Acute Radiation Syndrome

Acute Radiation Syndrome (ARS)

ARS, or radiation sickness, occurs in humans after whole-body reception of large doses of ionizing radiation delivered over a short period of time. Data from epidemiologic studies of human populations exposed to doses of ionizing radiation sufficient to cause this syndrome have been obtained from atomic bomb survivors of Hiroshima and Nagasaki, the Marshall Islanders who were inadvertently subjected to high levels of fallout during an atomic bomb test in 1954, nuclear radiation accident victims such as those injured in the 1986 Chernobyl disaster, and radiation therapy patients.

Early radiation responses are described as *deterministic*. Deterministic radiation responses are those that exhibit increasing severity with increasing radiation dose. Furthermore, there is usually a dose threshold.

Syndrome is the medical term that means a collection of symptoms. ARS is a collection of symptoms associated with high-level radiation exposure. Three separate dose-related syndromes occur as part of the total-body syndrome:

- hematopoietic syndrome
- gastrointestinal syndrome
- cerebrovascular syndrome.

ARS manifests itself in four major response stages: prodromal, latent period, manifest illness, and recovery or death.

- Prodromal (initial stage)
- Latent period
- Manifest illness
- Recovery

Prodromal stage

- occurs within hours after a whole-body absorbed dose of 1 Gy (100 rads) or more. Nausea, vomiting, diarrhea, fatigue, and leukopenia (an abnormal decrease in white blood corpuscles, usually below 5000/mm^3) characterize this initial stage. The severity of these symptoms is dose-related; the higher the dose, the more severe the symptoms. The length of time involved for this stage to run its course may be hours or a few days

