Early and Late Effects in Normal Tissues

A. What makes a normal tissue reaction during and after irradiation "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

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, whole body radiation syndromes, teratogenesis, 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.)

CONSEQUENTIAL LATE EFFECTS: follow the general pattern of regular late effects, but are worse than might otherwise be expected secondary to the tissue having first experienced severe early reactions

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)

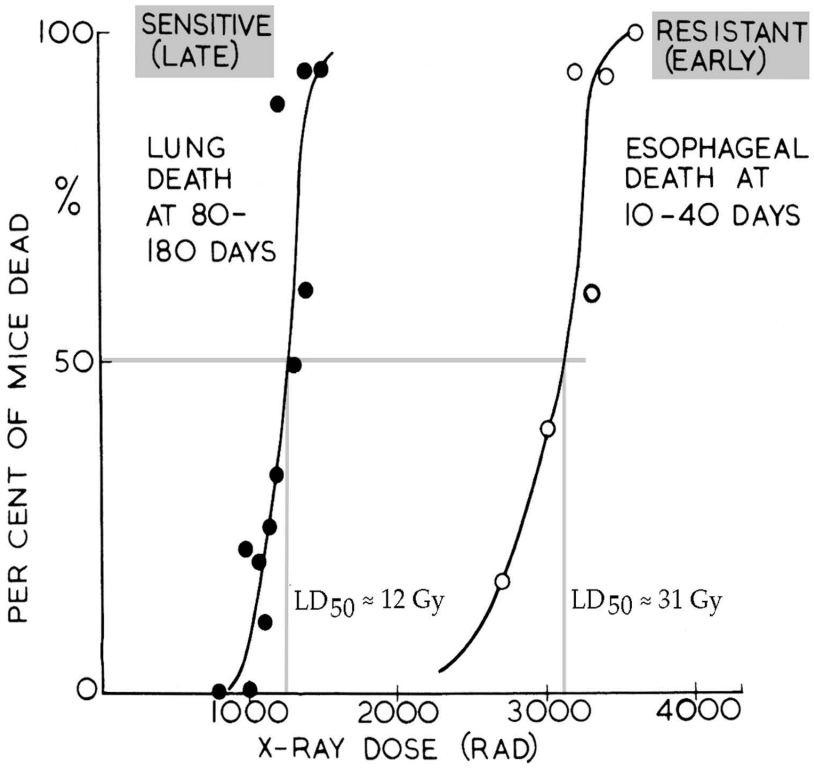
Late effects = fibrosis, pigmentation changes, edema (of a different type), telangiectasia (abnormal proliferation of small blood vessels)

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*

a] one interesting implication of this is that *even though an early reaction in a tissue might be severe after a given total dose of radiation (because the cells are sensitive), it doesn't necessarily mean that a later reaction in the same tissue will also be severe, because the cells responsible for that effect might be more resistant*



Proportion of mice killed by single doses of X-rays to the thorax only by 40 days (esophageal death) or between 80 and 180 days (lung death).

The more radiosensitive tissue expresses its radiation damage later.

From: Becker FF (ed), *Cancer 6: A Comprehensive Treatise*, 1977

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*

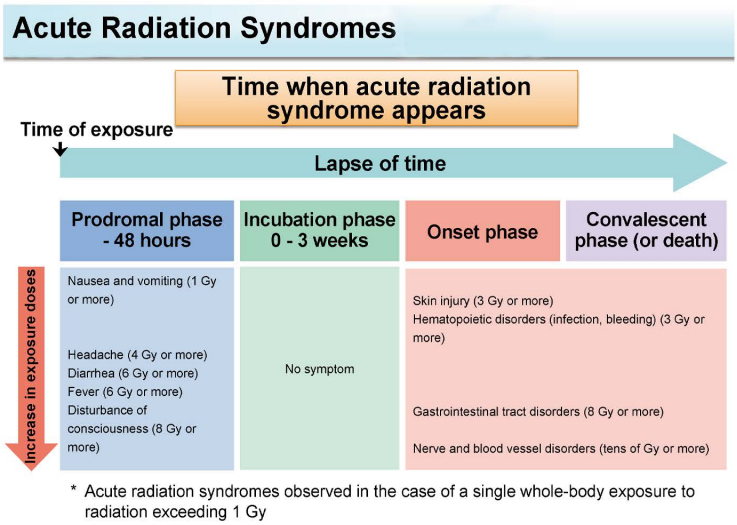
1) in an accident situation though, how do you know exactly what dose the victim received?

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.

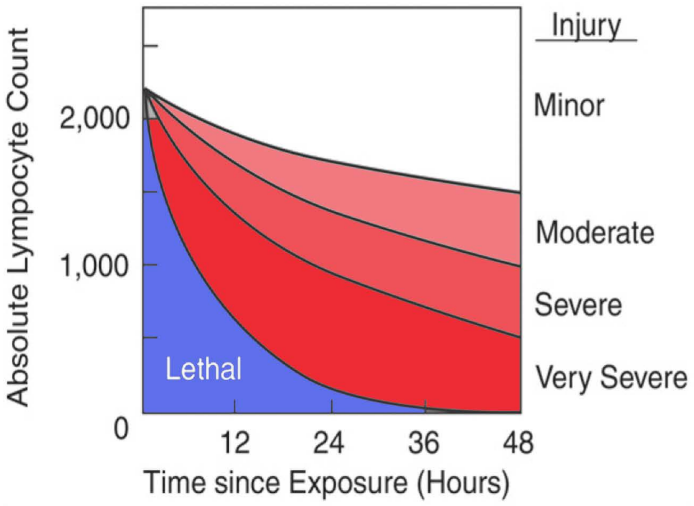
Prodromal Phase of Acute Radiation Syndrome and Exposure Doses

Vomiting that begins within ~2 hours of exposure suggests that the dose received was near (or past) the LD_{50}

Prodromal phase and exposure dose

Symptom	Mild (1-2 Gy)	Moderate (2-4 Gy)	Severe (4-6 Gy)	Very severe (6-8 Gy)	Lethal (> 8 Gy)
Vomiting	2 hours or later after exposure (Rate of incidence) Up to 50%	1 to 2 hours 70 to 90%	Within 1 hour 100%	Within 30 minutes 100%	Within 10 minutes 100%
Diarrhea	None	None	Moderate	Severe	Severe
Headache	Very mild	Mild	Moderate	Severe	Severe
Consciousness	Unaffected	Unaffected	Unaffected	Affected	Loss of consciousness
Body temperature	Normal	Slight fever	Fever	High fever	High fever

Source: Prepared based on IAEA Safety Reports Series No.2 "Diagnosis and Treatment of Radiation Injuries" (1998)



● 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)

Good Prognosis ARS

- Vomiting starts > **4 hours** after incident
- No significant change in serial lymphocyte counts within **48 hours** after an incident
- No other significant injuries

Uniformed Services University of the Health Sciences
Armed Forces Radiobiology Research Institute

Poor Prognosis ARS

- Coma, Seizures
- Vomiting **less than 4 hours** after incident
- Serial Lymphocyte counts drop more than **50% within 48 hours**
- Bloody vomitus or stool
- Other serious injuries

