, a 38-year old man, working in a ^{235}U recovery plant, was involved in an accidental nuclear excursion. He received a total body dose estimated to be about 8800 rads, made up of 2000 rads due to neutrons and 6600 rads do to γ rays. He recalled seeing a flash, and was hurled backwards and stunned; he did not lose consciousness and was able to run to a building 200 yards away. Almost at once he complained of abdominal cramps, headache, vomited, and was incontinent of diarrheal stools which were bloody. He died 49 hours after the accident.

4) The Gastrointestinal Syndrome -

a] ***this syndrome occurs for acute, whole body doses of about 8 Gy or more, and causes death within 5-10 days after irradiation***

b] the cause of death is well understood: destruction of the lining of the GI tract with collapse of the villi, leading to malabsorption, fluid imbalance, hemorrhage and massive infection (septicemia, which is the actual cause of death in most cases)

1. as discussed previously, the cells whose deaths precipitate the syndrome (the so-called "target cells") are the crypt cells at the base of the villi, that function to supply new epithelial cells to line the villi surfaces; without these cells, there is no way to absorb nutrients, blood and fluids leak into the gut, and there is also no barrier against infection



Photomicrographs of a mouse jejunal mucosa before (Panel A), 3 days after (Panel B) or 7 days after (Panel C) a large acute dose of 15 Gy of X-rays.

medical intervention (antibiotics, transfusions, fluid replacement) may prolong life somewhat, but remember that all such patients will also develop the bone marrow syndrome; in practice, no human being has survived a whole-body, acute dose of 10 Gy

Gastrointestinal Syndrome: Case Report

1946, a 32-year old white male of 1100 to 2000 rads, total-body exposure. The man's hands received as much as 30,000 rads. The patient vomited several times withinthe first few hours of the exposure. On admission his temperature and pulse rate were slightly elevated; the remainder of his physical examinations were normal.

His general condition remained relatively good until the sixth day, when signs of several paralytic ileus developed which could only be relieved by continuous gastric suction. Within 24 hrs, 10 liters of gastric aspirate were removed.
On the seventh day, liquid stools which were guaiac-positive of occult blood were noted. The patient developed signs of circulatory collapse and died on the ninth day post-irradiation. At the time of death, jaundice and spontaneous hemorrhages were observed for the first time.

5) The Hematopoetic or Bone Marrow Syndrome

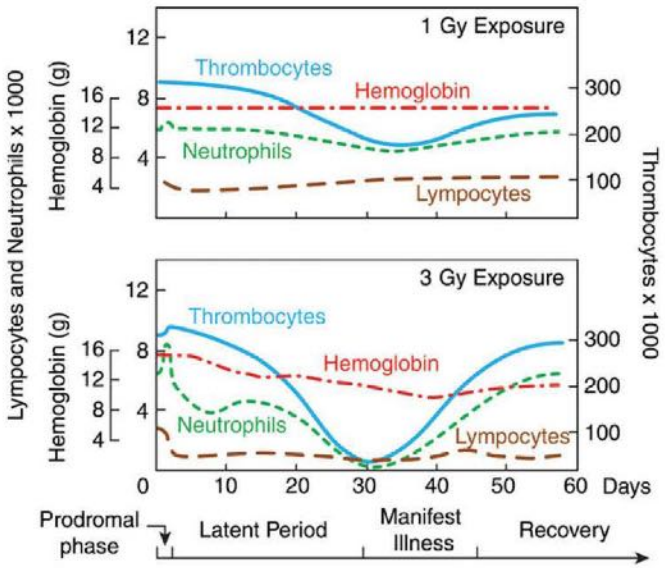
a] ***this syndrome occurs for whole body, acute radiation doses of approximately 2 Gy and above, and leads to death (in the absence of medical intervention) after about 30-60 days for humans***

b] in fact, **the human LD_{50} for ionizing radiation is estimated to be in the 3-4 Gy range (average: 3.5 Gy) and the hematopoetic syndrome is what is responsible for this**; most of this information is derived from studying victims of the Hiroshima and Nagasaki atomic bombings, other radiation accident victims, and more recently, Chernobyl accident victims

c] **the cause of the hematopoetic syndrome is radiation-induced destruction of the bone marrow that supplies all the elements of the peripheral blood** (i.e., red blood cells, white blood cells and platelets)

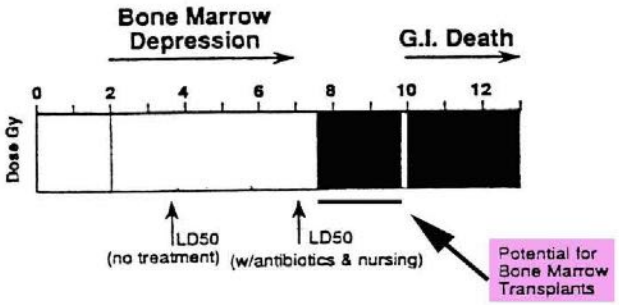
1. note that it is usually NOT the already-circulating blood cells that die (except for lymphocytes), but rather their precursors in the bone marrow...as a result, the circulating blood counts only drop relatively slowly over the 30-60 days after irradiation as they die off "naturally", but unfortunately, there are no replacements coming from the marrow

(a) ***the actual cause of the patient's death is usually either hemorrhage (no platelets = no blood clotting) and/or infection (no white blood cells = no immune sustem)***



d] the hematopoetic syndrome is unique for two reasons:

1. first, ***there is a treatment for it – bone marrow transplantation – and provided the dose the patient received is not so high as to cause them to die of the GI syndrome, it is possible to save the lives of victims who received doses up to twice the LD_{50}, or in the 7-8 Gy range, who otherwise would surely have died in the absence of intensive medical treatment***



2. **the second reason the bone marrow syndrome is unique is that medical science has actually harnessed it as a form of therapy for certain diseases, especially cancer**

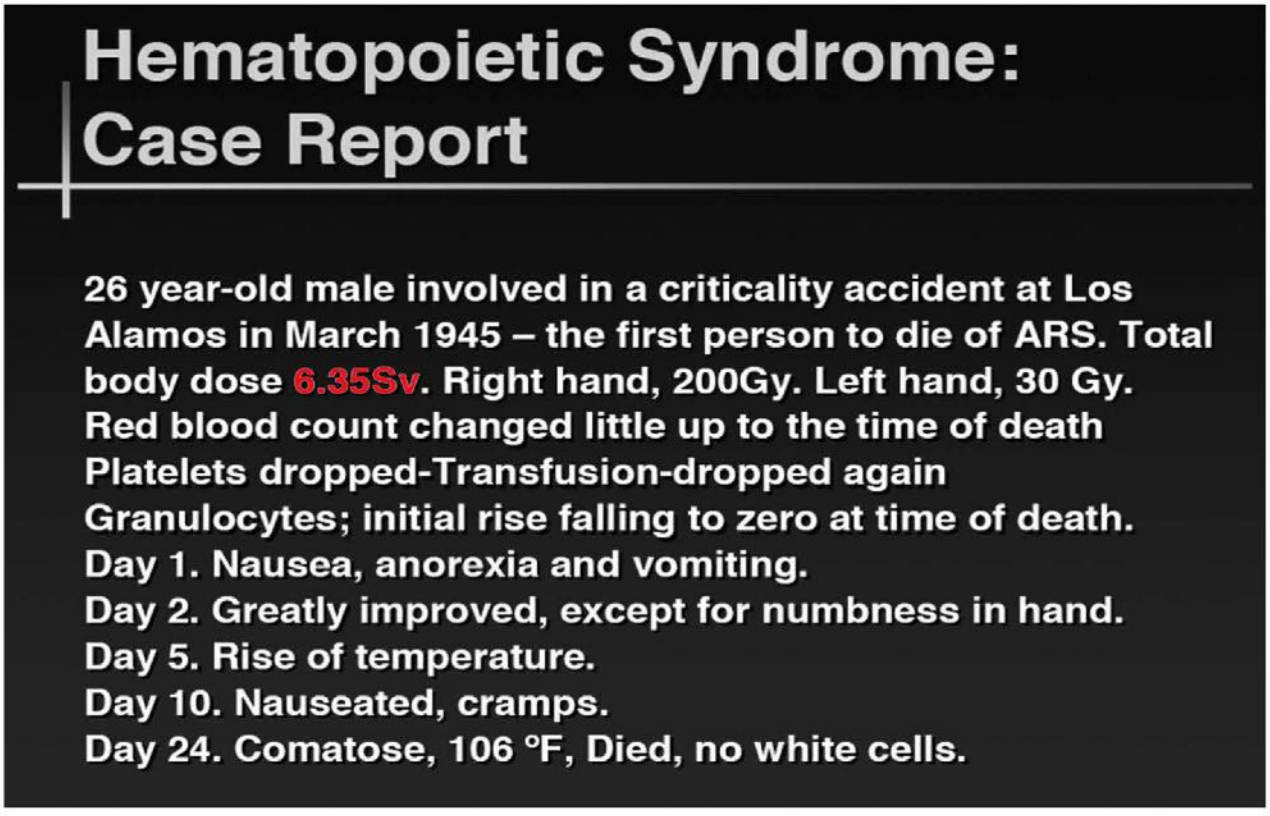
(a) for patients with leukemia or lymphoma (cancers of one or more elements of the bone marrow), certain non-malignant blood disorders (aplastic anemia, for example), and a few solid tumors that tend to metastasize to bone marrow (breast cancer, sometimes), they are deliberately given the bone marrow syndrome, followed by a bone marrow transplant several weeks later, in the hopes of totally destroying their diseased bone marrow

1} either radiation therapy (more common, and referred to as *TBI or "total body irradiation"*) or intensive chemotherapy can be used for this

2} patients receiving TBI often do get (unpleasant) symptoms of the prodromal syndrome, so one way to lessen the severity of this is to significantly reduce the dose rate of the irradiator, to split the total dose into a few fractions rather than all at once, and to split the body in half and rotate which part gets irradiated in a particular treatment session

(b) lives have obviously been saved thanks to bone marrow transplants, however the procedure is difficult and has a much higher mortality rate than most other medical procedures (as high as ~10% in the first 3 months following the transplant); this is in part because if the transplant doesn't "take", there's no other way to reliably save the patient, and also that even if the transplant does take, the bone marrow can be slow to fully grow back, leaving the patient immunocompromised and prone to potentially lethal infections

1} in addition, long term survivors of bone marrow transplants, especially those who were children at the time, can develop other problems later on, such as: cataracts, second cancers, weakened immune systems, lung fibrosis, etc.



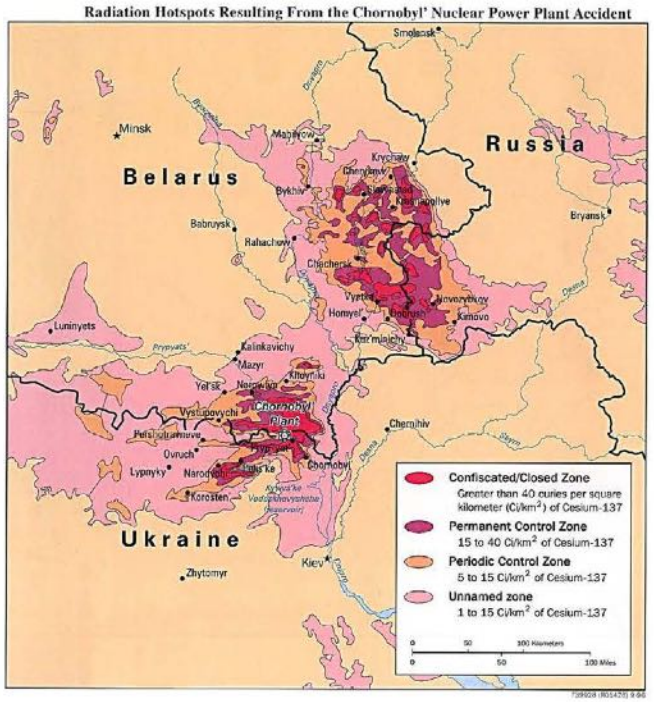
B. **How did we learn about the whole body radiation syndromes, the target cells involved, how long it took for death to occur, whether treatments were possible, etc.?**

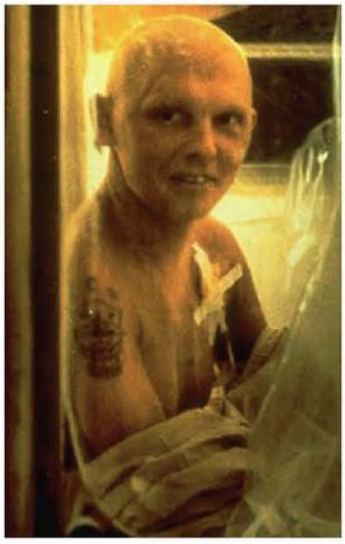
1) Answer: THE HARD WAY...by trial and error, and by carefully studying accident victims when they were available (very infrequently, and usually, in very low numbers)

The Chernobyl Accident Ukraine, 26 April 1986

- Worst accident in nuclear history
- 10 days of releases into the atmosphere under varying meteorological conditions
- Widespread and spotty fallout due to rain and changing wind directions

Medals awarded to the emergency response and site clean-up workers involved in the Chernobyl accident





Chernobyl Untoward Effects

Initial Deaths:	31
Injuries and hospitalization:	300
Emergency response in Russia:	$3 Billion
Italy compensated farmers for goods:	$500 Million
Reindeer slaughtered:	10,000
Late Effects:	Increase in Thyroid CA

- **Doses, Number, and Outcome of 134 Chernobyl Patients with Acute Radiation Sickness (ARS)**

Degree of ARS	Dose Range (Gy)	Number of Patients	Number of Short-Term Deaths	Number of Survivors
Mild (I)	0.8–2.1	41	0 (0%)	41
Moderate (II)	2.2–4.1	50	1 (2%)	49
Severe (III)	4.2–6.4	22	7 (32%)	15
Very severe (IV)	6.5–16	21	20 (95%)	1
Total	0.8–16	134	28	106

Mettler and Upton, *Medical Effects of Ionizing Radiation, Third Edition*, 2008

From: http://f40.iaea.org/worldatom/Press/Focus/Chernobyl15/liquidators.shtml

Memorial to the "Liquidators" in the village of Chernobyl which lies a few kilometres from the destroyed nuclear power plant.

Evacuation of residents under the plume was delayed by the government's unwillingness to publically acknowledge the accident. Throughout Europe many abortions of normal pregnacies were obtained out of fears of radiation from Chernobyl; studies suggest about 100 excess abortions in Italy and 400 excess abortions in Denmark in the months following the accident. Over the following years the principal observed chronic affect has been a highly significant increase in childhood thyroid cancer, affecting 700-1400 children with 10 deaths reported; these figures are far above background rates. A few excess cases of leukemia and lymphoma have occurred, although the elevation was NOT statistically significant; ***to date (35+years after the accident), a few excess solid tumors have also been noted, although again, the increase is not statistically significant***

Possibly the most profound "late effect" of the accident to date is socio-economic: hundreds of thousands of citizens suffering chronic post-traumatic stress disorder, who are unable to work, are taxing the healtcare system, and have come to be totally dependent on disability payments from the government.