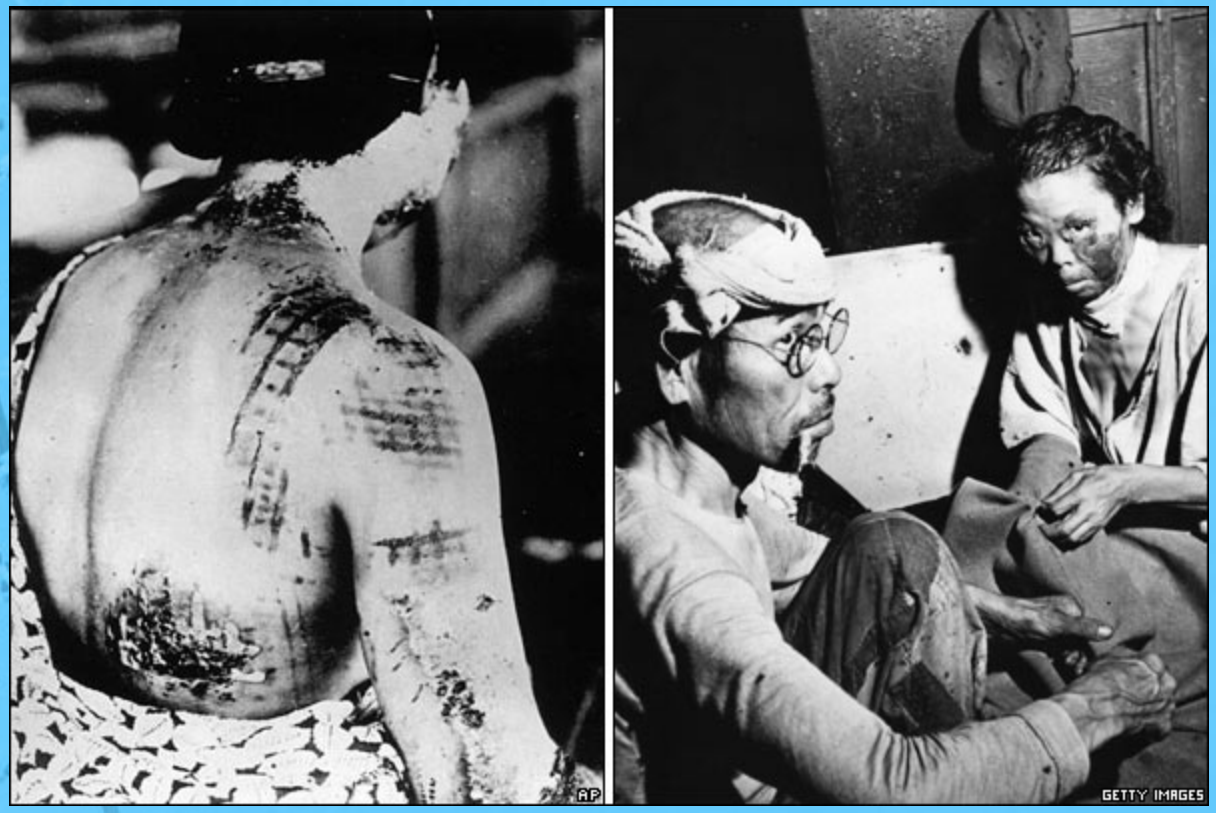
Latent period

- of about 1 week occurs, during which no visible symptoms occur. Actually, it is during this period that either recovery or lethal effects begin. Toward the end of the first week, the next stage commences.