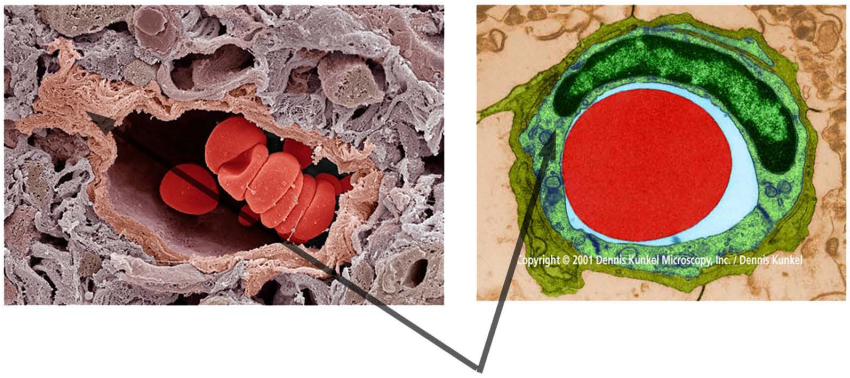
Uniformed Services University of the Health Sciences
Armed Forces Radiobiology Research Institute

3] The Neurovascular Syndrome (used to be called "cerebrovascular", and before that, "CNS" syndrome)

a] ***this syndrome occurs for acute, whole body doses of ≥20 Gy, and causes death within minutes to a couple of days; the syndrome results in massive damage to the central nervous system, and to progressive vascular collapse***

b] however, we now think that these cells are not the original targets of the radiation, but rather that they die secondary to damage to small blood vessels, that start to leak after irradiation

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 (see: NEJM 272: 755, 1965; Arch Path *83*: 446, 1967)

d] for doses at or above ~35 Gy, a sub-syndrome has been identified, called the "**Circulatory Collapse Syndrome**", caused by damage to large blood vessels (in addition to smaller ones)

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.

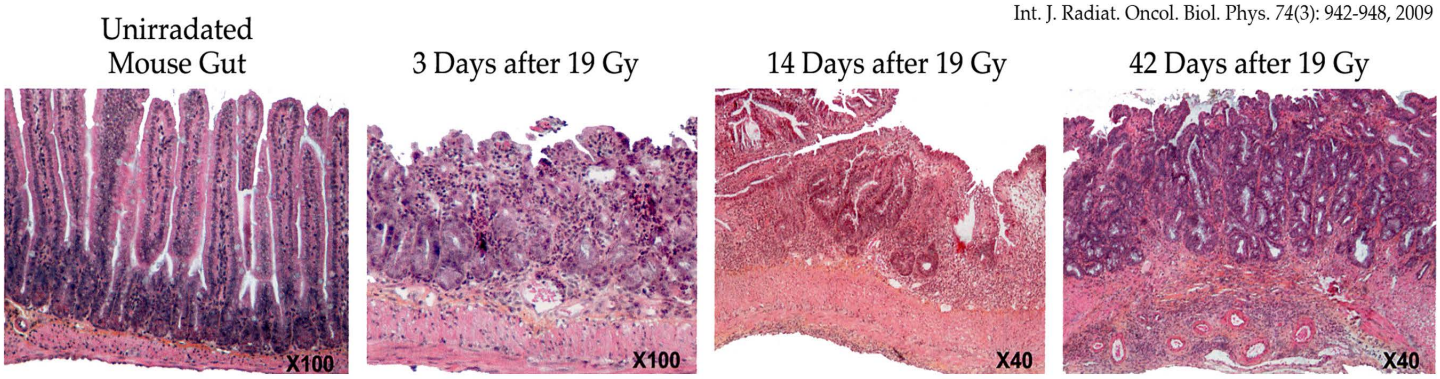
4) The Gastrointestinal Syndrome -

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. the cells whose deaths precipitate the syndrome (the so-called "target cells") are the crypt cells at the base of the villi; 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

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



a. 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

2. note that irradiation of the whole body is a prerequisite for development of the "full" gastrointestinal syndrome; **partial gut irradiation, such as in many radiotherapy protocols, produces some of the same symptoms (and for the same underlying reasons), but it doesn't produce the whole syndrome**

3. prior to the Chernobyl accident 30 years ago, there were only a couple of well-documented cases of victims dying of the GI syndrome however a dozen firefighters sent into the nuclear reactor soon after the meltdown ultimately did die of it

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 off 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

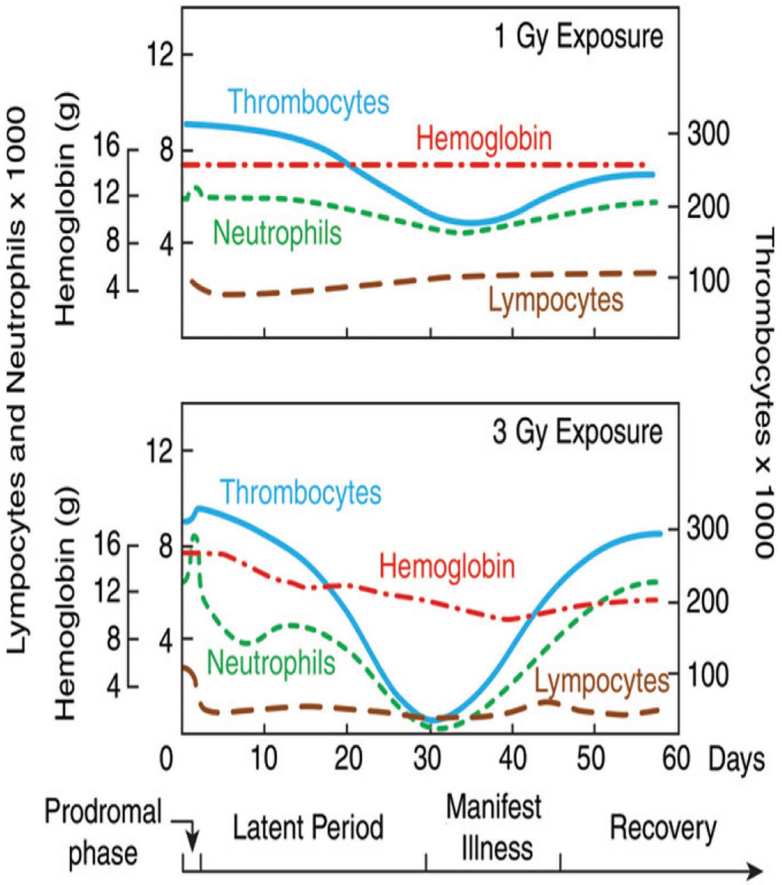
a] ***this syndrome occurs for whole body, acute radiation doses of approximately 2 Gy and above, and leads to death (in the absence of medical intervention) after about 30-60 days***

b] in fact, **the human LD_{50} for ionizing radiation is estimated to be in the 3-4 Gy range 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, 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**

1. note that it is 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) and/or infection (no white blood cells = no immune system)***