Excerpts from: https://johnstonsarchive.net/nuclear/radevents/index.html

More interesting reading...a photo and video travelogue from the Chernobyl Exclusion Zone over a 15 year period by intrepid motorcyclist Elena Filatova (aka "Kid of Speed"):

https://www.kiddofspeed.com/ *(Note: offline at times)*

Summary: Acute, Whole-Body Radiation Syndromes

DOSE–EFFECT RELATION AFTER ACUTE WHOLE-BODY RADIATION FROM GAMMA RAYS OR X-RAYS.

WHOLE-BODY ABSORBED DOSE	EFFECT
0.05 Gy	No symptoms
0.15 Gy	No symptoms, but possible chromosomal aberrations in cultured peripheral-blood lymphocytes
0.5 Gy	No symptoms (minor decreases in white-cell and platelet counts in a few persons)
1 Gy	Nausea and vomiting in approximately 10 percent of patients within 48 hr after exposure
2 Gy	Nausea and vomiting in approximately 50% of persons within 24 hr, with marked decreases in white-cell and platelet counts
4 Gy	Nausea and vomiting in 90% of persons within 12 hr, and diarrhea in 10% within 8 hr; 50% mortality in the absence of medical treatment
6 Gy	100% mortality within 30 days due to bone marrow failure in the absence of medical treatment
10 Gy	Approximate dose that is survivable with the best medical therapy available
>10–30 Gy	Nausea and vomiting in all persons in less than 5 min; severe gastrointestinal damage; death likely in 2 to 3 wk in the absence of treatment
>30 Gy	Cardiovascular collapse and central nervous system damage, with death in 24 to 72 hr

From: Mettler and Voelz, New Eng J Med *346*: 1554-1561, 2003

Neurovascular Syndrome = very high doses but shortest time to death (hours to days)

Gastrointestinal Syndrome = moderate doses and death within a week or so

Bone Marrow Syndrome = lower doses with death occurring within 1-2 months

Teratogenesis: Radiation Effects on the Developing Embryo and Fetus - usually considered early effects (although you could argue either way)

A. In the minds of the general public, there is no radiation effect more feared that teratogenesis...with the possible exception of carcinogenesis; is this concern justified?

1) Yes and No

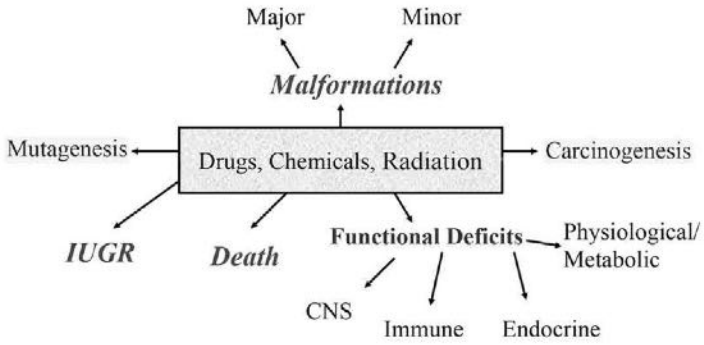
a] yes, because a measurable increase in the risk of radiation-induced birth defects can occur at *very* low doses relatively speaking (as in, around 10 cGy), **lower than for all other radiation effects**!

b] no, for two reasons: first, because we know that the risk of teratogenesis is high with ionizing radiation, we take special precautions when irradiating women of child-bearing age, e.g.,

...and second – contrary to popular belief – the natural incidence of miscarriages and birth defects, especially in woman over 35 years of age, is *much* higher than any radiation-induced excess (unless the doses are really high, in which case the mother's survival would be at risk as well)

B. How and why does teratogenesis occur?

Prenatal Exposures and Outcomes

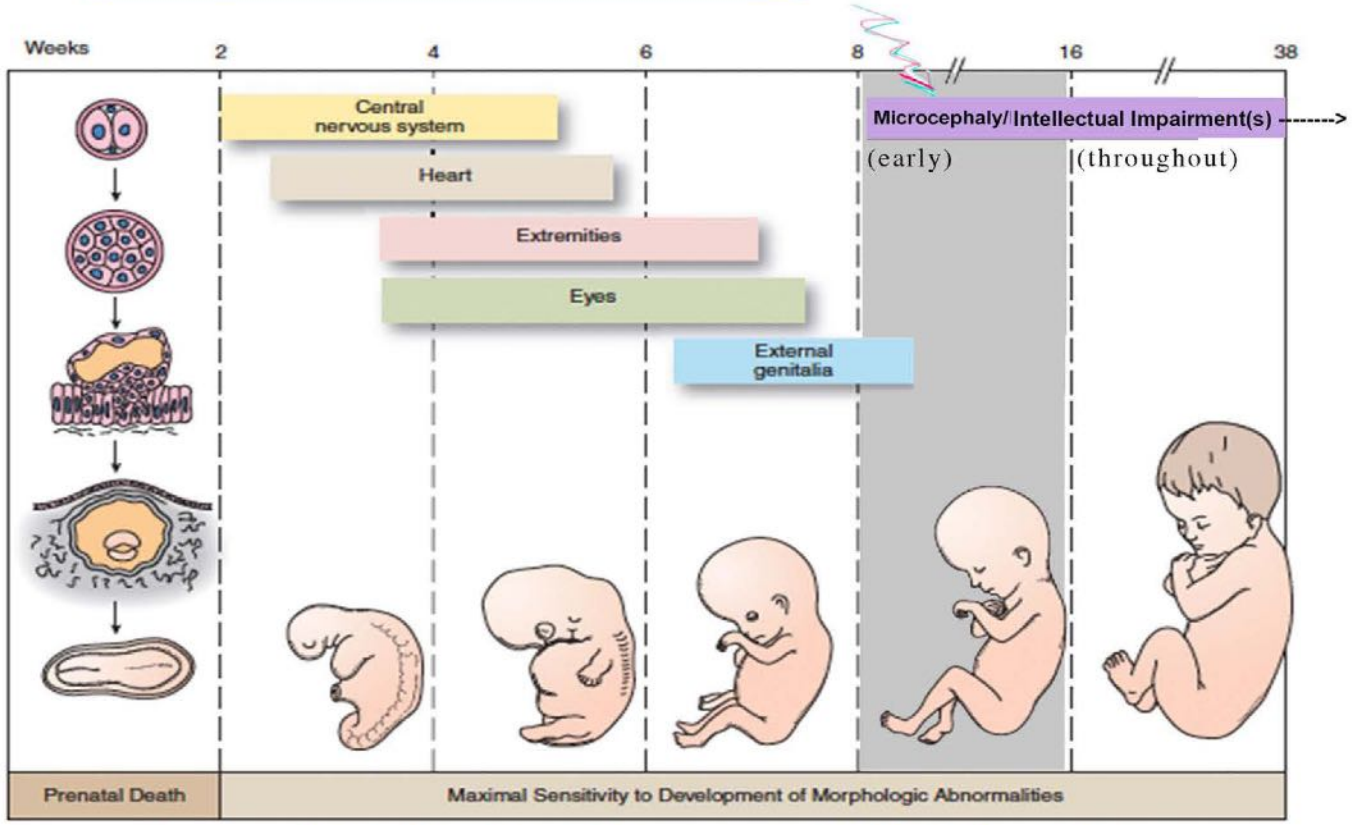


1) *teratogenesis occurs when a toxin ("teratogen"), such as, but not necessarily limited to, ionizing radiation, kills cells of the embryo right during the time when those cells are either in the process of developing specific body parts (early in gestation), or, when they are expanding their numbers as the fetus grows in size (later in gestation)*

a] as such, the exact time of irradiation relative to embryonic development critically determines what type of defect occurs (if any, because this is still a random process)

2) the principle effects of a teratogen on the developing embryo or fetus fall into 3 general categories:

- embryonic, fetal or neonatal death
- congenital malformations (includes intellectual effects)
- generalized growth retardation ("stunting" of growth) – *less common in humans than in laboratory animals*
- carcinogenesis (either in childhood or later in life)



Sensitivity of specific organs to teratogenic agents at critical stages of human embryogenesis. Exposure to adverse influences in the preimplantation and early postimplantation stages of development (*far left*) leads to prenatal death. Periods of maximal sensitivity to teratogens (*horizontal bars*) vary for different organ systems but overall are limited to the first 8 weeks of pregnancy.

a] general trends:

- exposure during the pre- and immediately post-implantation stage, the first 2 weeks of gestation, leads to embryonic death and miscarriage (in many cases, the woman might not have even known she was pregnant)

Important Note:

Sensitivity to radiation-induced intellectual impairments persists into early/mid childhood, which has serious implications for radiation therapy of brain tumors in young children

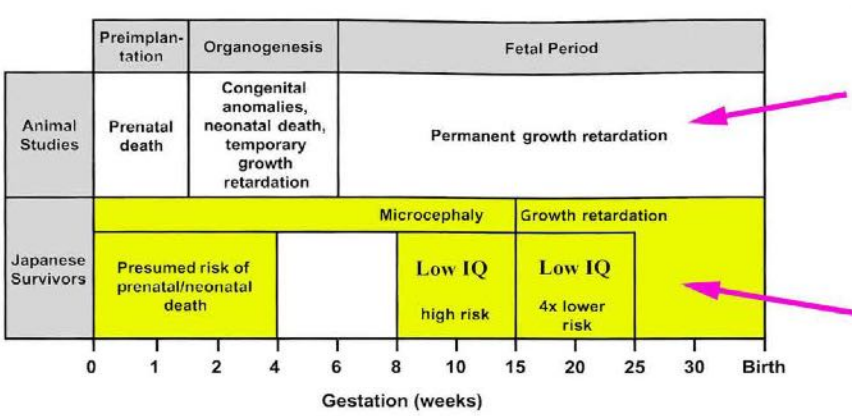
- exposure during the organogenesis period, generally from the 3rd to 8th week of gestation in humans, can lead to congenital malformations, some miscarriages, and later, stillbirths
- exposure during the fetal period – from about 8 weeks of gestation onward until birth – can cause damage to the nervous system, leading to intellectual impairments (low IQ, memory difficulties, reduced academic performance, etc.), microcephaly (small head size), and generalized stunting of growth.

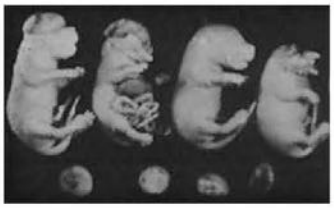
Microcephaly is more common for irradiation early in the fetal period, stunting of growth more common toward the end, and intellectual impairments throughout.

b] ***in practice however, the only teratogenic effects <u>significantly</u> elevated in humans who were irradiated in utero are microcephaly and intellectual impairment (especially, low IQ)***

(1) this does not mean that there are *no* cases of other congenital defects (because there are), only that these tend to be anecdotal in nature and not statistically significant

(2) the full gamut of radiation-induced gross congenital malformations has been studied in laboratory animals however, where the irradiations, and the pregnancies, can be carefully monitored and manipulated





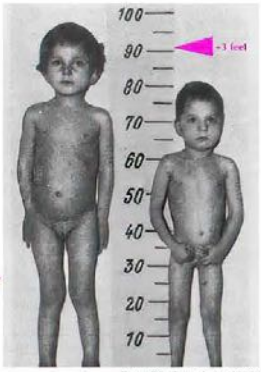


Chart illustrating the similarities and differences between teratogenesis findings from rodent studies versus for humans

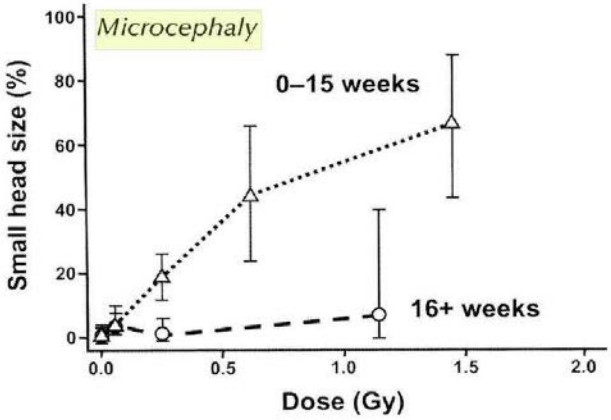
Illustration of growth retardation (and maybe slight microcephaly) in the child on the right, whose mother received ~4 Gy to the abdominal surface during the 14th week of gestation, compared to a normal child of the same age on the left

c] based on studies of survivors of the Hiroshima and Nagasaki bombings who were pregnant at the time, we have been able to conclude the following about radiation-induced teratogenesis in humans:

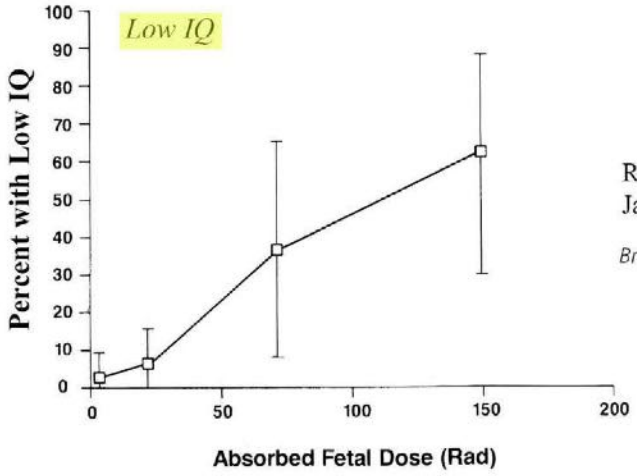
(1) air doses as low as **10-20 cGy**, corresponding to a direct fetal dose of about half that, can cause a measurable increase in microcephaly

(2) **for low IQ, the risk is highest during the 8-15th week of gestation** (the early fetal period), **and corresponds to an approximately 40% risk per Gy** (for x- and γ-rays)

(3) **at 16-25 weeks of gestation, the risk for is still elevated–a 10% risk per Gy**



Proportion of exposed individuals with small head sizes as a function of dose and gestational age. (Redrawn from the data of Otake M, Schull WJ: Radiation-related small head size among prenatally exposed A-bomb survivors. *Int J of Radiat Biol* 63:255–270, 1993.)



Risk of below normal IQ as a function of fetal dose for the Japanese A-bomb survivors who were irradiated *in utero*.

Br J Radiol 57:409–414,1984

3) another possible problem associated with irradiation during gestation: CARCINOGENESIS

a] several careful studies of large numbers of people have been conducted that seem to indicate that *diagnostic* radiation exposure during gestation is associated with an increased risk of childhood cancer, specifically, leukemia

b] on the other hand, studies of the Japanese A-bomb survivors that had been irradiated *in utero* with higher doses did **not** reveal an excess cancer risk in childhood...however they did show an elevated cancer risk much later in life (as they approached old age, when most people get cancer anyway)

c] in order to help resolve these conflicting findings, we err on the side of caution in terms of radiation protection, and assume that irradiated embryos and fetuses *are* at increased risk of developing cancer at some time in their lives, by approximately a factor of 1.5 - 2.0

4) **Radiotherapy during Pregnancy** - how big a problem is this?