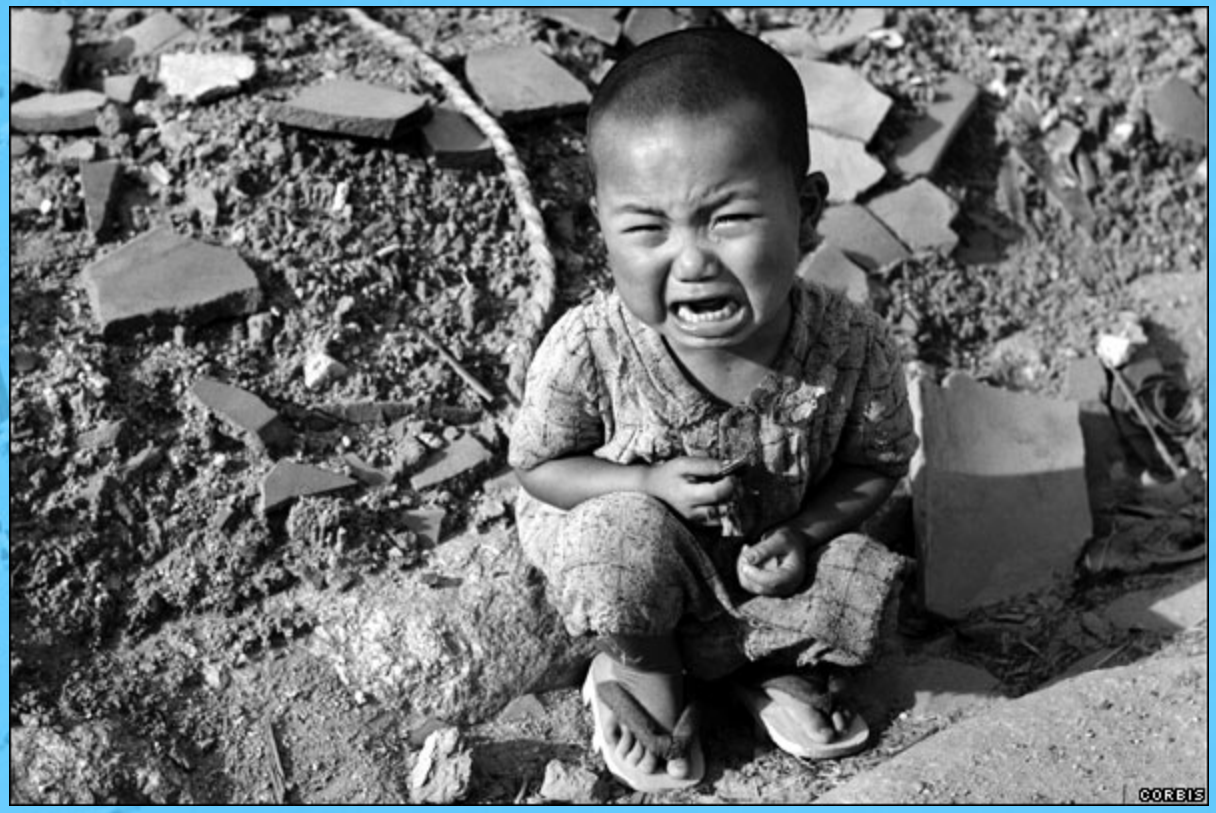
Manifest ilness stage

- is the period when symptoms that affect the hematopoietic, gastrointestinal, and cerebrovascular systems become visible. Some of these symptoms are apathy, confusion, a decrease in the number of red and white blood cells and platelets in the circulating blood, fluid loss, dehydration, epilation, exhaustion, vomiting, severe diarrhea, fever, headaches, infection, hemorrhage, and cardiovascular collapse. In severe high-dose cases, emaciated human beings eventually die.

Former Russian spy, Alexander Litvinenko, 43, is the first known victim to be poisoned with polonium-210 and to die from the resulting radiation sickness. He died on Nov. 23, three weeks after he fell ill in London.



About a third of Hiroshima's population was killed within a week of the bombing. Many more have since died through radiation sickness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If after a whole-body sublethal dose such as 2 to 3 Gy (200 to 300 rads), exposed persons pass through the first three stages but show less severe symptoms than those seen after super-lethal doses of 6 to 10 Gy (600 to 1000 rads), **recovery** may occur in about 3 months. However, those who recover may show some signs of radiation damage and experience late effects.

Chernobyl and ARS

Without effective physical monitoring devices, biologic criteria such as the occurrence of nausea and vomiting played an important role in the identification of radiation casualties during the first 2 days after the nuclear disaster. ARS caused the hospitalization of at least 203 people. A determination of the lapse of time from the incidental exposure of the victims to the onset of nausea and/or vomitting completed the biologic criteria. Dose assessment was determined from **biologic dosimetry.** This included serial measurements of levels of lymphocytes and granulocytes in the blood and a quantitative analysis of dicentric chromosomes (chromosomes having two centromeres) in blood and hematopoietic cells coming from bone marrow. The data were compared with doses and effects from earlier radiation mishaps.

Thirty people at Chernobyl experienced the acute radiation syndrome and died. A number of minor late effects have been observed. No one died or was even seriously exposed in the March 1979 incident at the nuclear power reactor at Three Mile Island, Pennsylvania. Employment in the nuclear power industry is a safe occupation.

Forms of ARS:

- Hematopoietic
- GI
- CNS

Hematopoietic syndrome

The hematopoietic form of ARS, or "**bone marrow syndrome,"** occurs when human beings receive whole-body doses of ionizing radiation ranging from 1 to 10 Gy (100 to 1000 rads). The hematopoietic system manufactures the corpuscular elements of the blood and is the most radiosensitive vital organ system in humans. Radiation exposure causes the number of:

1. red cells
2. white cells
3. platelets

In the circulating blood to decrease. Dose levels that cause this syndrome also may damage cells in other organ systems, causing the affected organ or organ system to fail.

The patient initially experiences mild symptoms of the prodromal syndrome, which appear in a matter of a few hours and may persist for several days.

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For example, radiation doses ranging from 1 to 10 Gy (100 to 1000 rads) produce a decrease in the number of bone marrow stem cells. When the cells of the lymphatic system are damaged, the body loses some of its ability to combat infection. Because the number of platelets also decreases with loss of bone marrow function, the body loses a corresponding amount of its blood-clotting ability. This makes the body more susceptible to hemorrhage

For persons affected with hematopoietic syndrome, survival time shortens as the radiation dose increases. Because additional bone marrow cells are destroyed as the radiation dose escalates, the body becomes more susceptible to infection (mostly from its own intestinal bacteria) and more prone to hemorrhage. When death occurs, it is a consequence of bone marrow destruction.