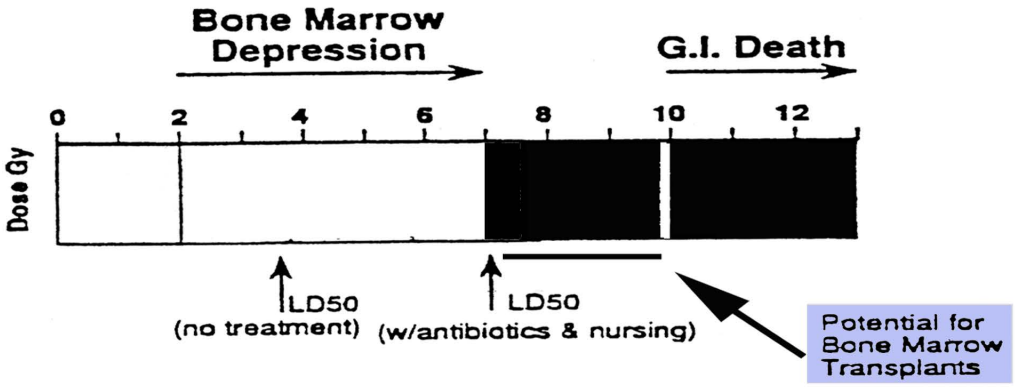


Hematopoietic Syndrome: Case Report

26 year-old male involved in a criticality accident at Los Alamos in March 1945 – the first person to die of ARS. Total body dose 6.35Sv. Right hand, 200Gy. Left hand, 30 Gy.
Red blood count changed little up to the time of death
Platelets dropped-Transfusion-dropped again
Granulocytes; initial rise falling to zero at time of death.
Day 1. Nausea, anorexia and vomiting.
Day 2. Greatly improved, except for numbness in hand.
Day 5. Rise of temperature.
Day 10. Nauseated, cramps.
Day 24. Comatose, 106 °F, Died, no white cells.

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**

1} either radiation therapy or intensive chemotherapy can be used for this

2} patients receiving TBI often do get 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

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.

Gonadal late effects in children treated more than 10 years before with two different doses and types of fractionated total body irradiation

		FTBI			
	3.3 Gy x 3	990 cGy	1200 cGy	*2 Gy BID x 3*	
Late effect	At risk	*n* (%)	*n* (%)	Total	*p*
		(*n* = 12)	(*n* = 7)	*n* = 19	
Permanent ovarian dysfunction	19	3 (25)	4 (57)	7 (37)	0.33
		n = 13	*n* = 10	*n* = 23	
Testicular germinal dysfunction	23	10 (77)	10 (100)	20 (87)	0.23

Late consequences in children treated more than 10 years before with two different doses and types of fractionated total body irradiation (FTBI)

	FTBI			
Late effects	990 cGy (*n* = 25) *n* (%)	1200 cGy (*n* = 17) *n* (%)	Total (*n* = 42)	*p*
Posterior subcapsular cataract	19 (79)	13 (76)	32 (78)	1
Hypothyroidism	4 (16)	1 (6)	5 (12)	0.63
Thyroid nodules	20 (80)	4 (27)	24 (57)	0.002
Thyroid carcinoma	5 (20)	1 (6)	6 (14)	0.37
Pulmonary insufficiency	12 (48)	7 (41)	19 (45)	0.66
Osteochondroma	10 (40)	2 (12)	12 (28)	0.08

Faraci *et al.* IJROBP *63*: 1568-1575, 2005

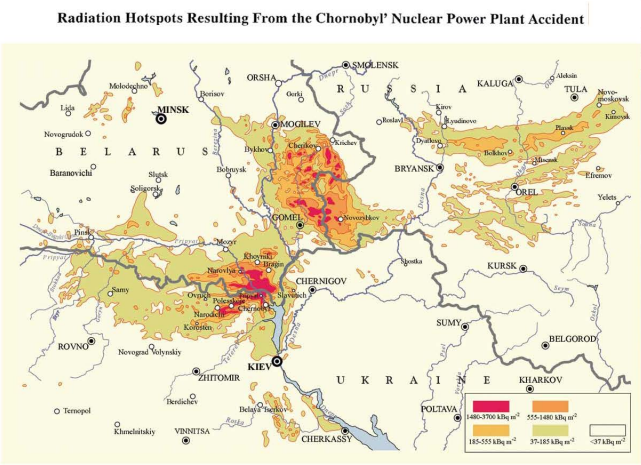
B. **How did we learn about the whole body radiation syndromes, the target cells involved, how long it took for death to occur, whether treatments were possible, etc.?**

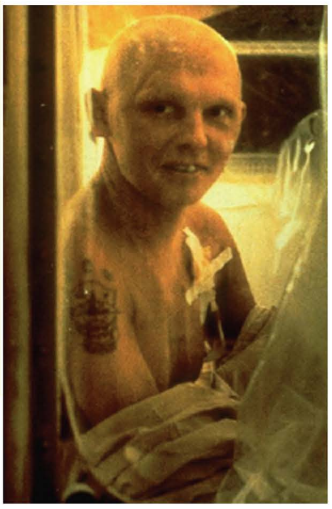
1) Answer: THE HARD WAY...by trial and error, and by carefully studying accident victims when they were available (very infrequently, and usually, in very low numbers)

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

(none of which did them any good if they were dead)

Chernobyl Firefighters and Liquidators – cohorts being studied (where possible) for the appearance of late radiation effects





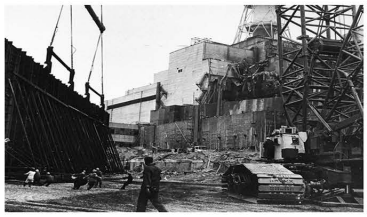
Chernobyl Untoward Effects

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; at the 35+ year mark since the accident, there is still **no** *compelling evidence for a statistical excess of solid tumors*

Why don't there seem to be many excess solid tumors?

Population (years exposed)	Number	Average total in 20 years (mSv)[1]
Liquidators (1986–1987) (high exposed)	240 000	~130
Evacuees (1986)	116 000	>33
Residents SCZs (>555 kBq/m2)(1986–2005)	270 000	>50
Residents low contam. (37 kBq/m2) (1986–2005)	5 000 000	10–20
Natural background	2.4 mSv/year (typical range 1–10, max >20)	48
Approximate typical doses from medical x-ray exposures per procedure:		
Whole body CT scan	12 mSv	
Chest x-ray	0.08 mSv	

[1] These doses are additional to those from natural background radiation.

ANSWER: Not counting the few plant workers and first responders who received lethal doses, even the most highly exposed of the cleanup workers (liquidators), did not receive really high doses.

This table shows estimated *cumulative* doses over the first 20 years after the accident for the liquidators, evacuees and residents who continued to live in both high and low contamination areas. Most received less than the corresponding amount of natural background radiation over the same time period.

Even so, accident victims are not without "late effects"!

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.