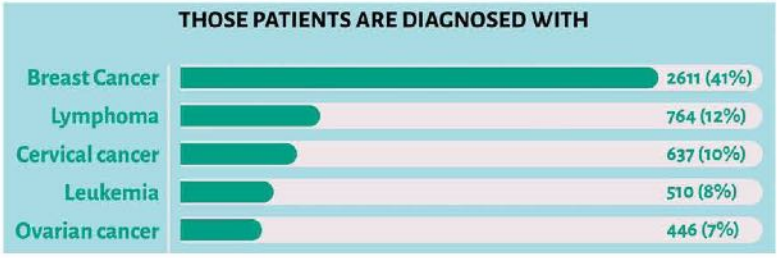
a] Answer: quite rare...but it can happen

1. *about one out of every thousand pregnant women is diagnosed with cancer, with breast cancer being the most likely (although note that two GYN cancers - cervical and ovarian - are also in the top five)*

CANCER DURING PREGNANCY

1/1000

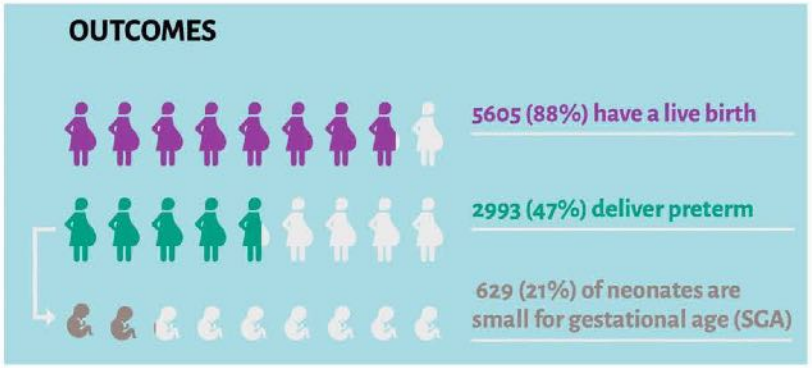
patients who are pregnant are diagnosed with cancer, an estimated 6,369 cases per year



b] Do pregnant women opt to treat their cancers, despite possible risks to the embryo or fetus (not to mention themselves)?

1. about two-thirds do, however **radiotherapy is only used if absolutely necessary**

c] What about pregnancy outcomes in treated patients?



- About 90% of treated patients have live births, although almost half deliver pre-term
- About 20% of the newborns are small for their gestational ages, but usually catch up to their peers by adolescence
- Almost no reports of teratogenic effects other than low birth weight, possibly because radiotherapy is seldom used and that doses would be very low regardless, except in the case of GYN cancers

d] But what if it *is* a GYN cancer and radiotherapy would be indicated? Should the pregnancy be terminated?

1. Given the highly personal and politically-charged nature of abortion, a radiation oncologist obviously can't tell a woman what to do about her pregnancy...

...however a reasonable rule of thumb is that if the embryo or fetus - especially during the most sensitive period of gestation - is expected to receive ≥10 cGy, it is appropriate for the physician to discuss possible risks and options with the patient (including therapeutic abortion)

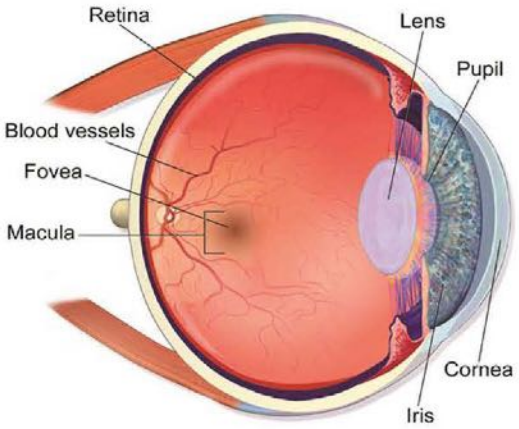
(a) please note that *this cut-off dose of 10 cGy would correspond to, at most, about a 4% excess risk of teratogenesis, which, depending on how you look at it, might not be considered all that high (i.e., about 1 chance in 25), especially when considering that the spontaneous risk of a congenital malformation is already at least 2%*

Radiation-Induced Cataracts - a unique type of late effect, recently with changing science and changing safety standards

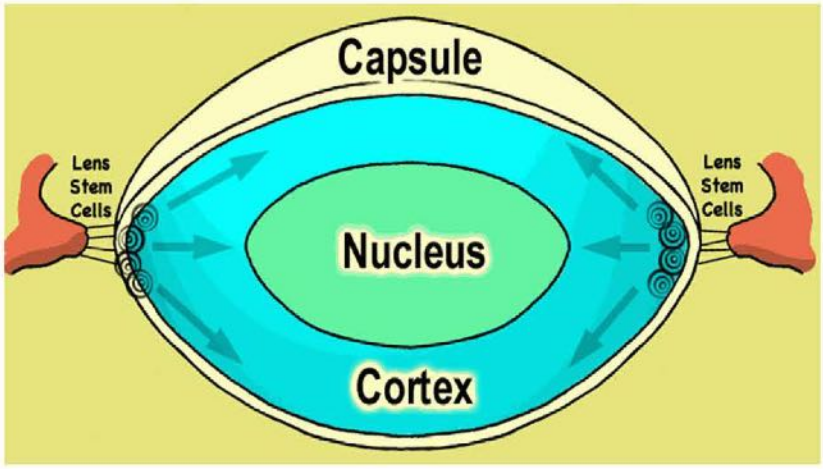
A. Cataracts are unique as radiation late effects are concerned, so if you can keep track of the handful of unique features, you should be able to answer any standardized test questions on the subject

1. **Unique Feature #1**: while the epithelial cells that make up the lens of the eye are skin-like in many respects (a hierarchical tissue with an anatomically defined stem cell compartment), ***there is no mechanism of cell loss, so damaged lens fibers are retained rather than gradually eliminated***

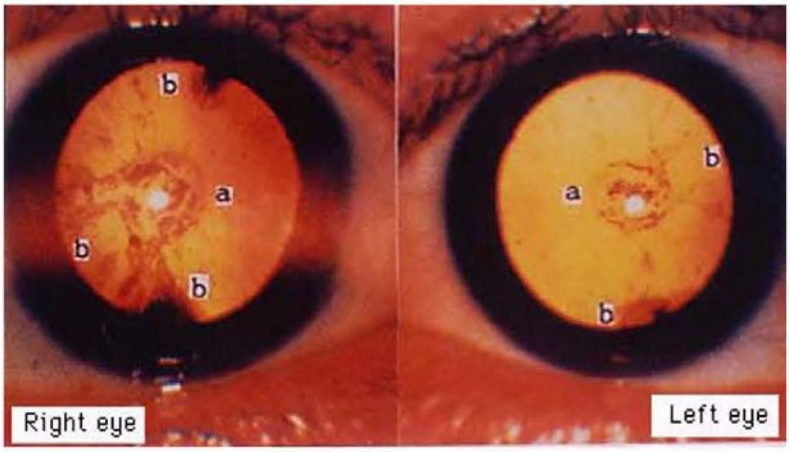
a. this explains why cataracts are permanent rather than temporary, however luckily, they can be corrected surgically



Eye Anatomy



2. **Unique Feature #2**: radiation-induced cataracts are unique in that ***they CAN be distinguished from "regular", age-related cataracts***; they are the only radiation effect (to date, anyway), where this is possible



a: A-bomb cataract
b: Senile cataract

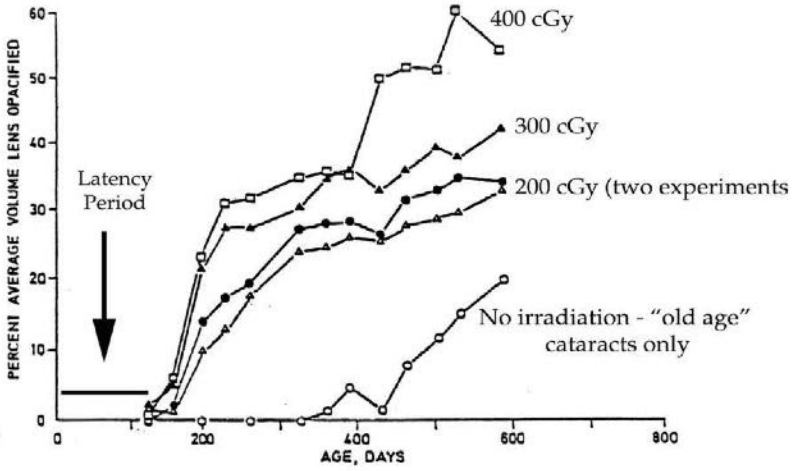
Ionizing radiation-induced cataracts tend to be more toward the deep, central part of the lens, whereas age-related cataracts tend to be more superficial and marginal

3. **Unique Feature #3**: ***cataracts show a threshold radiation dose response***, i.e., there is a dose below which no cataracts occur, and for doses above the threshold, both the frequency and severity of the cataract increase with increasing dose

Mice irradiated soon after birth with single X-ray doses of 2, 3 or 4 Gy begin to develop cataracts a few months later.

The higher the dose, the more severe the cataract.

Age-related cataracts not associated with irradiation don't begin to develop until the mice are over a year old.



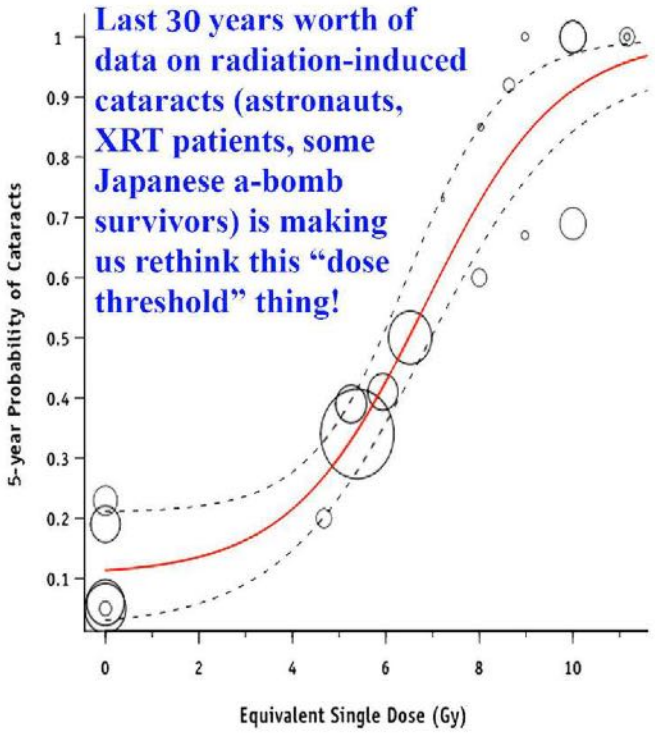
The severity of radiation cataracts formed in mice after irradiation with different doses of X-rays:

a. ***radiation effects that show a threshold dose response are termed "non-stochastic", "deterministic" and/or "tissue reactions"***; other radiation effects that are deterministic include most of the other early and late effects that occur during and after radiotherapy

(1) meanwhile, effects that do *not* show a dose threshold (i.e., there is always some risk of the effect, no matter how small the dose) and do *not* vary in severity (i.e., they either "are" or "aren't", with no middle ground) are called **stochastic effects**; examples include cell killing, mutation induction and carcinogenesis

b. ***So what is the dose threshold for cataracts?*** Answer: the historical values – based on lab animals and Japanese a-bomb survivors receiving high doses – have been updated recently, as new data from astronauts, radiation accident victims, radiotherapy patients and a-bomb survivors who only received small doses have been added

Threshold dose of 500 mSv



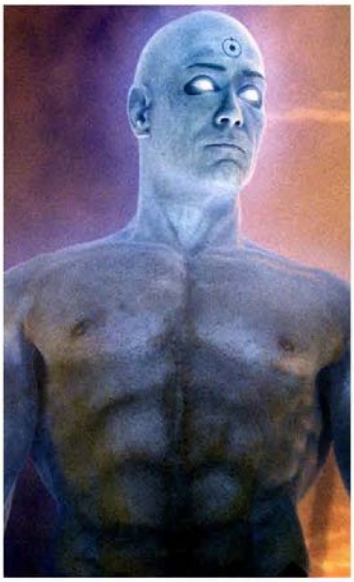
Note: The dose thresholds quoted here apply to ANY cataract (no matter how small and mild) and not necessarily the clinically significant ones that affect vision. ***To cause a symptomatic cataract, higher doses are required. That explains why the $TD_{5/5}$ for cataracts is more like 10 Gy (and not 0.5 Gy).***

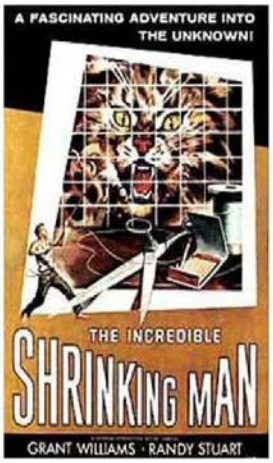
4. **Unique Feature #4**: ***the latency period for radiation-induced cataracts is variable***; for moderate doses (1- 6 Sv), the latency period before the clinical detection of a cataract is typically in the 7-10 year range, but for higher total doses (over ~7 Sv), the latency period can be less than 5 years

Genetic Effects of Ionizing Radiation - considered late effects because the damage appears in the *offspring* of irradiated parents (whose germ cells suffered mutations)

A. Great Truths of Radiation Genetics!

1) ***There is absolutely nothing unique or different about the genetic changes produced by ionizing radiation...it simply increases the frequency of the same types of mutations that already occur naturally***





Not. Gonna. Happen.

a] ***In fact, the spontaneous incidence of most of these mutations is MUCH higher than any increase attributable to radiation exposure*** (in other words, in the grand scheme of things, radiation is *not* a particularly potent mutagen)

1. this is no small part of the reason why it is practically impossible to prove (scientifically or legally) that a certain effect in a certain individual was caused by a prior radiation exposure

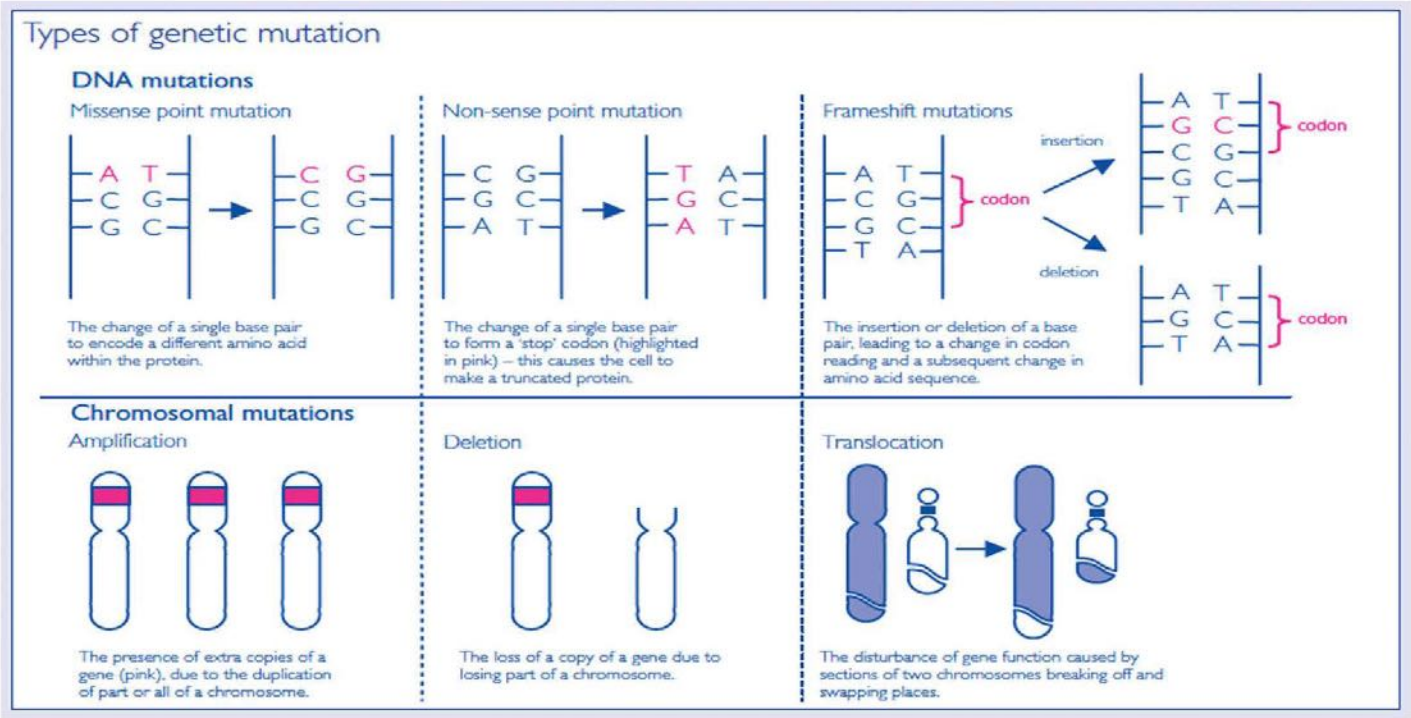
2) ***If they're so hard to quantify, especially at low radiation doses, and especially in human populations, why study radiation-induced mutations at all?***

a] **first, it is clear that one of, if not *the*, earliest event that starts off the process of carcinogenesis is mutations in cellular DNA...so it follows that if we study radiation-induced mutations, we can also learn something about radiation-induced cancers**

b} **a second reason to study mutations caused by radiation is for risk assessment and radiation protection of the public; especially important is an understanding of the shape of the dose response curve for mutation induction, and also, what happens at the very low doses that everybody is exposed to** (and the somewhat higher doses radiation workers are exposed to)

B. Gene Mutations Caused by Radiation

1) What do we mean by "mutation" anyway????