Death may occur 6 to 8 weeks after irradiation in some sensitive human subjects who receive a whole-body dose exceeding 2 Gy (200 rads). As the whole-body dose increases from 2 to 10 Gy (200 to 1000 rads), irradiated individuals die sooner. If the radiation exposure is not lethal, perhaps in the range of 1 to 2 Gy (100 to 200 rads), bone marrow cells will eventually repopulate to a level adequate to support life in most individuals. Many of these people recover 3 weeks to 6 months after irradiation.

The actual dose of radiation received and the irradiated person's general state of health at the time of irradiation determine the possibility of recovery. When death occurs in exposed individuals, it results from bone marrow destruction. The severe reduction of blood cells causes anemia and permits exposed individuals to become susceptible to infection. This results in death of those individuals.

Survival probability of patients with hematopoietic syndrome is enhanced by intense supportive care and special hematologic procedures.

Gastrointestinal syndrome

In human beings the gastrointestinal form of ARS appears at a threshold dose of approximately 6 Gy (600 rads) and peaks after a dose of 10 Gy (1000 rads). Without medical support to sustain life, exposed persons receiving doses of 6 to 10 Gy (600 to 1000 rads) may die 3 to 10 days after being exposed. Even if medical support is provided, the exposed person will live only a few days longer. **Survival time does not change with dose in this syndrome**.

A few hours after the dose required to cause the gastrointestinal syndrome has been received, the prodromal stage occurs. Severe nausea, vomiting, and diarrhea persist for as long as 24 hours.

This is followed by a latent period, which lasts as long as 5 days. During this time the symptoms disappear. The manifest illness stage follows this period of false calm. Again, the human subject experiences severe nausea, vomiting, and diarrhea. Other symptoms that may occur include fever (as in hematopoietic syndrome), fatigue, loss of appetite, lethargy, anemia, leukopenia (decrease in the number of white blood cells), hemorrhage (gastrointestinal tract bleeding occurs because the body loses its blood-clotting ability), infection, electrolyte imbalance, and emaciation.

Death occurs primarily because of catastrophic damage to the epithelial cells that line the gastrointestinal tract. Such severe damage to these cells results in the death of the exposed person within 3 to 5 days of irradiation, as a result of infection, fluid loss, or electrolytic imbalance.

Death from gastrointestinal syndrome is not exclusively from damage to the bowel but also can be induced from damage to the bone marrow. The latter is usually sufficient to cause death in hematopoietic syndrome.

The small intestine is the most severely affected part of the gastrointestinal tract. Because epithelial cells function as an essential biologic barrier, their breakdown leaves the body vulnerable to infection (mostly from its own intestinal bacteria), dehydration, and severe diarrhea. Some epithelial cells regenerate before death occurs. However, because of the large number of epithelial cells damaged by the radiation, death may occur before cell regeneration is accomplished. The workers and firefighters at Chernobyl are examples of humans who died as a result of gastrointestinal syndrome.

Cerebrovascular syndrome

The cerebrovascular form of the ARS results when the central nervous system and cardiovascular system receive doses of 50 Gy (5000 rads) or more of ionizing radiation. A dose of this magnitude can cause death within a few hours to 2 or 3 days after exposure. After irradiation the prodromal stage begins. Symptoms include excessive nervousness, confusion, severe nausea, vomiting, diarrhea, loss of vision, a burning sensation of the skin, and loss of consciousness. A latent period lasting up to 12 hours follows. During this time, symptoms lessen or disappear. After the latent period the manifest illness stage occurs.