Two other sub-syndromes you might hear about:

1. The Cutaneous Syndrome - occurs when the skin receives an acute, moderate-to-extremely-high dose, usually ≥7 Gy (low LET); could accompany any of the other main syndromes assuming the exposure was "penetrating", but if mostly superficial, then would more likely stand alone

Injury	Threshold Dose to Skin (Sv)	Weeks to Onset
Early transient erythema	2	<<1
Temporary epilation	3	3
Main erythema	6	1.5
Permanent epilation	7	3
Dry desquamation	10	4
Invasive fibrosis	10	
Dermal atrophy	11	>14
Telangiectasis	12	>52
Moist desquamation	15	4
Late erythema	15	6-10
Dermal necrosis	18	>10
Secondary ulceration	20	>6

2. The Pulmonary Syndrome - lung pneumonitis acutely (with ~4 months of exposure), possibly followed by lung fibrosis (>6 months after exposure, depending on dose) secondary to an acute dose ≥6 Gy *to most or all of the lungs*

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

...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

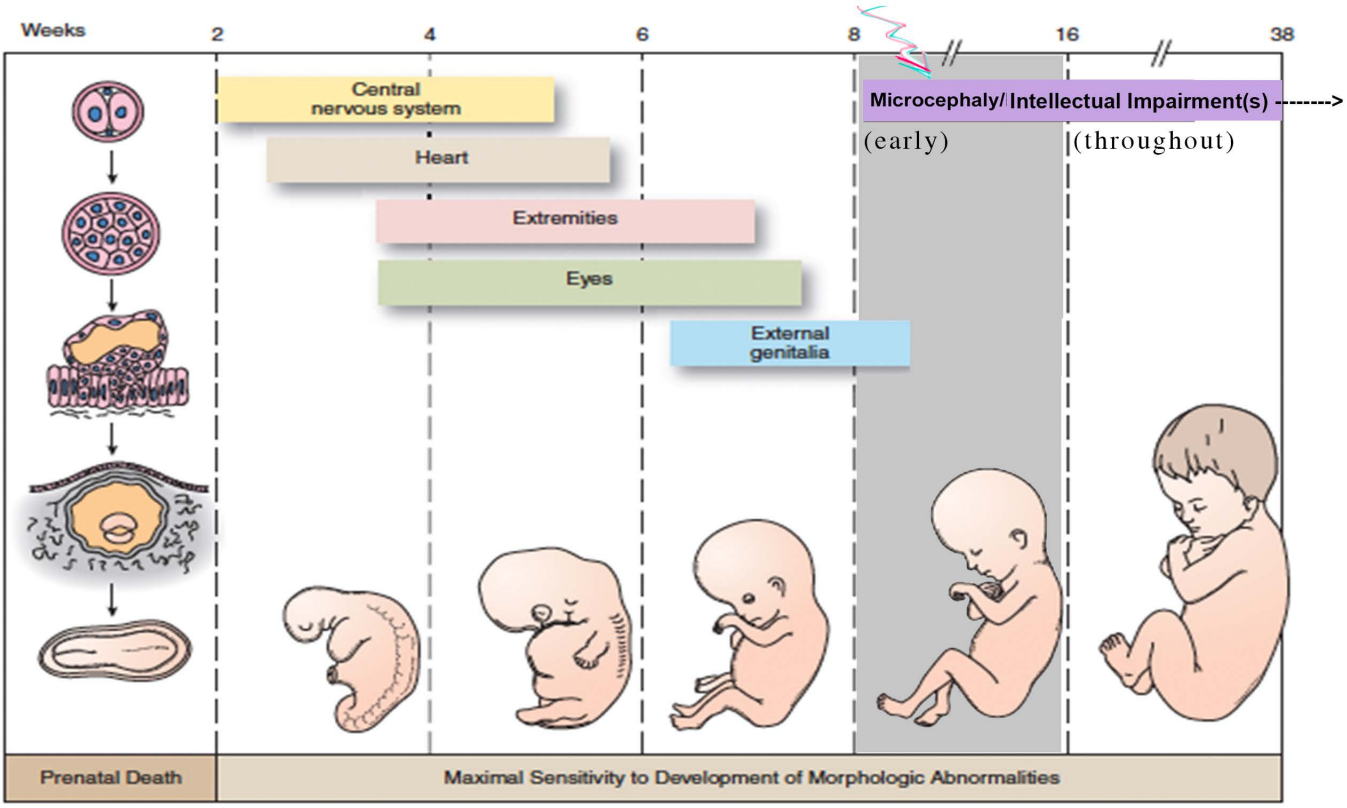
B. How and why does teratogenesis occur?

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 4 general categories:

- embryonic, fetal or neonatal death
- congenital malformations (includes intellectual effects)
- generalized growth retardation ("stunting" of growth) – relatively uncommon in humans
- 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)

- 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

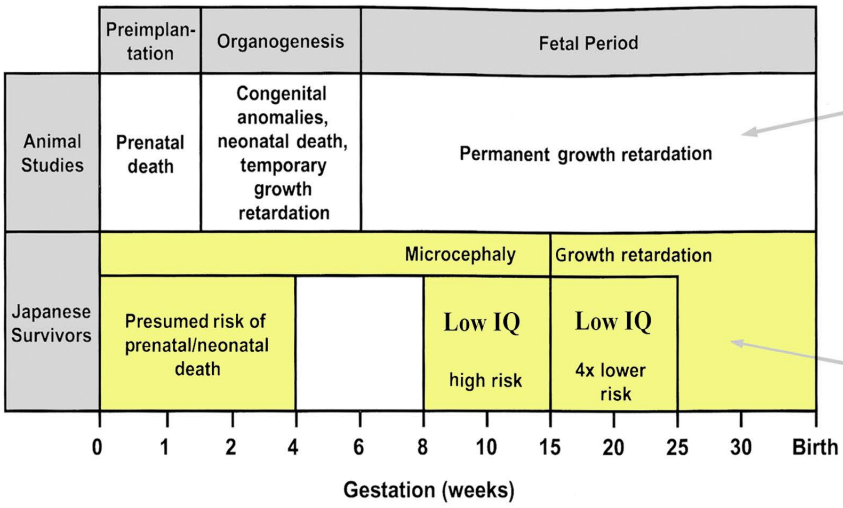
- exposure during the fetal period – from about 8 weeks of gestation onward until birth – can cause damage to the nervous system, leading to **intellectual impairments** (low IQ, memory difficulties, reduced academic performance, etc.), **microcephaly** (small head size), and generalized stunting of 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 significantly elevated in humans who were irradiated in utero are intellectual impairments (e.g., low IQ) and microcephaly (small head size)***

(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



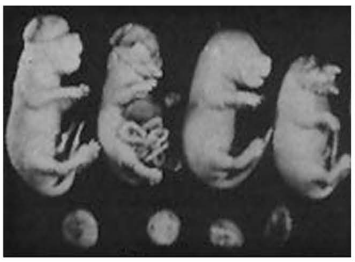


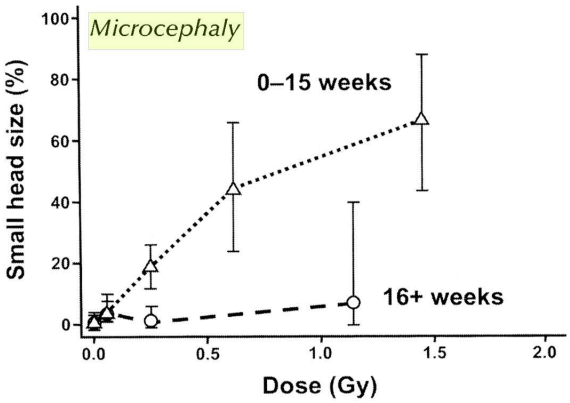
Chart illustrating the similarities and differences between data from small laboratory animals and data from the Japanese survivors of the atomic-bomb attacks.