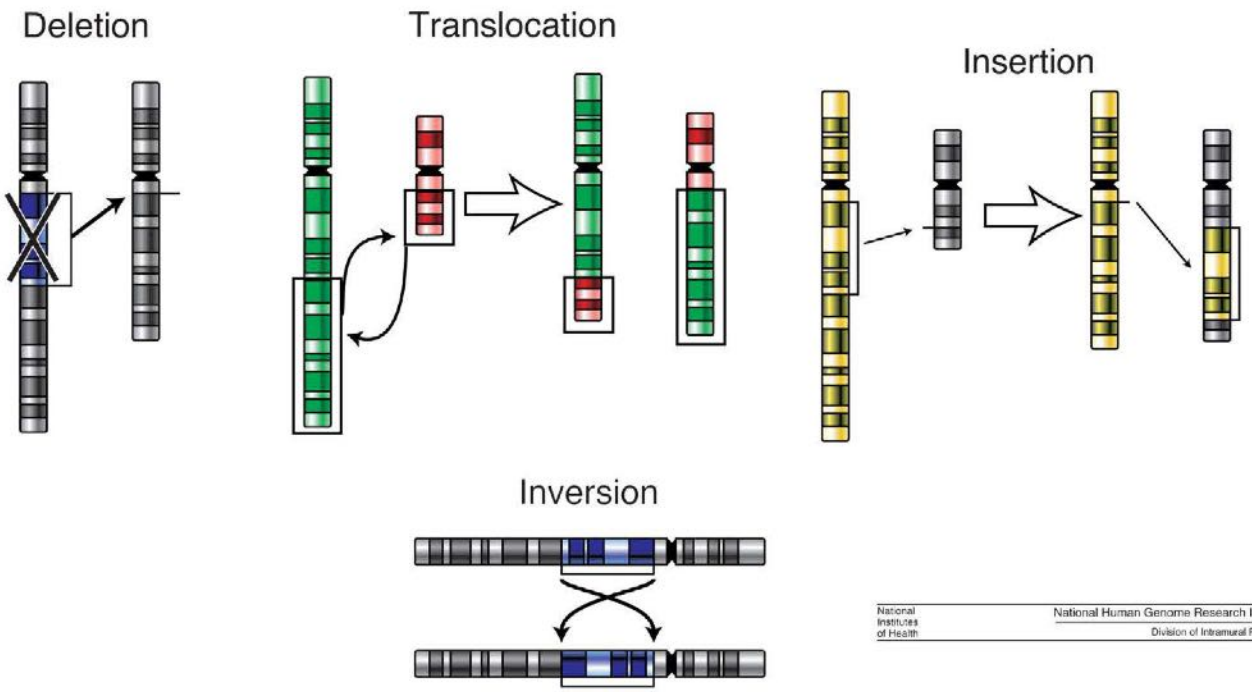
Small Mutations: result from the substitution, insertion or deletion of one or a few DNA bases; this has the net effect of changing the "reading frame" of the gene, and ultimately, the production of a defective (or absent) protein

- many carcinogenic chemicals - including a lot of chemotherapy agents - UV radiation, and ionizing radiation can produce these

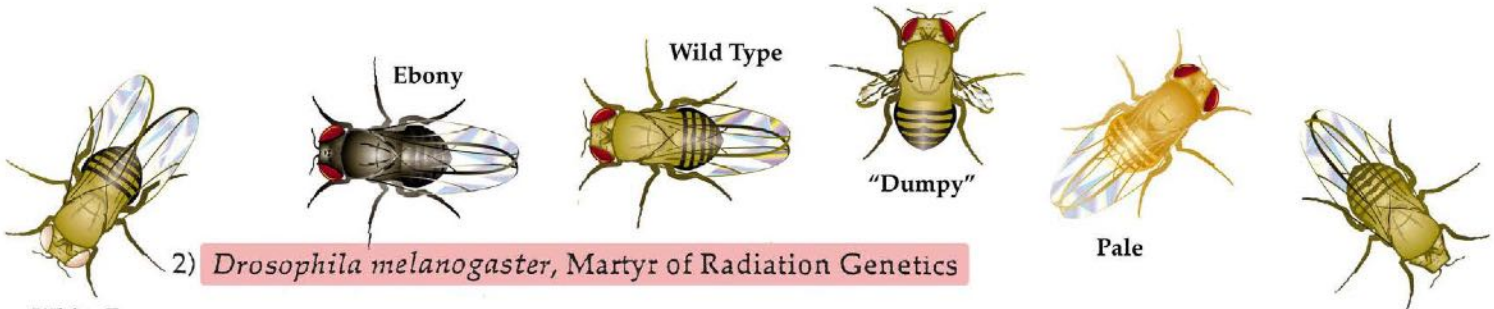
Big or small however, the effects of these mutations can range from none at all to completely catastrophic!

Large Mutations: result from the insertion, deletion, duplication or rearrangement of large chucks of chromosomes that likely contain dozens of genes or more; this can have the net effect of either activating or inactivating one or several genes, or producing "hybrid" genes that go on to produce weird proteins that don't exist under normal conditions...some of which are inactive and others overactive

- this is ionizing radiation's main claim to fame, and explains why it is both a toxin *and* a carcinogen



Large-Scale Mutations Commonly Produced by Ionizing Radiation

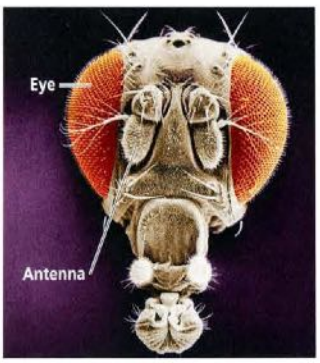


2) *Drosophila melanogaster*, Martyr of Radiation Genetics

a. fruit flies served as an excellent system for the study of genetics in general, and radiation genetics in particular for a number of reasons:

readily observable mutations
huge numbers of "subjects" for study
short overall lifespans
ability to control breeding patterns

http://www.ergito.com



Normal

Legs instead of Antennae

Eyeball on Leg

Double Thorax

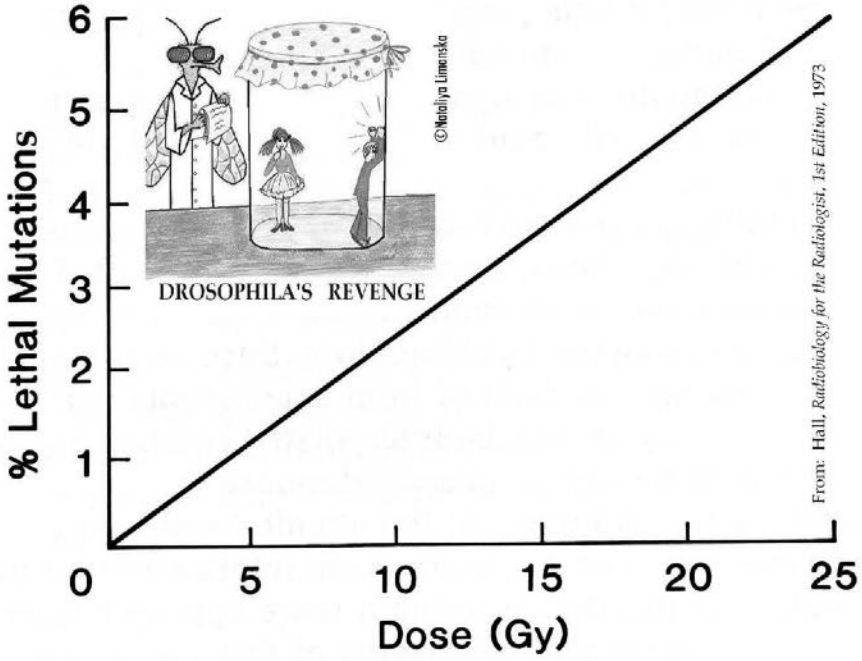
b. What did we learn from studies of mutations in fruit flies (most work done in the 1920's and 1930's)?

the dose it took to double the spontaneous incidence of a particular mutation was estimated to be between about 0.05 - 2.0 Sv

this is called the *genetic doubling dose*

there was NO difference in mutation rate if the dose was delivered all at once versus fractionated over time, that is, there was *NO DOSE RATE EFFECT*

(That 0.05 Sv - 50 mSv - is where our maximum exposure limit as radiation workers originally came from)

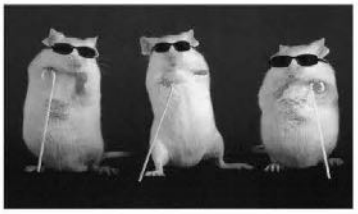


All well and good...BUT...to what extent were data derived from insects applicable to the human situation?

3) The Megamouse Project: conducted by Russell and Russell of the Oak Ridge National Lab during the 1950's and 1960's (7 million mice evaluated!)

a. in the mouse studies, several different autosomal traits (such as hair color and ear structure) were used

b. endpoints assessed:



- mutation frequencies for the different traits
- gender differences in mutation rates
- changes in mutation frequency as a function of dose fractionation
- changes in mutation frequency for low versus high LET radiation

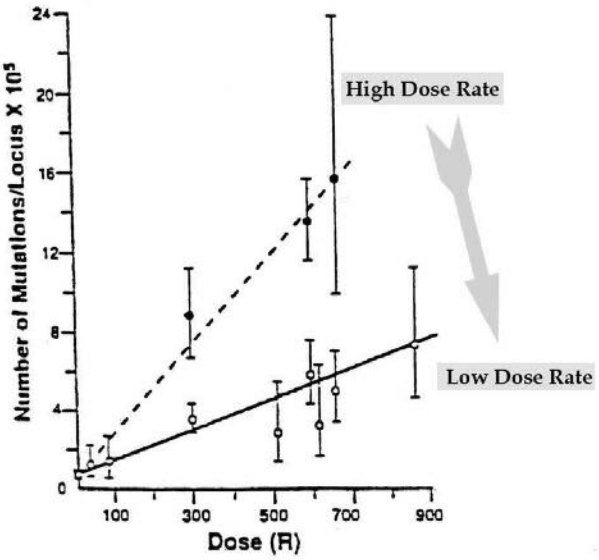
c. the important conclusions of these studies were:

1] **there was a 20-fold difference in the mutation frequencies for the 7 different traits studied, and the frequency of mutations increased linearly as a function of dose with no indication of a dose threshhold**

2] unlike the case of the fruit fly, there WAS a large dose rate effect; on average, **the frequency of radiation-induced mutations was at least a factor of 3 lower when the dose was fractionated or protracted rather than given as a large single dose...**

3] **genetic doubling dose for mice ~1-2 Sv**

GOOD NEWS for (human) radiation protection purposes!



Mutation frequency in mouse spermatogonia as a function of X-ray dose given at either a high or low dose rate.

Redrawn from Hall and Giaccia, Radiobiology for the Radiologist, 6th Edition, 2006.

In other words, the mouse was almost 10X more sensitive to radiation-induced mutations than the fruit fly, however the mammal DID show a dose rate effect (lessening biological effect as the total dose is protracted), while the insect did not. This has profound implications for radiation safety!

4) **The Human Experience** : about 30,000 children were born to survivors of the Hiroshima and Nagasaki atomic bombings (note that these children were NOT exposed *in utero)*

a. these children were assessed for indicators of genetic damage:

Doubling Dose (Gametic) in the Offspring of Survivors of the A-bomb Attacks on Hiroshima and Nagasaki

GENETIC INDICATOR	DOUBLING DOSE (REMS)*
Untoward pregnancy outcome	69
Childhood mortality	147
Sex chromosome aneuploidy	252
Simple average	156

**Divide by 100 to obtain doubling dose in sievert.*
(From Schull WJ, Otake M, Neal JV: Science 213:1220–1227, 1981)

Assumed to be the approximate genetic doubling dose for humans =

1.5 Sv.

(This is a frequent question on certification exams.)

Summary of Findings on Radiation-Induced Mutations with Relevence to Human Radiation Protection:

1. Mutation induction is a stochastic effect, that is, the risk of excess radiation-induced mutations rises linearly with dose, and with no evidence of a dose threshold.

2. The genetic doubling dose for humans has been estimated as approximately 1.5 Sv.

3. That being said, the mutation rate drops significantly if the radiation is delivered in increments over time, as opposed to all at once.

This is all useful information to know, but it still doesn't quite answer the $64,000 question, namely, is the dose response relationship for radiation-induced mutations the same as for radiation-induced carcinogenesis?