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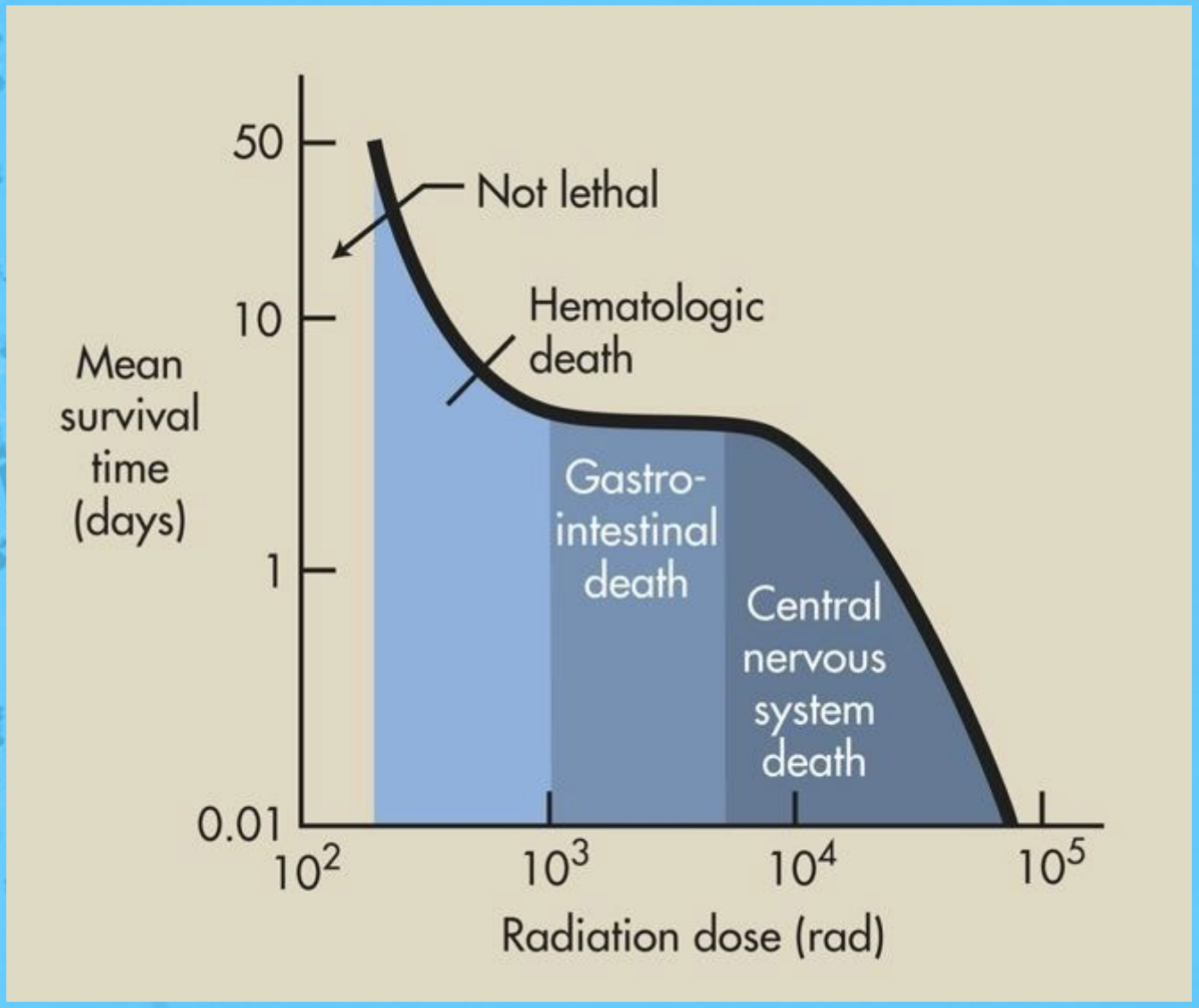
During this period the prodromal syndrome recurs with increased severity, and other symptoms appear, including disorientation and shock, periods of agitation alternating with stupor, ataxia (confusion and lack of muscular coordination), edema in the cranial vault, loss of equilibrium, fatigue, lethargy, convulsive seizures, electrolytic imbalance, meningitis, prostration, respiratory distress, vasculitis, and coma. Damaged blood vessels and permeable capillaries permit fluid to leak into the brain, causing an increase in fluid content. This creates an increase in intracranial pressure, which causes more tissue damage. The final result of this damage is failure of the central nervous and cardiovascular systems, which causes death in a matter of minutes.