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:

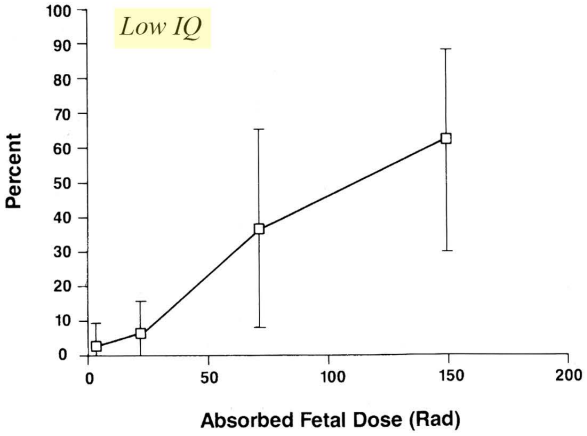
(1) air doses as low as **10-20 cGy**, corresponding to a direct fetal dose of about half that, can cause a measurable increase in microcephaly

(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**

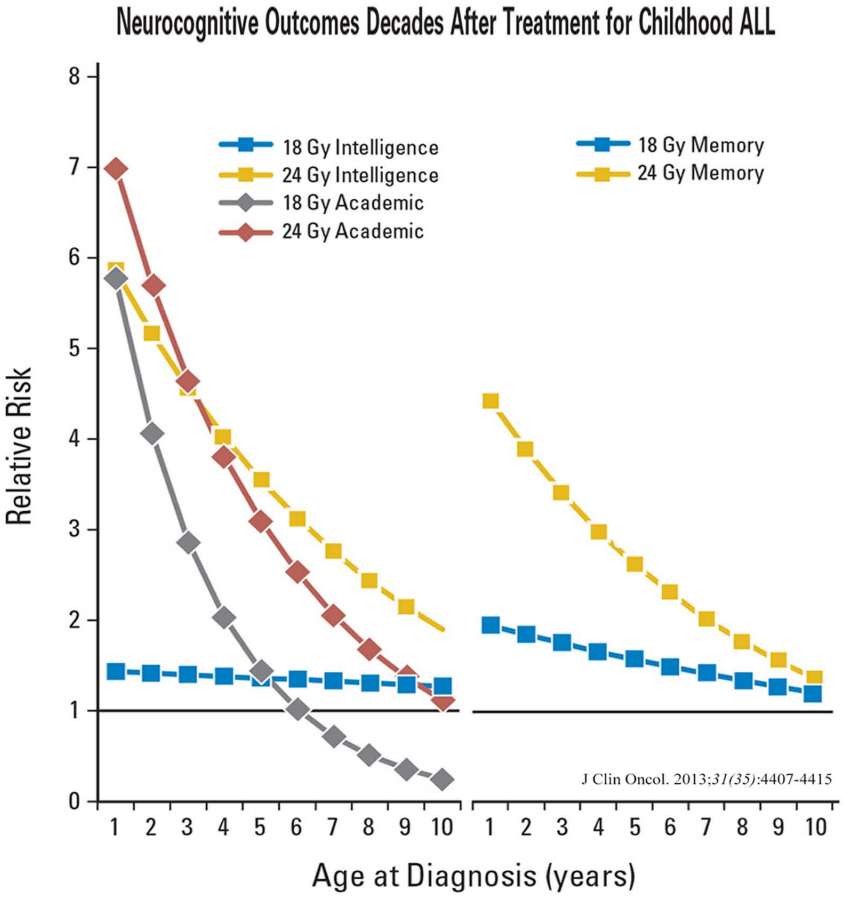


Proportion of exposed individuals with small head sizes as a function of dose and gestational age. (Redrawn from the data of Otake M, Schull WJ: Radiation-related small head size among prenatally exposed A-bomb survivors. *Int J of Radiat Biol* 63:255–270, 1993.)



Risk of mental retardation as a function of fetal dose for Japanese A-bomb survivors who were irradiated *in utero*.

Br J Radiol 57:409–414, 1984



And as we know, the CNS remains sensitive to radiation injury even after birth, e.g., brain irradiation during the first few years of life causes IQ deficits and other cognitive difficulties.

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) What about terminating pregnancy in the event of accidental or medically-necessary (including radiation therapy) irradiation of the mother?

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)

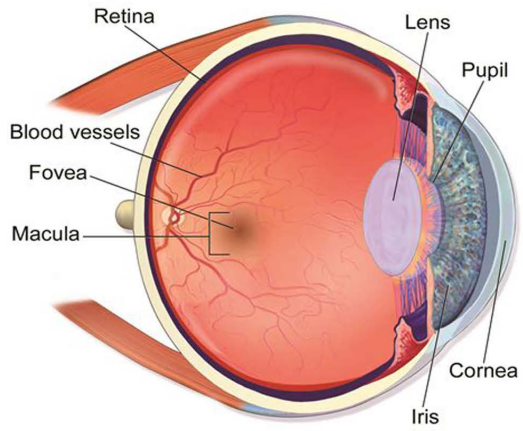
(a) please note that *this cut-off dose of 10 cGy would correspond to, at most, about a 4% excess risk of teratogenesis, which, depending on how you look at it, might not be considered all that high (i.e., about 1 chance in 25), especially when considering that the spontaneous risk of a congenital malformation is already at least 5%*

Radiation-Induced Cataracts - important facts and changing perspectives

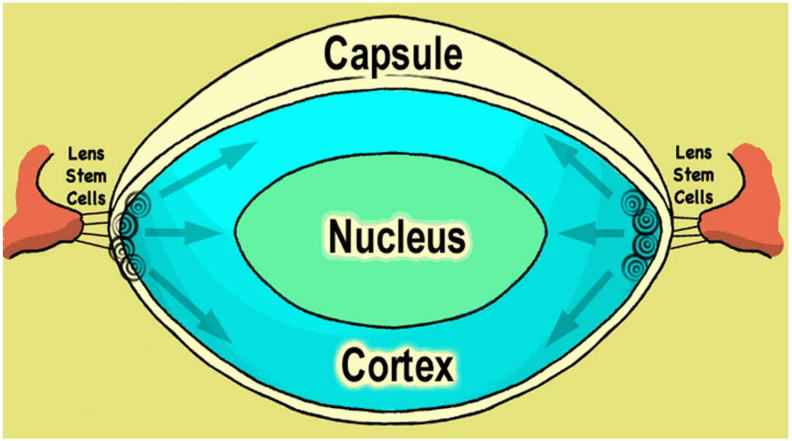
A. Radiation-induced cataracts are unique among radiation effects for several reasons

1) although the lens of the eye is a hierarchical-type tissue with an anatomically-distinct stem cell compartment that produces mature lens cells, it is unusual in that **there is no mechanism of cell loss**