Answer: We do know that cancer formation requires mutations in cellular DNA, but usually more than one of them, and also, the different mutations are thought to react in complex ways with each other, meaning that ***we can't be absolutely sure that just because the dose response curve for mutations is linear with no threshold, the same will hold true for carcinogenesis!***

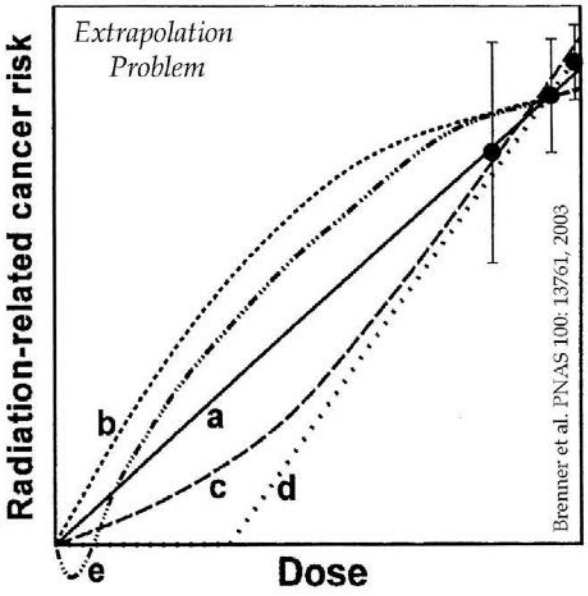
This is why it is even more important to study radiation-induced cancers in humans...unfortunately there are assorted "logistical" problems in doing so:

Problem #1 : There are not vast numbers of humans whohave been irradiated, meaning that detecting a small excess of cancer cases will be difficult statistically. This situation is made worse by the fact that cancer is quite common "naturally". ("*Data sensitivity issue*")

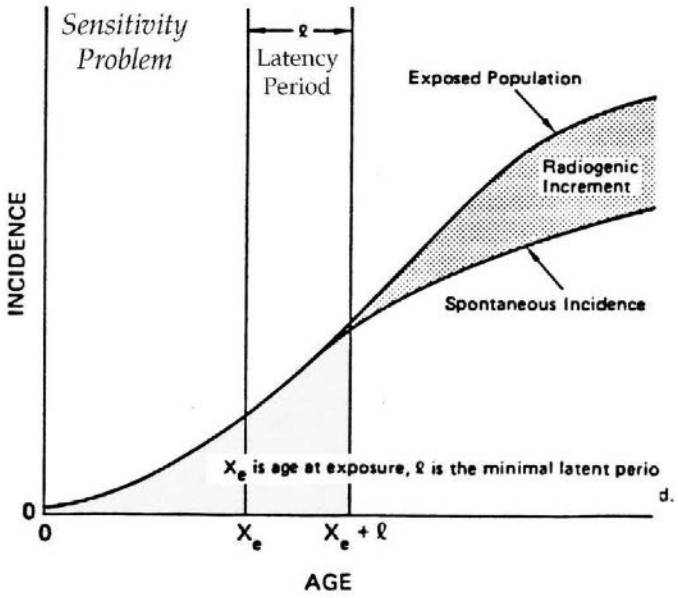
Problem #2 : Of the human populations that have been irradiated, most have received relatively high doses (more than about 50 cGy...because of bombings and accidents and such), and mostly, these doses have been delivered all at once. Unfortunately, what we really want to know in terms of radiation saftety is what happens when a population is exposed to very small doses over extended periods of time. ("*Data extrapolation issue*")

Problem #3 : Most radiation-induced cancers take at least years, if not decades, to develop, meaning that there will be no quick answers to what we want to know...plus it will cost tons of money to do the actual studies. ("*Latency period issue*")

Problem #4 : Human populations are much more variable in their responses to radiation (and most other things as well) when compared to cells, fruit flies, laboratory rodents, etc., meaning that the data that is obtained will be "scattered", and may be hard to interpret ("*Heterogeneity issue*")



Schematic representation of different possible extrapolations of measured radiation risks down to very low doses, all of which could, in principle, be consistent with higher-dose epidemiological data. Curve a, linear extrapolation; curve b, downwardly curving (decreasing slope); curve c, upwardly curving (increasing slope); curve d, threshold; curve e, hormetic.



Superimposition of radiogenic effect on spontaneous incidence.

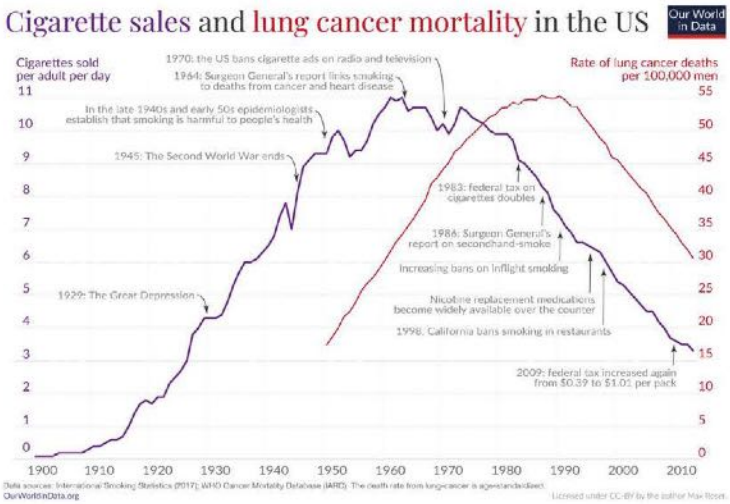
Carcinogenesis in Irradiated Human Populations - usually the latest of all late effects, and the one of most concern for human radiation safety purposes

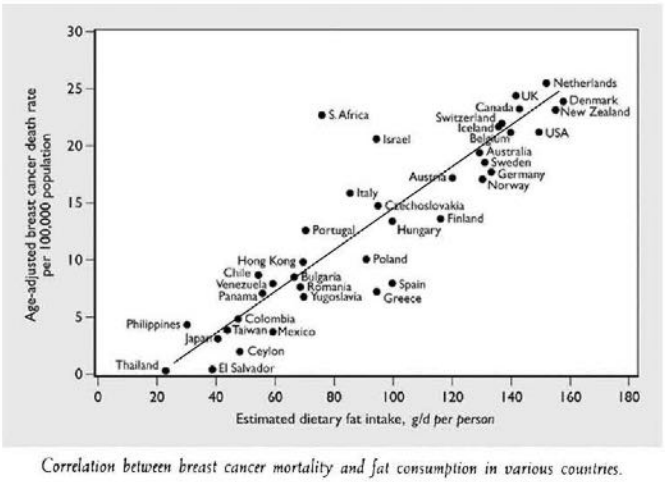
A. How is carcinogenesis (radiation-induced or otherwise) studied in humans?

1] the scientific discipline used to study carcinogenesis is called **epidemiology** (Def: *"the study of factors associated with, or controlling, the presence or absence of a disease in a human population"*)

a) please note that epidemiology does not absolutely "prove" causation, only that an association exists that may or may not *imply* causation

1. this "association-but-not-proof" concept is important (at least historically) becasue it provides an "out" for corporations that deal in carcinogens (cigarette and pesticide industries, for example)





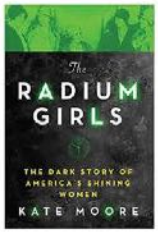
Correlation between breast cancer mortality and fat consumption in various countries.

B. Radiation Carcinogenesis: The Human Experience

1. the human populations that have been studied long-term for cancer incidence following exposure to ionizing radiation generally fall into four main categories:

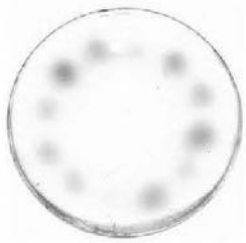
Source of Exposure	Details of Exposure	Cancer Sites and Types
Nuclear Weapons-Related		
Japanese A-bomb survivors (and their children and grandchildren); *1945*	Prompt radiation from blasts (γ-rays and neutrons), plus fallout (mostly β); up to ~6 Gy total dose	Leukemia and most types of solid tumors
Polynesian Islanders; *1954*	Fallout from US weapons tests (mostly radioiodine)	Thyroid
Diagnostic Imaging Procedures		
Multiple fluoroscopies; in the US and Canada; *1930's – 1950's*	To monitor lung status in TB patients (X-rays); up to several Gy over extended periods	Breast
Thorotrast (nuclear medicine); *1930's – 1950's*	Contrast agent for limb and liver angiography (4-5Gy of α's)	Liver
Imaging of "high-risk" (or not) pregnancies resulting in prenatal exposure; *1940's – 1950's*	Repeat adominal/pelvic diagnostic X-rays	Leukemia in resulting offspring, usually during childhood
Therapeutic Procedures		
Postpartum mastitis; *1940's – 1950's*	X-ray doses (1-6 Gy total) to lactating breasts	Breast
Ankylosing spondylitis; *1930's – 1950's*	Up to 30 Gy X-rays to spine (and bone marrow) for relief of pain and stiffness	Leukemia and a few solid tumors (including thyroid and sarcomas)
Treatment for enlarged thymus or hemangiomas at birth; epilation for treatment of tinea capitis; *1940's – 1950's*	A few Gy of X-rays	Thyroid and a few other tumor types (including sarcomas, gliomas, leukemia and lymphoma)
Long-term survivors of radiation therapy; *mostly since the 1970's*	Up to 100 Gy external beam X-rays and/or brachytherapy	Especially leukemia, breast and sarcomas, and maybe lung (and a few others too)

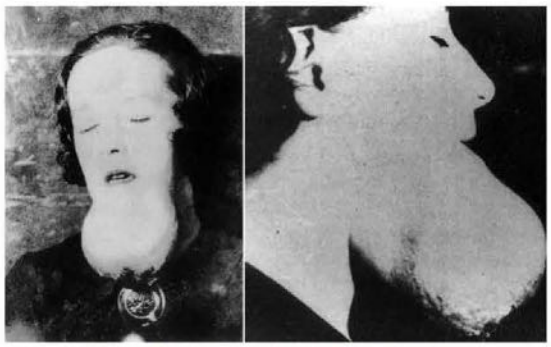
Source of Exposure	Details of Exposure	Cancer Sites and Types
Occupation-Related		
Radiology professionals (prior to modern radiation protection standards); *1920's – mid-1950's*	Unknown doses of X-rays protracted over long periods	Leukemia and so-called "non-specific life shortening", most likely a consequence of cancer (so it really isn't "non-specific")
Miners; *up to the present day*	Exposure to uranium, radium and mostly, radon gas deep underground (mostly α-emitters)	Lung
Watch dial painters; *1910's - 1930*	Ingestion of radium-based paints used for luminous watch dials; bone doses as high as 500 Gy from α-emitters	Bone sarcomas, especially of the head and neck
General public living in vicinity of the Chernobyl nuclear power plant at the time of the accident (mostly from Belarus and Ukraine)	Exposed to fallout after the reactor explosion, especially radioactive iodine; other than to the thyroid, exposures above background but otherwise pretty low (worst case: about 1 cGy)	Large excess of thyroid cancer among children living in the immediate area in the decade following the accident; where possible, others being monitored for the appearance of excess solid tumors



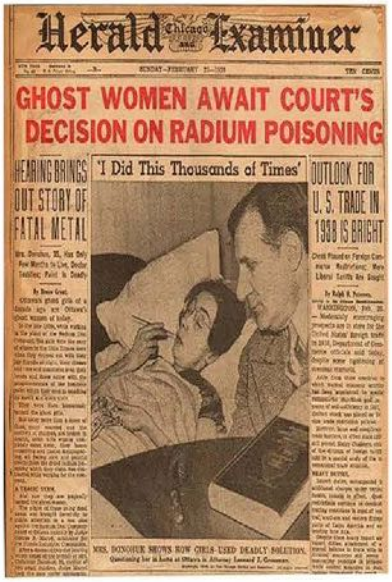
The Sad Story of the Radium Dial Painters

It was not long before the "wonder" of radium was exploited commercially. It was considered trés chic to own a radium-enhanced luminous watch for example. Unfortunately, workers (predominantly women) in the radium dial factories often paid the ultimate price in support of this latest fashion trend...





Front and side views of a dial painter with a radium-induced sarcoma of the chin.
Collection of Ross Mullner



2. some of the general findings of the human radiation carcinogenesis studies:

a. **radiation carcinogenesis was found to be a stochastic effect,** i.e., you either get cancer or you don't ("all or nothing" effect), **and that there is apparently no threshold dose** (that is, a dose below which there isn't *some* cancer risk)

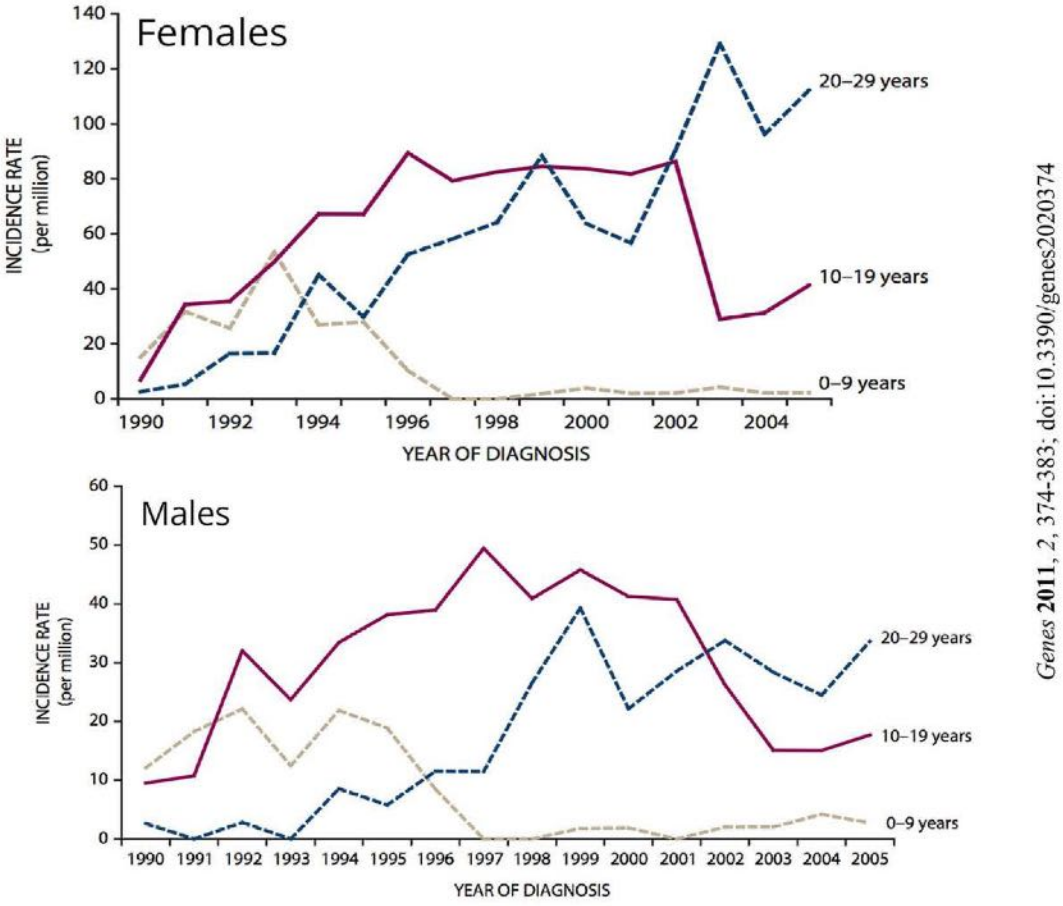
b. **the shapes of the dose response curves for the induction of cancer as a function of radiation dose appear to be either linear, linear-quadratic, or sometimes, "bell-shaped"** (the latter mostly observed in animal studies)

c. **for low LET radiation, the risk of carcinogenesis is lower if the dose is fractionated or protracted over time, that is, that there *is* a dose rate effect**

d. **for a given dose, high LET radiation is more carcinogenic than low LET radiation**