Because the gastrointestinal and hematopoietic systems are more radiosensitive than the central nervous system, they also are severely damaged and fail to function after a dose of this magnitude. However, because death occurs quickly, the consequences of the failure of these two systems are not demonstrated

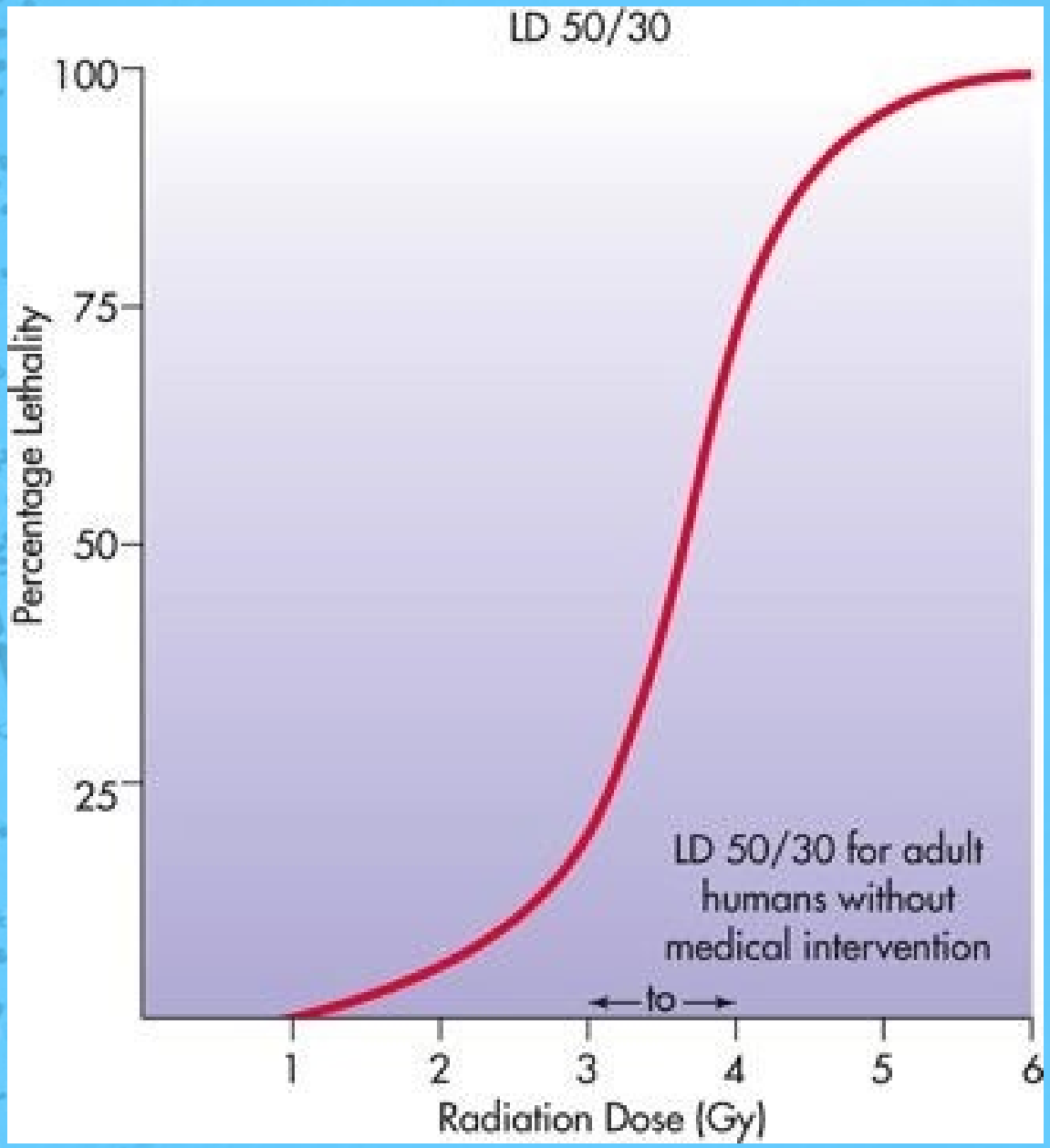

50
10
1
0.01
Mean survival time (days)
Not lethal
Hematologic death
Gastro-intestinal death
Central nervous system death
10^2
10^3
10^4
10^5
Radiation dose (rad)