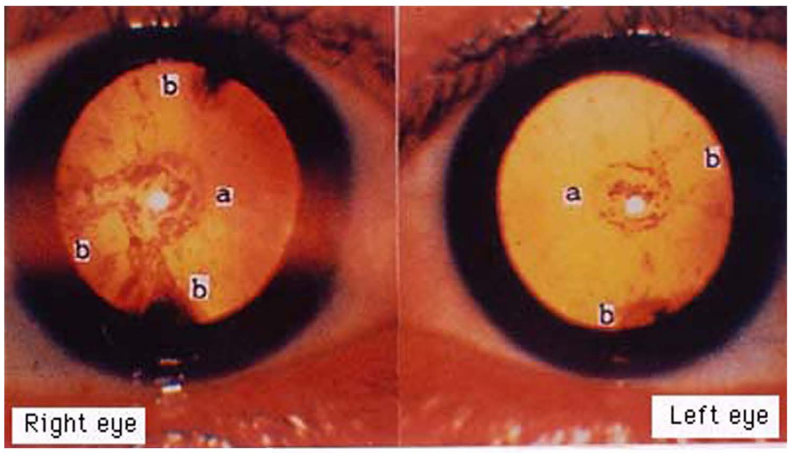
a) this means that *any damage to the stem cells will result in a generation of abnormal lens fibers (i.e., that are opaque instead of translucent), and these will be retained indefinitely* rather than "washed out" over time



Eye Anatomy



2) radiation-induced cataracts are also unique in that **they usually CAN be distinguished from age-related cataracts in terms of their appearance (plaque-like opacity) and location in the lens (posterior pole)**



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) **the severity of the cataract – that is, the fraction of the total lens that has become opaque, and the degree of opacity – increases with increasing radiation dose**

a) accordingly, there is a difference between "any radiation-induced cataract" versus "a clinically-significant radiation-induced cataract"

4) **the latency period for the development of a radiation-induced cataract is variable**; for moderate doses (2-7 Sv), it typically takes 7-10 years for the cataract to become clinically-evident, but for higher doses (>7 Sv), cataracts can occur as soon as 5 years after irradiation

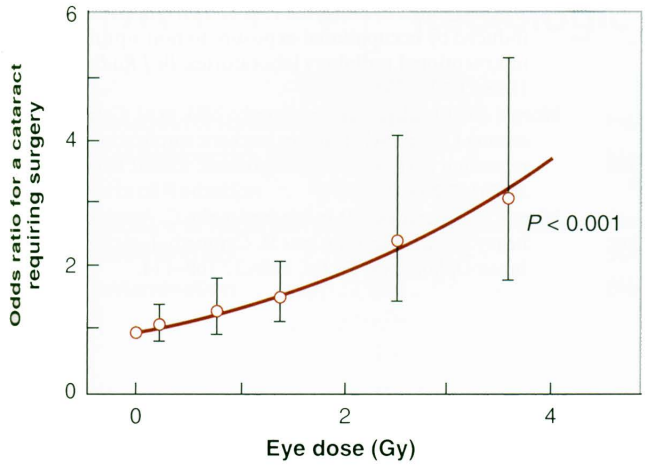
5) in laboratory animals, **neutron and heavy ion RBEs for cataract formation have been measured as high as 50** (when many small dose fractions are used)

B. Dose Response for Radiation-Induced Cataracts

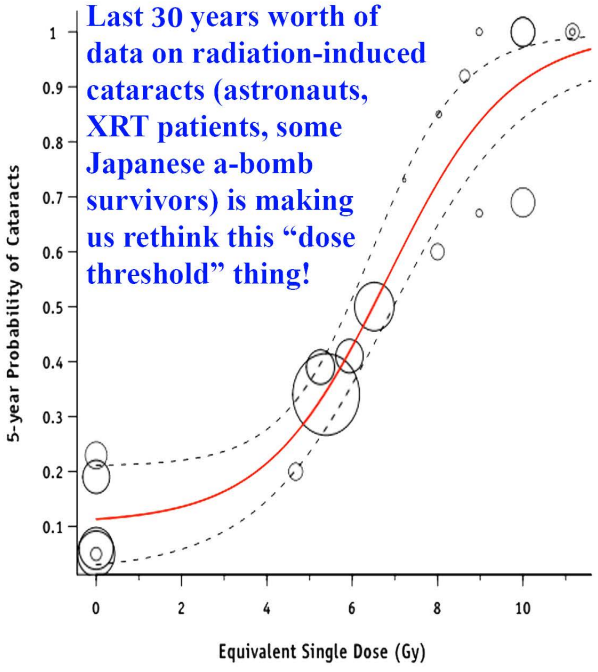
1) **radiation-induced cataracts are a non-stochastic effect (now called a "tissue reaction")** in that they exhibit a dose threshold below which no cataracts occur, and then an increasing risk and increasing severity of cataracts for increasing doses above the threshold

a. **the threshold dose in humans is now estimated to be around 500 mSv** (50 cGy of X-rays), much lower than the assumed threshold dose historically

1] *the lowering of the threshold dose was thanks to data on the a-bomb survivors who received the lowest doses, astronauts on extended space missions, and long-term radiotherapy survivors*



Odds ratio as a function of dose for the induction of a cataract requiring surgical lens removal in Japanese A-bomb survivors. (Redrawn from Neriishi K, Nakashima E, Minamoto A, et al. Postoperative cataract cases among atomic bomb survivors: radiation dose response and threshold. *Radiat Res.* 2007;168:404–408, with permission.)



2] this also explains why the ICRP (in 2011), and then the NCRP (in 2017), reduced their occupational and public annual exposure limits for the lens of the eye:

NCRP = 50 mSv per year for radiation workers, and 15 mSv per year for the general public

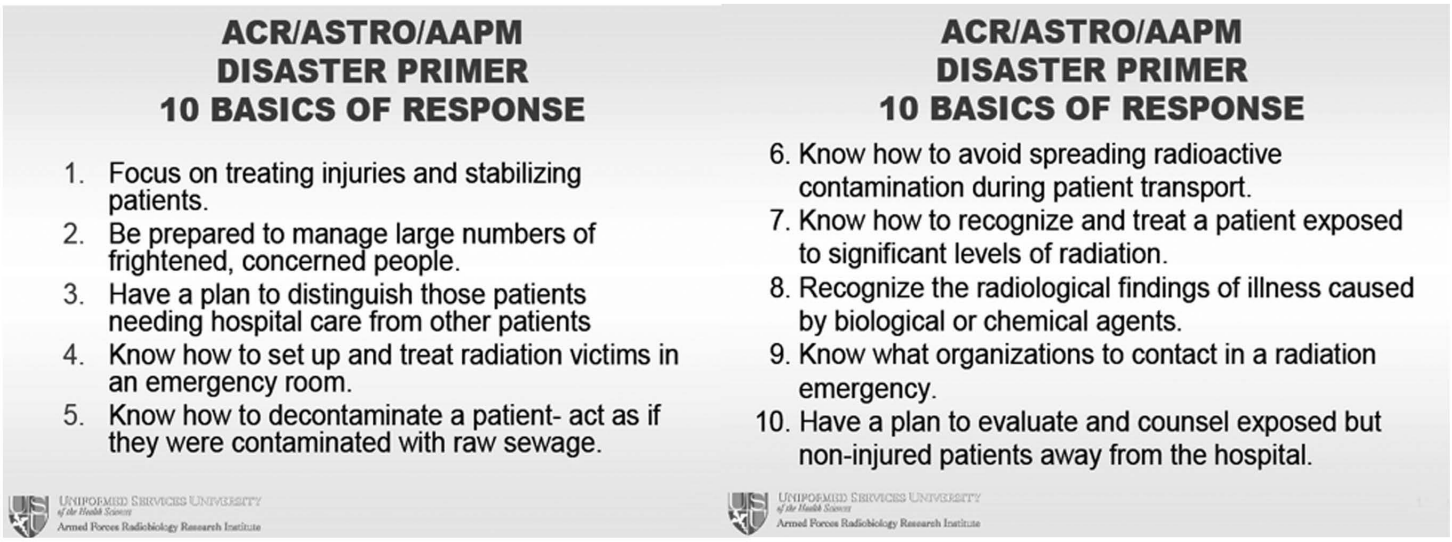
ICRP = no more than 20 mSv per year averaged over 5 years, and no more than 50 mSv per year in any single year

Medical Response to Radiation Accidents or Radiologic Terrorism

Taken from the Preface of *Disaster Preparedness for Radiology Professionals: Response to Radiologic Terrorism* (complete document attached as an Appendix)...