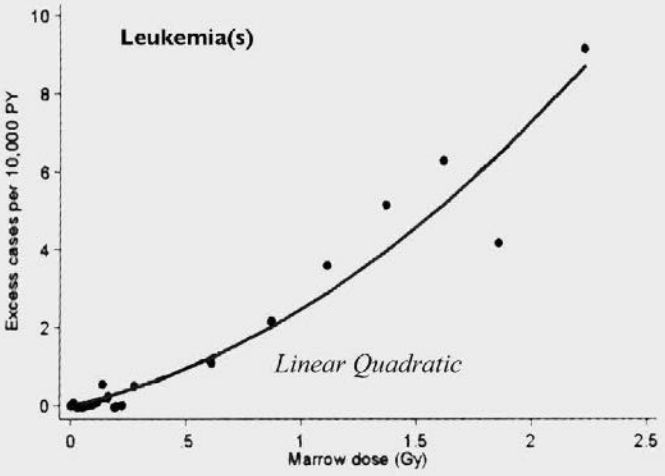
3. OK, let's look at some of the actual data that was used to reach the above conclusions (its limitations should become obvious...):

Thyroid cancer incidence rates for different age groups of the total Belarusian population



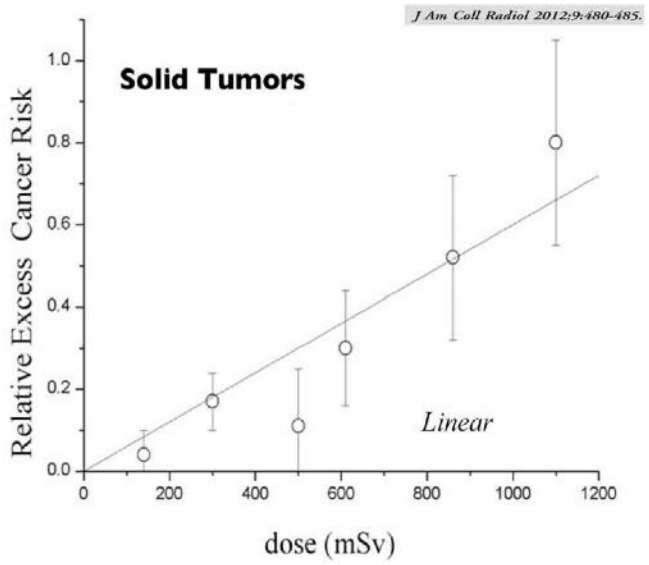
Genes **2011**, *2*, 374-383; doi:10.3390/genes2020374

Leukemia and Solid Tumors in Japanese A-Bomb Survivors



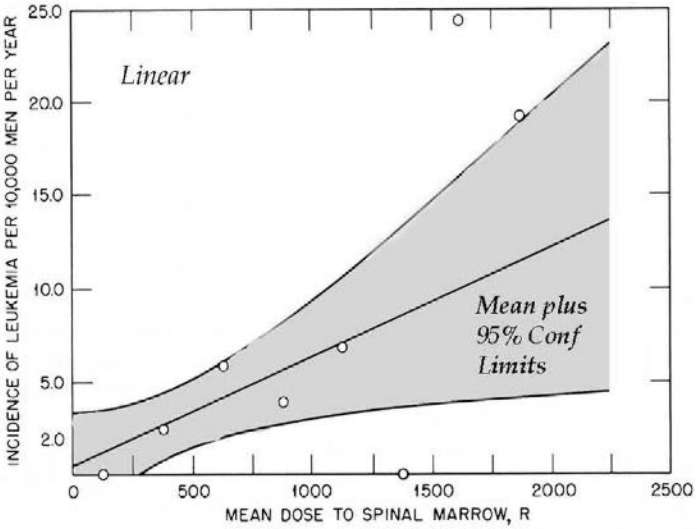
Dose response curve for radiation-induced leukemia based on data from Japanese a-bomb survivors, from 1950 to 2000.

(From: Preston, Radiat Res 2004;162(4):377-389)



Excess relative risks of solid cancer for Japanese atomic bomb survivors. Plotted points are estimated excess relative risks of solid cancer incidence (averaged over both genders for exposure at age 30 years and surviving to age 60 years). The linear no-threshold model is illustrated using regression analysis to construct a line passing through the origin that best fits these data. The operating region for CT scans and medical x-ray examinations is below 100 mSv, and the risks of radiation exposure in this range are based on extrapolation rather than primary data.

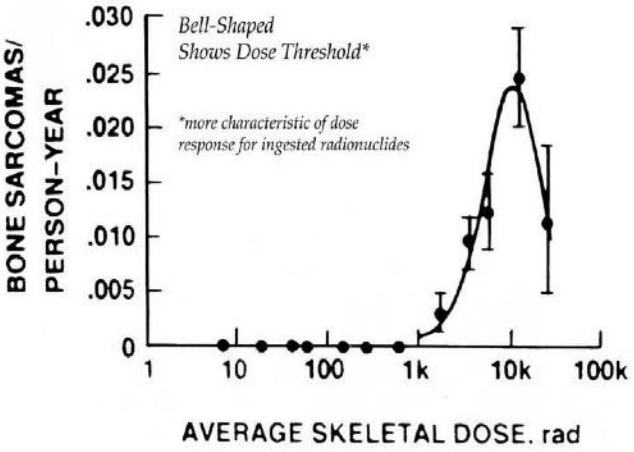
Leukemia in Patients Treated for Ankylosing Spondylitis



Incidence of leukemia in relation to mean spinal-marrow dose of therapeutic irradiation for ankylosing spondylitis.

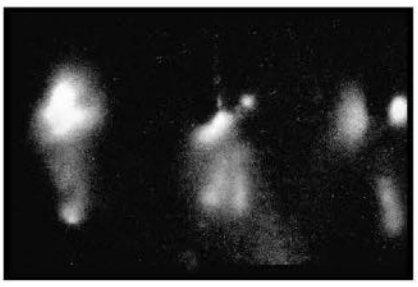
[From *Report of the United Nations Scientific Committee on the Effects of Atomic Radiation*, p. 146, 1962.]

Bone Tumors in Radium Dial Painters



Dose response relation for bone sarcomas.
There is an apparent threshold at about 10 Gy (1000 rad).

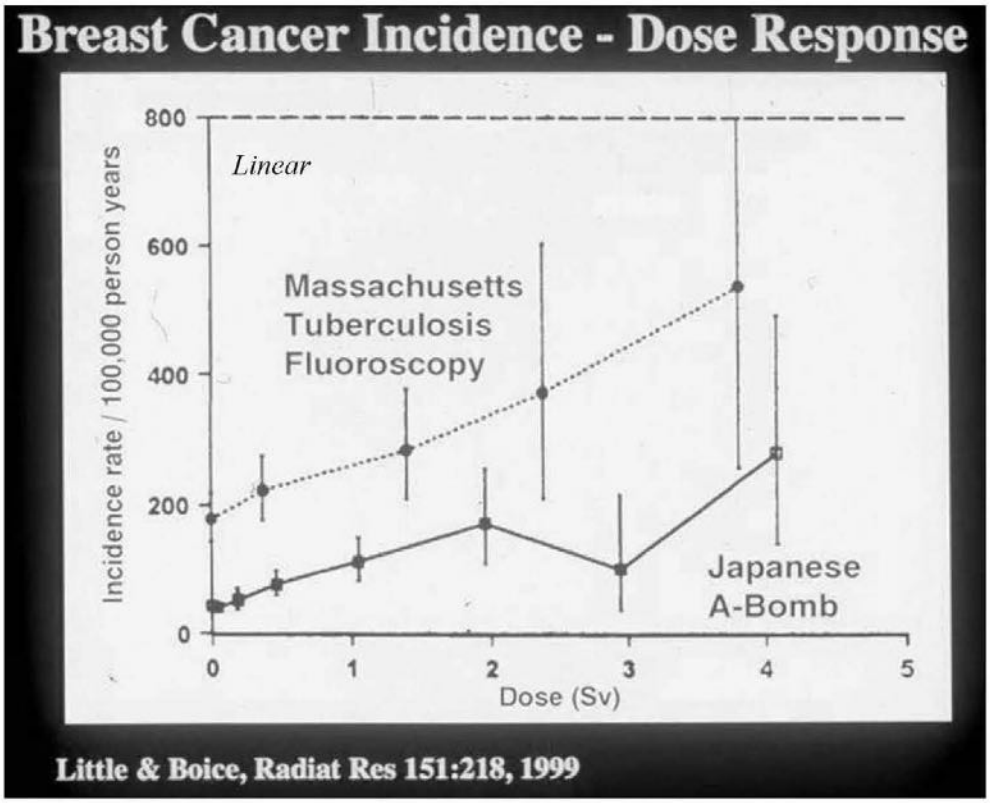
From BEIR IV: Report of the National Academy of Sciences, Washington, D.C., National Academy Press, 1988



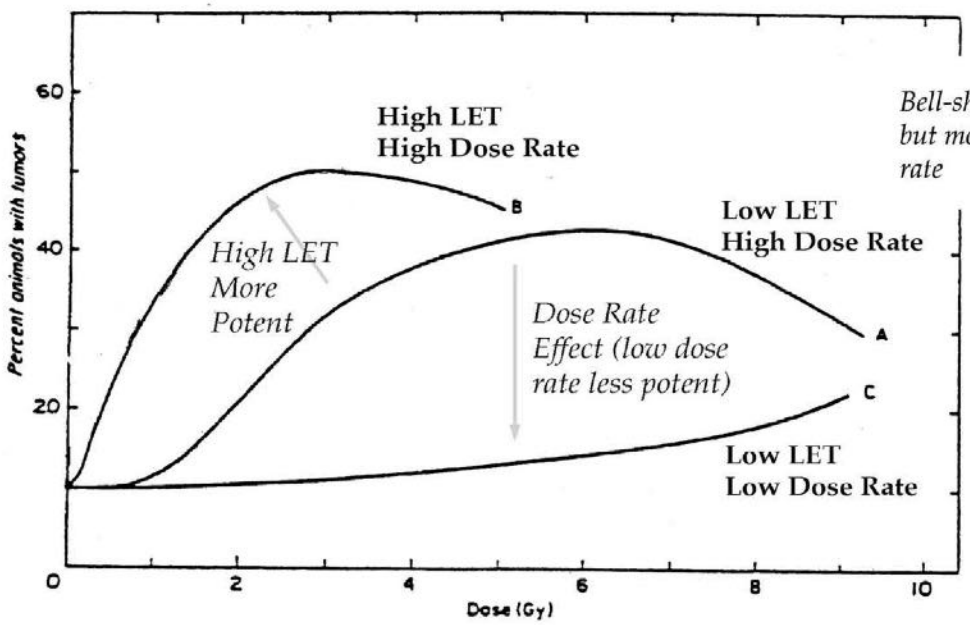
So who needs an X-ray machine for a dental study?

Teeth from radium dial painters expose X-ray film all by themselves!

Radiation-induced breast cancer among A-bomb survivors and TB patients receiving multiple fluoroscopies



Radiation carcinogenesis in mice as a function of LET or dose rate



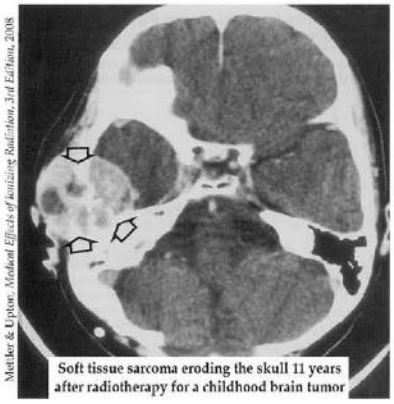
Bell-shaped for high dose rate, but more linear for low dose rate

Schematic diagram of induction of a specific tumor type in mice exposed to various doses of ionizing radiation given to the whole body based on a review of a number of different in vivo results. *Curve A:* Tumors induced by single acute doses of low-LET ionizing radiation. *Curve B:* Tumors induced by single acute doses of high-LET radiation. *Curve C:* Tumors induced by fractionated doses (e.g., 1 Gy/day), of low-LET radiation.

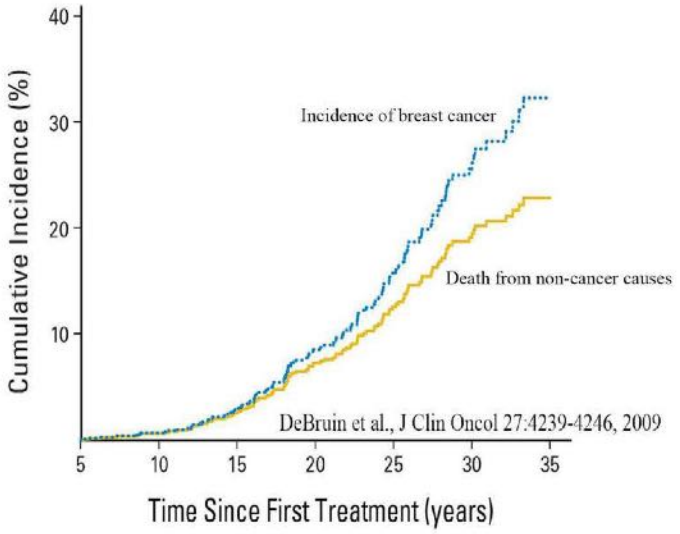
4. **Special Case: Second Malignancies in Long-Term Cancer Survivors Who Received Radiotherapy** - usually considered separately from the epidemiological studies of people who did NOT already have cancer at the time of irradiation

a] ***an increasing number of epidemiological studies of long-term cancer survivors do show an elevated risk of getting a different type of cancer in or near a previously-irradiated treatment field (receiving 40 Gy or more total dose)***; the most common types of second malignancies seem to be:

leukemia
thyroid cancer
breast cancer
soft tissue sarcoma
lymphoma
lung cancer



...although most other types are probably induced as well, but at lower frequencies



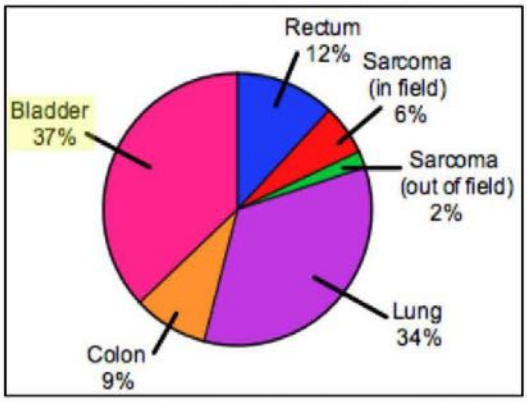
Cumulative incidence of breast cancer in nearly 800 long-term survivors of childhood or adolescent Hodgkin lymphoma as a function of time after their initial treatment.

Most received both radiation and chemotherapy, making their likelihood of getting a second cancer even higher than if they had received either radiation or chemotherapy alone.

Note that there is also an increased risk of dying of non-cancer conditions, also assumed to be due to the toxic effects of the prior treatment on specific normal tissues (like the heart or the immune system).