Stage	Dose—Gy (Rads)	Average Survival Time	Symptoms
Prodromal	1 (100)	—	Nausea, vomiting, diarrhea, fatigue, leukopenia
Latent	1–100 (100–10000)	—	None
Hematopoietic	1–10 (100–1000)	6 to 8wk (doses over 2Gy)	Nausea; vomiting; diarrhea; decrease in number of red blood cells, white blood cells, and platelets in the circulating blood; hemorrhage; infection
Gastrointestinal	6–10 (600–1000)	3–10 days	Severe nausea, vomiting, diarrhea, fever, fatigue, loss of appetite, lethargy, anemia, leukopenia, hemorrhage, infection, electrolytic imbalance, and emaciation
Cerebrovascular	5 and above (5000 and above)	Several hours to 2 or 3 days	Same as hematopoietic and gastrointestinal, plus excessive nervousness, confusion, lack of coordination, loss of vision, a burning sensation of the skin, loss of consciousness, disorientation, shock, periods of agitation alternating with stupor, edema, loss of equilibrium, meningitis, prostration, respiratory distress, vasculitis, coma

LD 50/30

The term *LD 50/30* signifies the whole-body dose of radiation that can be lethal to 50% of the exposed population within 30 days.

This is a quantitative measurement that is fairly precise when applied to experimental animals. Humans exposed to substantial whole-body doses of ionizing radiation, however, take longer to recover than do laboratory animals. Hence, the LD 50 for humans may require more than 30 days for its full expression. The LD 50/30 for adult humans is estimated to be 3.0 to 4.0 Gy (300 to 400 rads) without medical support). For x-rays and gamma rays, this is equal to an equivalent dose of 3.0 to 4.0 Sv (300 to 400 rem). Whole-body doses greater than 6 Gy (600 rads) may cause the death of the entire population in 30 days without medical support. With medical support, human beings have tolerated doses as high as 8.5 Gy (850 rads)


LD 50/30
100
75
50
25
Percentage Lethality
LD 50/30 for adult humans without medical intervention
to
1
2
3
4
5
6
Radiation Dose (Gy)

When medical treatment is given promptly, the patient is supported through initial symptoms, but the question of long-term survival may simply be delayed. Thus survival over a 60-day period may be a more relevant indicator of outcome for humans than survival over a 30-day period. This is the reason that **LD 50/60** for humans may be more accurate.

Regardless of treatment, whole-body equivalent doses of greater than 12 Gy (1200 rads) are considered fatal.

Species	$LD_{50/60}$ (rad)
Pig	250
Dog	275
Human	350
Guinea pig	425
Monkey	475
Opossum	510
Mouse	620
Goldfish	700
Hamster	700
Rat	710
Rabbit	725
Gerbil	1050
Turtle	1500
Armadillo	2000
Newt	3000
Cockroach	10,000

Repair and Recovery

Because cells contain a repair mechanism inherent in their biochemistry (repair enzymes), repair and recovery may occur when cells are exposed to sublethal doses of ionizing radiation. After irradiation, surviving cells begin to repopulate. This permits an organ that has sustained functional damage as a result of radiation exposure to regain some or most of its functional ability. However, the amount of functional damage sustained determines the organ's potential for recovery. In the repair of sublethal damage, oxygenated cells receiving more nutrients have a better prospect for recovery than do hypoxic (poorly oxygenated) cells receiving less nutrients. If both oxygenated and hypoxic cells receive a comparable dose of low-LET radiation, the oxygenated cells are more severely damaged but those that survive repair themselves and recover from the injury. Even though they are less severely damaged, the hypoxic cells do not repair and recover as efficiently

Research has shown that repeated radiation injuries have a cumulative effect. Hence a percentage (about 10%) of the radiation-induced damage is irreparable, whereas the remaining 90% may be repaired over time. When the processes of repair and repopulation work together, they aid in healing the body from radiation injury and promote recovery.