> As we learned on September 11, 2001, a large-scale disaster can strike without warning. The attacks on the World Trade Center and the Pentagon and several incidents of anthrax in the mail placed our colleagues on the front lines in New York, Washington, DC, and other venues, triaging the injured and diagnosing those infected with biological agents. Government officials have issued warnings about the possible use of radiological and chemical weapons in future attacks.
>
> A radiation disaster is a possibility for which we must be prepared. Radiologists, radiation oncologists, and medical physicists will play a vital role as responders and as sources of accurate information for patients, the public, and the medical community.

...conspicuous in its absence is any reference to "radiobiologists", meaning that, like it or not, YOU will be the ones called in the event of a radiation emergency. Accordingly, YOU will need to understand what to do in the (hopefully unlikely) event of such an accident or attack.



APPENDIX MATERIALS

Radiation Disaster Preparedness - everybody should have a copy of at least one review article!

- Mettler, FA and Voelz, GL. Major radiation exposure: What to expect and how to respond. New Eng J Med *346*: 1554-1561, 2002.
- Armed Forces Radiobiology Research Institute (AFRRI) Pocket Guide: Emergency Medical Response to Radiation Accidents, 2011. (**Attached**)
- Koenig *et al.* Medical treatment of radiological casualties: Current concepts. Annals Emergency Med *45(6)*: 643-652, 2005.
- ACR, AAPM and ASTRO Disaster Planning Task Force, "Disaster Preparedness for Radiological Professionals: Response to Radiological Terrorism. A Primer for Radiologists, Radiation Oncologists and Medical Physicists", 2006.
- REAC/TS (Radiation Emergency Assistance Center/Training Site). The medical aspects of radiation incidents handbook, 2011. http://www.orise.orau.gov/reacts
- iPhone App: Mobile REMM http://www.remm.nlm.gov