- Brenner et al compared relative risk for secondary cancers among men who underwent RT (51, 584) vs. surgery (n = 70, 539) for prostate cancer
- No evidence for an increase in leukemia
- *Significant increase in risk for second solid tumors (34% increase after 10+ y)*
- Largest risk was for bladder at 10+ y past diagnosis

Distribution of radiation-induced cancer 5+ y



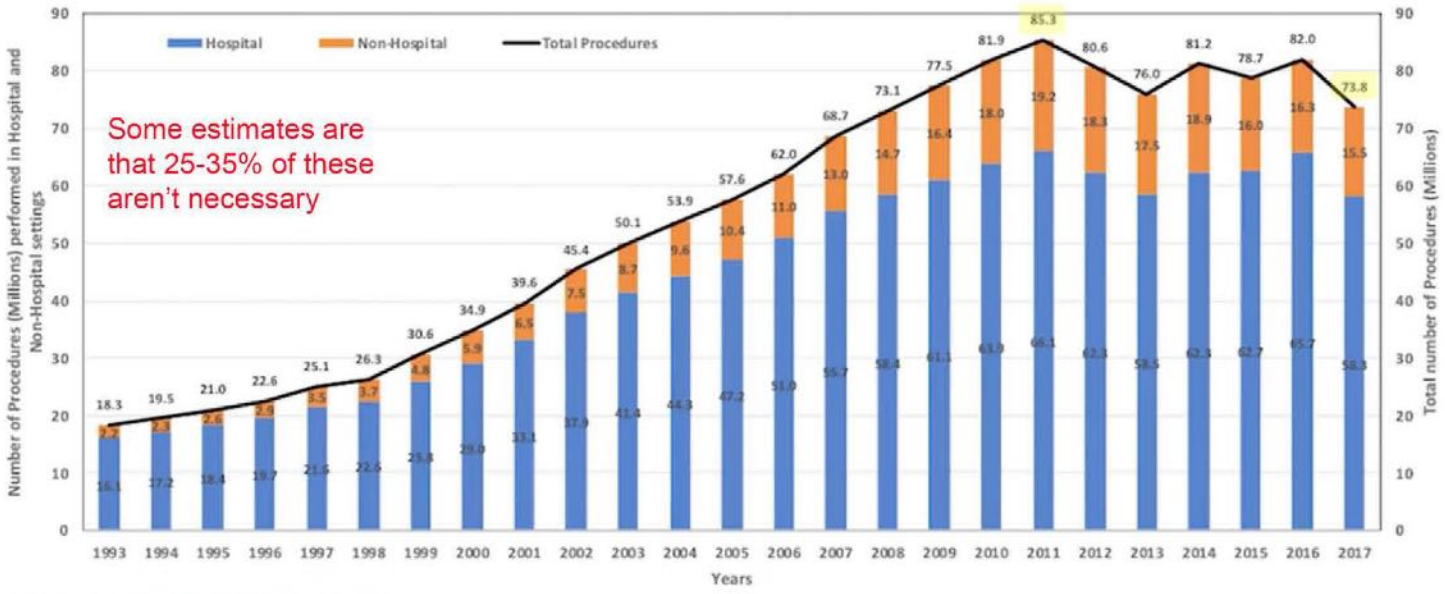
Brenner DJ et al. *Cancer* 2000

5. Last but by no means least: **Do Diagnostic Imaging Procedures Cause Cancer????**

a) *because the radiation doses are orders of magnitude lower for diagnostic scans than for radiation therapy, the risk of causing a malignancy will also be much, much lower…but NOT zero, because there is always some risk*

b) *however, there are many, many more diagnostic scans performed per year than radiation therapy treatments, so with a very large number of patients, even a very small risk might manifest itself;* also remember that many individuals will get more than one scan during the course of a procedure

c) <u>one warning</u>: **the use of CT scanning in particular (which gives a higher dose than other diagnostic procedures relatively speaking) has increased dramatically over the past 30 years, especially in the pediatric population**



Average effective dose for an <u>adult</u> abdominal/pelvic CT scan = 10 mSv

Average effective dose for a <u>neonatal</u> abdominal/pelvic CT scan = 20-25 mSv

Estimated Number of CT Scans Performed Annually in the United States.

a. *since children are more sensitive to radiation carcinogenesis, and since children also should have the longest remaining lifespan in order to develop radiation-induced malignancies, some scientists in the radiation protection community think that the use of pediatric CT should not be allowed to further proliferate unnecessarily…or at minimum, that the amperage should be turned down some in order to reduce the doses involved*

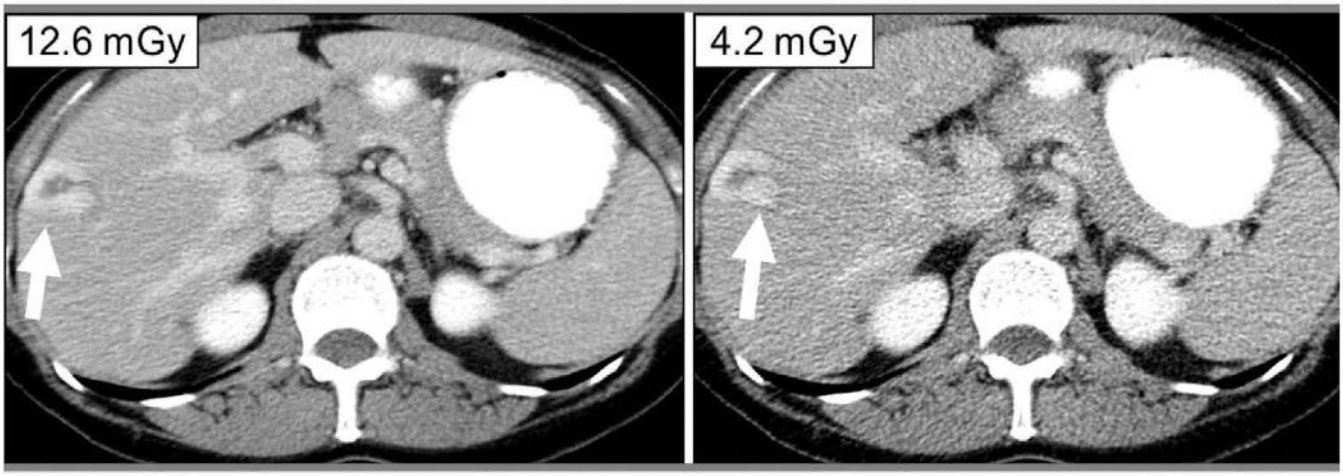
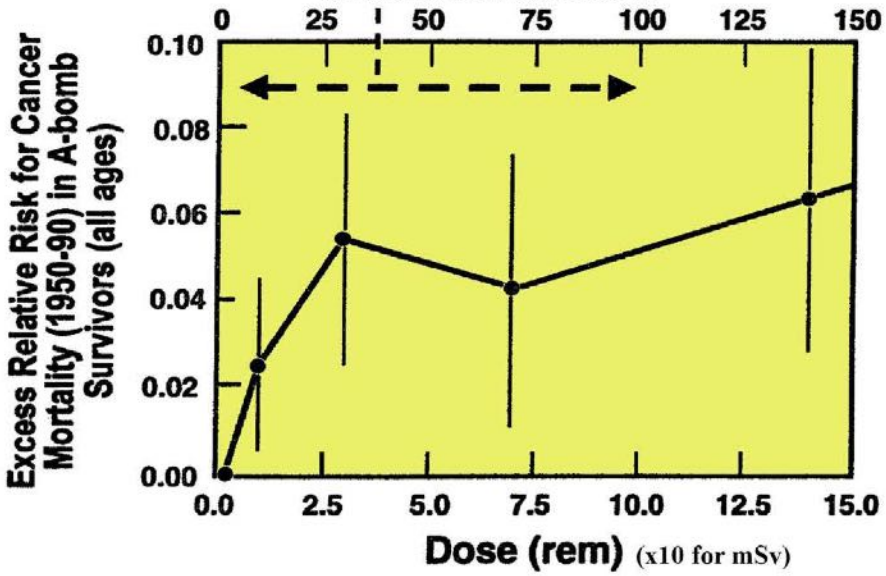


Image Quality: Unnecessarily high Image Quality: Adequate for diagnosis

High quality, crisp CT images certainly look better (all images, actually), but they also deliver significantly higher radiation doses. For the sake of patient safety, the radiology community should be willing to accept somewhat "noisier" images so long as they still provide the necessary diagnostic information.

Images courtesy of: MK Kalra, S. Singh, MGH Webster Center for Advanced Research and Education in Radiation



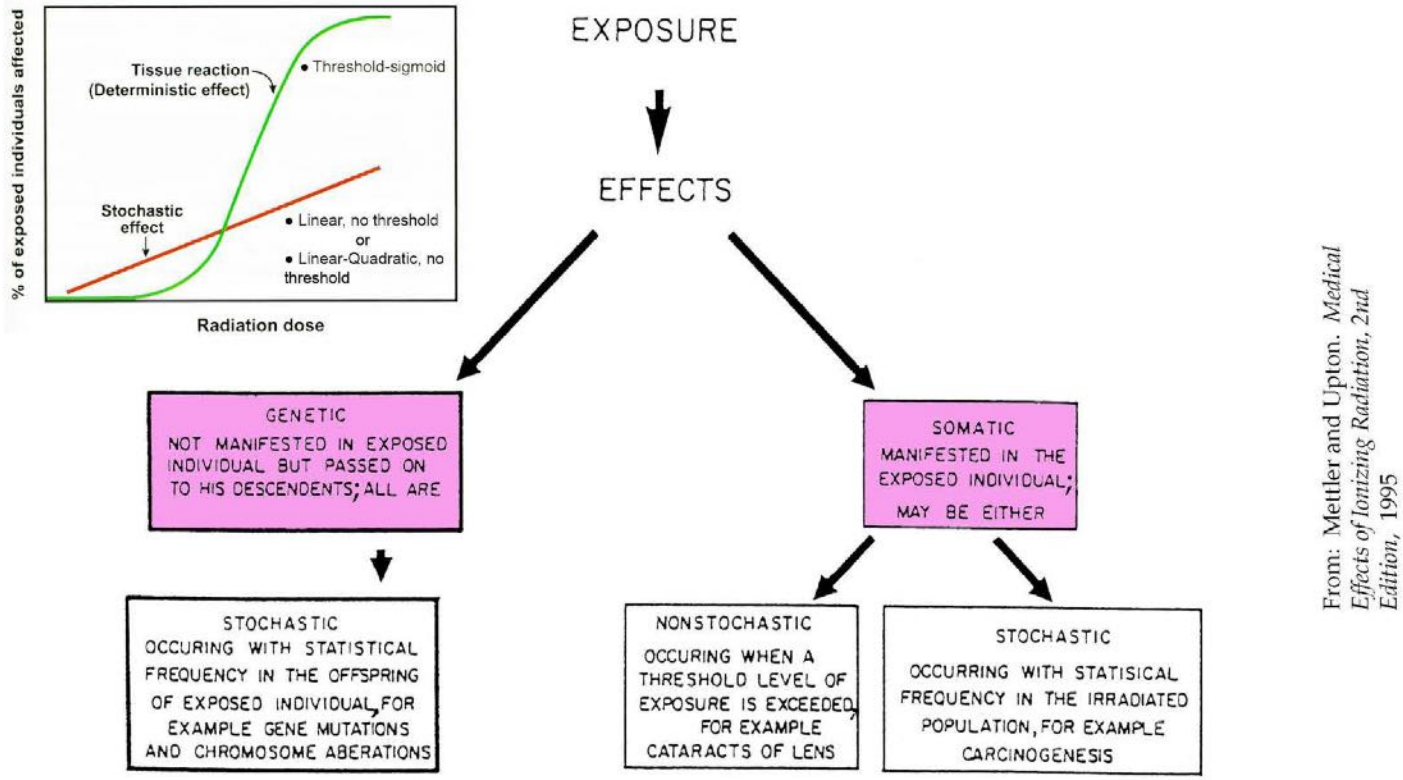
The 35,000 A-bomb survivors who were exposed to doses below 150mSv and who have been followed for over 75 years show a small, but statistically significant, excess cancer incidence. This dose range is comparable to that applicable to helical CT studies in children.

Pediatr Radiol (2002) 32: 225–227

Radiation Protection Standards - how all the negative biological consequences of exposure to ionizing radiation are redefined in terms of numerical risk estimates and maximum permissible doses

1. **What are the radiation-induced effects that we want to protect ourselves from?**

   a. answer: *both the possible genetic and somatic consequences of exposure to ionizing radiation*



From: Mettler and Upton. *Medical Effects of Ionizing Radiation, 2nd Edition*, 1995

1) **"genetic effects" occur in the descendants of the individual who received the exposure, and are stochastic in nature (example: mutagenesis, carcinogenesis)**

2) **"somatic effects" occur in the exposed individual, and may be stochastic (example: carcinogenesis) or non-stochastic (example: cataracts) in nature**

Radiation Protection Terminology

Stochastic vs. Non-Stochastic

1) **stochastic effects are "all or nothing", and occur with a certain statistical frequency in an irradiated population, and show no dose threshold**

2) **non-stochastic (deterministic) effects are now called "tissue reactions", and only occur once a threshold level of exposure is exceeded, and will vary in severity depending on dose**

Absorbed dose vs Equivalent dose

the absorbed dose is the energy imparted by ionizing radiation per unit mass of irradiated material; the current unit is the Gray (Gy)

the dose equivalent is the quantity used for radiation protection purposes, that corrects the absorbed dose by a factor related to the biological potency of the type of radiation (low vs. high LET); the current unit of dose equivalent is the Sievert (Sv)

the correction factor that converts absorbed dose to dose equivalent is called the ***radiation weighting factor*** (W_R) :

Equivalent dose (**Sv**) = Radiation weighting factor w_R × Absorbed dose (**Gy**)

Type of radiation	Radiation weighting factor w_R
γ-rays, X-rays, β-particles	**1**
Proton beams	**2**
α-particles, heavy ions	**20**
Neutron beams	**2.5∼21**

ICRP Publication 92, Oxford, UK, Elsevier Science Ltd, 2004.

Equivalent dose vs. Effective dose

Even knowing the equivalent dose is still not sufficient to fully describe the biological consequences of a radiation exposure because typically, multiple tissues/organs are exposed, and some are more or less radiosensitive than others

therefore, a new term is needed: **the effective dose, which is the dose equivalent corrected by another factor (the *tissue weighting factor,* W_T) that corrects for the radiosensitivity of different tissues; also expressed in units of Sv**

Effective dose (Sv) = Σ (Tissue weighting factor w_T × Equivalent dose)

Tissue	Tissue weighting factor w_T
Red bone marrow, colon, lungs, stomach, breasts	**0.12**
Gonad	**0.08**
Bladder, esophagus, liver, thyroid	**0.04**
Bone surface, brain, salivary gland, skin	**0.01**
Total of the remaining tissues	**0.12**

Source: 2007 Recommendations of the ICRP

And there's more!

Quantities and Units Used in Radiation Protection

Quantity	Definition	Unit	
		New	Old
Absorbed dose	Energy per unit mass	Gray	Rad
For individuals			
Equivalent dose (Radiation weighted dose)	Average dose × radiation weighting factor	Sievert	Rem
Effective dose	Sum of equivalent doses to organs and tissues exposed, each multiplied by the appropriate tissue weighting factor	Sievert	Rem
Committed equivalent dose	Equivalent dose integrated over 50 years (relevant to incorporaated radionuclides)	Sievert	Rem
Committed effective dose	Effective dose integrated over 50 years (relevant to incorporated radionuclides)	Sievert	Rem
For populations			
Collective effective dose	Product of the average effective dose and the number of individuals exposed	Person-sievert	Man-rem
Collective committed effective dose	Integration of the collective dose over 50 years (relevant to incorporated radionuclides)	Person-sievert	Man-rem

From: Hall and Giaccia, *Radiobiology for the Radiologist, 6th Edition*, 2006

Who is in charge of evaluating the scientific data, formulating the radiation exposure standards, and enforcing radiation safety compliance in the workplace?