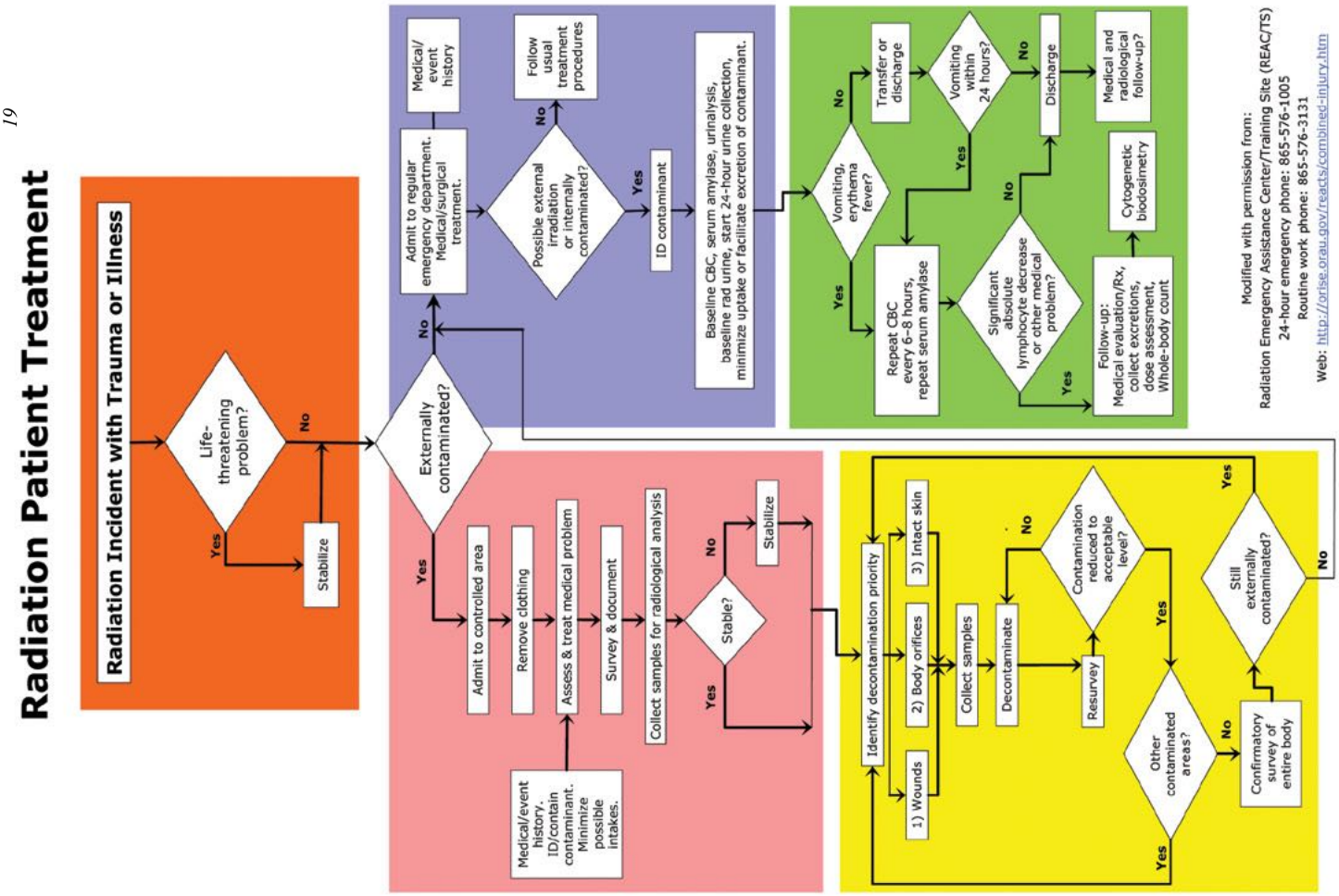


Table 1. Acute radiation syndrome (ARS)—healthy adults*

Whole-body Irradiation from Acute Photon Equivalent Doses							
Phase of Syndrome	Survivability	Highly Survivable		Survivable to Lethal		Lethal	
	Degree of ARS		Mild	Moderate to severe	Very severe	Lethal	
	Dose range (cGy‡)	0–100	100–200	200–600	600–800	800–3000	>3000
Initial or Prodromal	Vomiting: Time of onset: Duration:		5–50% 3–6 hours <24 hours	50–100% 1–6 hours <24 hours	75–100% <2 hours <48 hours	98–100% <1 hour <48 hours	100% <1 hour <48 hours
	Lymphocyte count (cells/mm^3)		<1400 at 4 days	<1400 at 48 hours	<1000 at 24 hours	<800 at 24 hours	
	CNS function	No impairment	No impairment	Routine task performance; cognitive impairment for 6–20 hours	Simple & routine task performance; cognitive impairment for >24 hours	Transient incapacitation	
Latent	Duration	N/A	7–15 days	0–21 days	0–2 days	0–2 days	
Manifest (obvious) Illness	Signs and symptoms	None	Moderate leukopenia	Severe leukopenia, purpura, hemorrhage, pneumonia, hair loss after 300 rad (cGy)		Severe diarrhea, fever, electrolyte disturbance	Convulsions, ataxia, tremor, lethargy
	Time of onset		>2 weeks	2 days–2 weeks		0–2 days	
	Critical period		None	4–6 weeks		5–14 days	1–48 hours
	Principal organ system	None	Hematopoietic	Hematopoietic and gastrointestinal		Gastrointestinal (mucosal surfaces)	CNS
Hospitalization	% Duration	0	<5% 45–60 days	90% 60–90 days	100% 90+ days	100% 2 weeks	100% 2 days
Fatality		0%	0%	0–80%	80–100%	98–100%	
Time of Death				3–12 weeks		1–2 weeks	1–2 days

*Adapted from TM 8-125, Nuclear Handbook for Medical Service Personnel, US Army, 1969. Tabulated data for fatality incidence assumes no treatment.
‡See table 3, Conversion units.

Table 2. Symptom clusters following significant radiation exposures

Headache Fatique Weakness	Partial and full thickness skin damage Epilation (hair loss) Ulceration
Anorexia Nausea Vomiting Diarrhea	Lymphopenia Neutropenia Thromboctopenia Purpura Opportunistic Infections

III. Confirmation of cases

- Contact radiation safety officer (RSO) or health physicist (HP) for help.
- For projecting clinical effects, contact:
  - Nuclear medicine or radiation oncology physician
  - Medical Radiobiology Advisory Team at AFRRI: (301) 295-0530
  - REAC/TS: (865) 576-3131/1005
  - CDC: (770) 488-7100
- Obtain baseline serum amylase and complete blood count (CBC) then repeat CBC every 6–8 hours for 2–3 days. Collect another serum amylase at 24 hours postexposure.
  - Absolute lymphocyte count <500 / mm^3 suggests very severe exposure.
- Check for internal contamination: swab both nostrils; collect 24-hour stool and 24-hour urine samples.

IV. Treatment considerations

- Evaluate ABCs, stabilize any life threatening injuries and then decontaminate.
  - If inhalation or ingestion of radioiodine is suspected (e.g., reactor accident), consider administering potassium iodide within 6 hours and every 24 hours as needed to protect thyroid. For KI dosage levels, see AFRRI's Medical Management of Radiological Casualties, Third Edition (Nov. 2009).
- Provide supportive care based on ARS signs, symptoms, and diagnostic tests: clean environment, fluids, blood products, antiemetics, antibiotics, pain management, etc.
  - Treat symptomatically and close wounds within 36–48 hours.
  - Provide skin and burn care to prevent infection.
  - Focus on prevention and mitigation of infection and sepsis.

V. Decontamination considerations

- Exposure without contamination: no decontamination (RSO measurement).
- Exposure with contamination: use universal precautions, remove and bag patient's clothing, decontaminate with soap and water or saline.
- Suspected internal contamination: contact RSO, HP, or nuclear medicine physician.
- Advanced decontamination planning: where feasible, set up a separate decontamination site for nonurgent patients to avoid contaminating treatment facility.

VI. Reporting

- If reasonable suspicion of a radiation event, contact hospital leadership.
- Immediately discuss hospital emergency planning implications.
- Contact local public health office (city, county, or state) or CDC: (770) 488-7100.

Table 3. Conversion units

Gy = gray Sv = sievert Bq = Becquerel Ci = curie dpm = disintegrations per minute		
p = pico = 10^{-12} n = nano = 10^{-9} μ = micro = 10^{-6} m = milli = 10^{-3} c = centi = 10^{-2} M = mega = 10^{6} G = giga = 10^{9}		
1 Bq = 60 dpm = 27 pCi 37 GBq = 1 Ci 37 MBq = 1 mCi 37 Bq = 1 nCi	1 Gy = 100 rad 1 cGy = 1 rad 10 μGy = 1 mrad 10 nGy = 1 μrad	1 Sv = 100 rem 1 cSv = 1 rem 10 μSv = 1 mrem 10 nSv = 1 μrem

- If terrorism suspected, contact FBI (see www.fbi.gov/contactus.htm).

I. Understanding exposure to radiation

- Exposure may be known and recognized or clandestine through:
  - Large recognized exposures (nuclear bomb or damage to a nuclear power station)
  - Small radiation source emitting continuous gamma radiation, producing group or individual chronic intermittent exposures from medical treatment devices or from water or food pollution
- Exposure may result from any one or a combination of the following:
  - External sources (uncontrolled nuclear reaction, radioisotope outside the body)
  - Skin contamination with radioactive material (external contamination)
  - Internal radiation resulting from inhaled, absorbed, or ingested radioactive material

II. Diagnosis

- Acute radiation syndrome (ARS, table 1)—Expressed in different organ systems at different times after substantial exposure to radiation. Common symptoms include:
  - Skin erythema—Often cyclic, appearing hours to days after exposure and recurring 2–3 weeks later; blistering, desquamation, and ulceration occur a few weeks after high doses.
  - Nausea/vomiting—Appearing within hours after exposure then subsiding (time of onset is inversely related to dose and directly related to severity and duration of exposure).
  - Immunological dysfunction—Beginning a few hours after exposure with secondary infection manifesting days or weeks later.
  - Hemorrhagic tendencies (epistaxis, gingival bleeding, petechiae) within days of exposure.
  - Marrow suppression (lymphopenia, neutropenia, and thrombocytopenia) within initial exposure and, if seen, would suggest at least a moderate exposure; time to nadir is inversely related to dose; order of suppression is lymphocytes, neutrophils, platelets, erythrocytes.
  - Epilation if dose over 300 cGy with onset 10–20 days postexposure.
- Following significant (>100 cGy) acute, chronic, or repeated exposures from hidden or contaminated sources, victims may also present individually with symptom clusters (table 2).

Key references and websites

AFRRI (2009) Medical Management of Radiological Casualties, Third Edition. Bethesda, MD: Armed Forces Radiobiology Research Institute.

Koenig K, et al. (2005) Medical Treatment of Radiobiological Casualties: Current Concepts. Ann Emerg Med, 45(6): 643–52

Waselenko J, et al. (2004) Medical Management of the Acute Radiation Syndrome: Recommendations of the Strategic National Stockpile Radiation Working Group. Ann Intern Med, 140:1037–51.

www.usuhs.edu/afrri/
www.orau.gov/reacts/guidance.htm
http://remm.nlm.gov
www.bt.cdc.gov/radiation

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Armed Forces Radiobiology Research Institute
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AFRRI Pocket Guide

Emergency Radiation Medicine Response

Uniformed Services University of the Health Sciences
Armed Forces Radiobiology Research Institute

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