Answer: A veritable alphabet soup of different committees, agencies and organizations!

- Evaluates the current scientific data on radiation effects

  Biological Effects of Ionizing Radiations (BEIR) Committee - made up of senior radiation scientists appointed by the National Academy of Sciences; they meet every 5-7 years and make recommendations about whether the safety standards need to change or not

- Formulates the language of radiation safety and establishes exposure limits for radiation workers and the general public

  National Council on Radiological Protection and Measurement (NCRP) - made up of senior radiation safety experts and administrators appointed by Congress, who review the BEIR Committee findings and come up with the radiation safety standards accordingly

- Enforcers of NCRP regulations - can vary or overlap depending on the situation

  Environmental Protection Agency (EPA) - mainly concerned with radioactive materials (radon, radionuclides, radiation sources, etc.) released into the environment

Nuclear Regulatory Commission (NRC) - enforces radiation safety standards at nuclear power plants and experimental reactors, but **also is in charge of radioactive materials used medically and in research**

Food and Drug Administration (FDA) - along with food and drugs, **also has regulatory oversight of "medical devices", including those that generate radiation (equipment) and/or facilitate its delivery (software, etc.)**

Occupational Safety and Health Administration (OSHA) - mainly involved with employee safety in the workplace, sometimes including radiation safety

Department of Energy (DOE) - enforces radiation safety standards at national laboratories and military installations

Department of Transportation (DOT) - concerned with the safety of inter- and intra-state transport of hazardous materials, including radioactive ones

Department of Homeland Security (DHS) - concerned with reducing the likelihood of domestic terrorism, including that involving the use of radioactive materials (cesium-137 in particular)

Current (US) Radiation Protection Standards

today's radiation protection standards are designed to keep the risks of stochastic and non-stochastic radiation effects to members of the whole population no greater than the comparable annual risk of a fatal accident in other, so-called "safe" industries (estimated at about 2 fatalities/10,000 workers or 2 x 10^{-4})

these calculations are based on the assumption that the dose response for radiation effects is linear, with no threshold dose; this is a consevative approach, and probably overestimates the risk in some situations

Risk Estimates for a Radiation-Induced, FATAL Cancer

Risks of Cancer Lethality by Radiation

"Infrequent Exposure" — applies to accidental or medically-necessary exposures

"Frequent Exposure" — applies to day-to-day low-level exposure (like occupational)

	High Dose High Dose Rate	Low Dose Low Dose Rate
Working population	8×10^{-2} per Sv	4×10^{-2} per Sv
Whole population (includes children and the elderly)	10×10^{-2} per Sv	5×10^{-2} per Sv

International Commission on Radiological Protection: Recommendations. *Annals of the ICRP Publication 60*, Oxford, England, Pergamon Press, 1990

Summary of Recommended Annual Radiation Dose Limits:

Occupational Exposure:	
Stochastic effects: effective dose limits	
Cumulative	10 mSv × age
Annual	50 mSv/y
Deterministic effects: dose equivalent limits for tissues and organs (annual):	
Lens of eye	50 mSv/y *New as of 2018*
Skin, hands, and feet	500 mSv/y
Embryo/Fetus Exposure:	
Effective dose limit after pregnancy declared	0.5 mSv/month
Public Exposure (annual):	
Effective dose limit, continuous or frequent exposure	1 mSv/y
Effective dose limit, infrequent exposure	5 mSv/y
Dose equivalent limits; lens of the eye	15 mSv/y
Skin and extremities	50 mSv/y
Education and Training Exposure (annual):	
Effective dose limit	1 mSv/y
Dose equivalent limit for lens of eye	15 mSv/y
Skin and extremities	50 mSv/y
Negligible Individual Dose (annual):	0.01 mSv/y

Based on National Council on Radiation Protection and Measurements: *Recommendations on Limits for Exposure to Ionizing Radiation.*

Lots of Ways of Expressing Risk

Activities That have been Estimated to Increase Risk of Death by One Chance in a Million

Activity	Cause of Death
Smoking 1 cigarette	Cancer, heart disease
Drinking ½ liter of wine	Cirrhosis of the liver
Spending 1 hr in a coal mine	Black lung disease
Spending 3 hrs in a coal mine	Accident
Living 2 days in New York or Boston	Air pollution
Rock climbing for 1½ min	Accident
Traveling 6 min by canoe	Accident
Traveling 10 mi by bicycle	Accident
Traveling 30–60 mi by car	Accident
Flying 1000 mi by jet	Accident
Flying 6000 mi by jet	Cancer caused by cosmic radiation
Living 2 mo in Denver	Cancer caused by cosmic radiation
Living 2 mo in an average city	Cancer caused by natural radioactivity
Being a man age 60 for 20 min	Illness
One chest x-ray taken in a good hospital	Cancer caused by radiation
Living 2 mo with a cigarette smoker	Cancer, heart disease
Eating 40 tsp of peanut butter	Liver cancer caused by alfatoxin B
Drinking Miami drinking water for 1 yr	Cancer caused by chloroform
Drinking 30 cans (12 oz) of diet soda	Cancer caused by saccharin
Living 5 yrs at site boundary of a typical nuclear power plant in the open	Cancer caused by radiation
Drinking 1000 soft drinks from recently banned (24 oz) plastic bottles	Cancer from acrylonitrile monomer
Living 20 yrs near PVC plant	Cancer caused from vinyl chloride (1976 standard)
Living 150 yrs within 20 mi of a nuclear power plant	Cancer caused by radiation
Eating 100 charcoal-broiled steaks	Cancer from benzopyrene
Risk of accident by living within 5 mi of a nuclear reactor for 50 yrs	Cancer caused by radiation

From: Mettler and Upton, *Medical Effects of Ionizing Radiation, 2nd Edition*, 1995.

Average Reduction in Lifespan (Days)

Occupation	For 1 yr of Working Life	For 35 yrs of Working Life
Deep sea fishing	32	923
Coal mining	3.6	103
Oil refinery	2.6	74
Railways	2.2	63
Construction	2.1	62
Industry (average value)	0.5	13.5
Occupational exposure to radiation at the annual limit of 50 mSv	1.3	32
Occupational exposure to radiation at 5mSv	0.1	3

Annual Risk of Dying from Various Activities

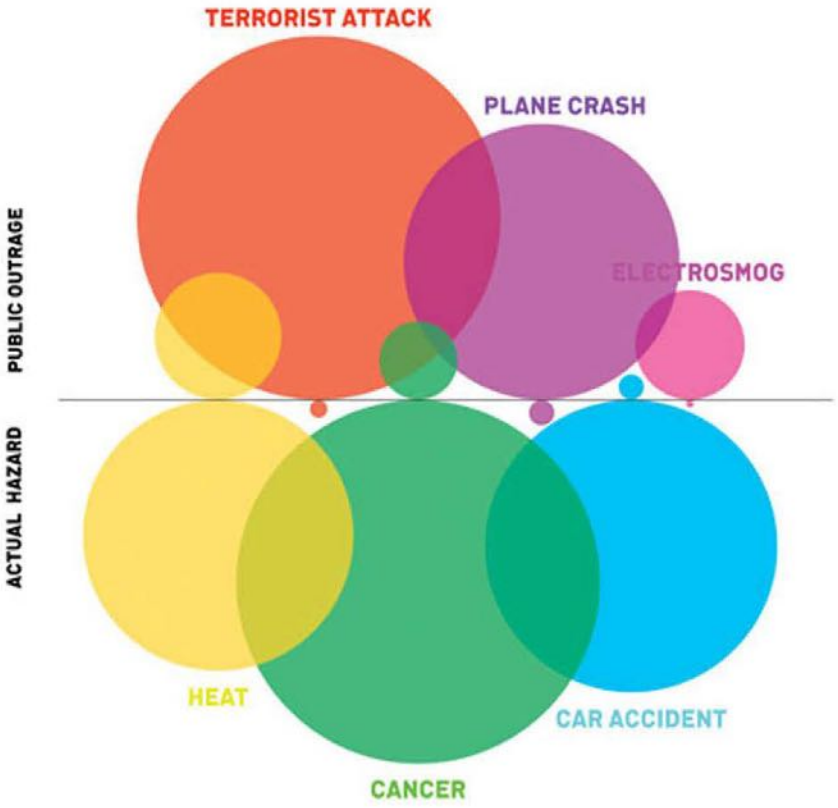
Risk Comparisons: Annual Risk of Dying in the U.S. per Million Persons at Risk	
Cause Deaths	**Death per 1,000,000/year**
Heart disease	2800
All cancers	2050
Parachutist	2000
Fire fighter; Hang glider	800
Lung cancer	590
Pneumonia	320
Diabetes; Police officer	230
Motor vehicle accidents; Breast cancer	160
Homicide	80
Falls	50
Foodborne bacteria	36
Accidental poisoning (drugs and medication)	30
Fires and burns; Drowning	15
Tuberculosis; Firearms	5
Choking, inhalation or ingestion of foreign object/food	4
Electric current; Railway	2
Airline crash (one trip)	0.6
Floods	0.4
Lightning; Insect bite or sting	0.2
Hit by falling aircraft	0.06
Hurricane	0.04
Sources: 1997 US Statistical Abstract; National Safety Council (1995), *Accident Facts;* Crouch & Wilson (1982), *Risk/Benefit Analysis.*	

Comparison of the Risks of Some Medical Exams

Procedure	Effective Dose (mSv)	Risk of Fatal Cancer (per million)	Equivalent to Number of Cigarettes Smoked	Equivalent to Number of Highway Miles Driven	Comparable to typical background radiation for...
Chest Radiograph	0.04	1.6	12	29	5-10 days
Skull Exam	0.1	4.0	29	71	
Mammography	0.1	4.0	29	71	3 months
Thoracic Spine	1.0	40.0	292	714	
Pelvis	1.1	44.0	321	786	
Abdomen	1.2	48.0	350	857	
CT Head	1.8	72.0	526	1286	
Lumbar Spine	2.1	84.0	613	1500	
Intravenous Urography	4.2	168.0	1226	3000	
CT Pelvis	7.1	284.0	2073	5071	~2 years
CT Abdomen	7.6	304.0	2219	5429	~2.5 years
CT Chest	7.8	312.0	2277	5571	~3 years
Barium Enema (with fluoro)	8.7	348.0	2540	6214	

Not Everybody Has the Same Concept of "Risk"

Truth is, most of us are *really* bad at estimating what's risky and what isn't...

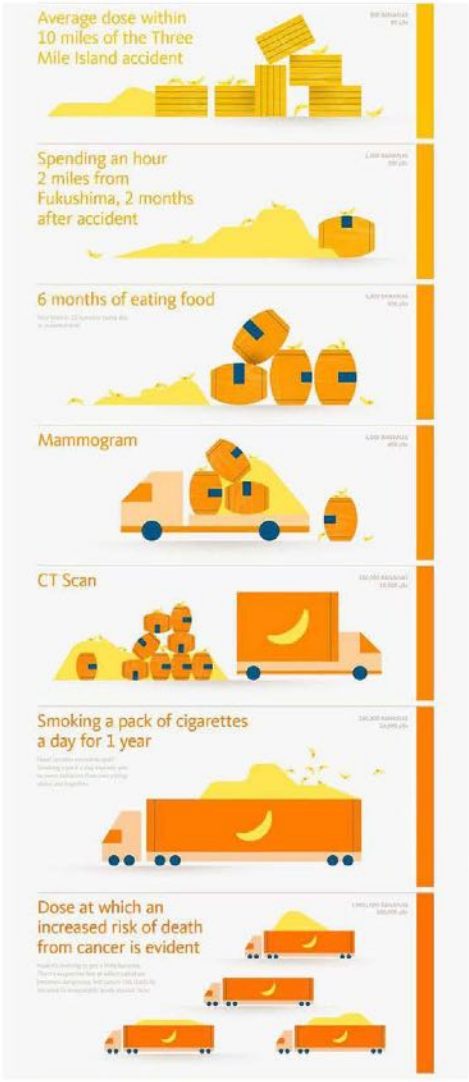


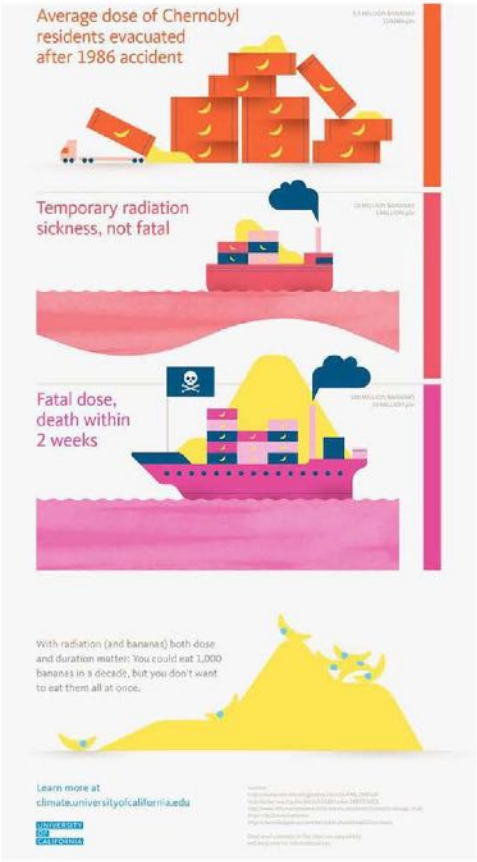
The public tends to way overestimate the risk of terrorist attacks and plane crashes, but underestimate risks associated with getting cancer, driving and global warming.

The risks posed by "electrosmog" – electromagnetic radiation emissions from cell phones, cell phone towers, wifi networks, power lines, microwave ovens, etc. – is likewise way overestimated by the public.

The risk of exposure to ionizing radiation *from nuclear power plants* is also overestimated, however the risks associated with *medical imaging* are viewed as minimal, even for exposure to similar doses of the same types of radation. Go figure!


What to know before you go bananas about radiation
When it comes to nuclear radiation, the general feeling is that any amount is too much – but, in truth, we're all exposed to radiation every day.
Take a banana: a tasty source of potassium, but also a natural source of radiation from potassium-40 isotopes. How much? Scientists measure the amount of damage radiation would do to a human body in sieverts; eating one average-sized banana is equivalent to 0.1 microsieverts.
= 0.1 MICROSIEVERT
The sources of radiation that people worry about, are they a real source of concern, or are they just a bunch of bananas?
Living within 50 miles of a nuclear power plant for a year
Airport security scan
Dental X-ray
1 day on Earth
Flight from NY to LA
Living in a concrete stone, or brick building for a year


Average dose within 10 miles of the Three Mile Island accident
Spending an hour 2 miles from Fukushima, 2 months after accident
6 months of eating food
Mammogram
CT Scan
Smoking a pack of cigarettes a day for 1 year
Dose at which an increased risk of death from cancer is evident


Average dose of Chernobyl residents evacuated after 1986 accident
Temporary radiation sickness, not fatal
Fatal dose, death within 2 weeks
With radiation (and bananas) both dose and duration matter: You could eat 1,000 bananas in a decade, but you don't want to eat them all at once.
Learn more at climate.universityofcalifornia.edu
UNIVERSITY OF CALIFORNIA