Early Lethal Effects: Acute Radiation Syndrome

Acute Radiation Syndrome (ARS) (sometimes known as radiation toxicity or radiation sickness) is an acute illness caused by irradiation of the entire body (or most of the body) by a high dose of penetrating radiation in a very short period of time (usually a matter of minutes).

The major cause of this syndrome is depletion of immature parenchymal stem cells in specific tissues.

Examples of people who suffered from ARS are the survivors of the Hiroshima and Nagasaki atomic bombs, the firefighters that first responded after the Chernobyl Nuclear Power Plant event in 1986, and some unintentional exposures to sterilisation irradiators.

The four stages of ARS are:

1. **Prodromal stage** (N-V-D stage): Symptoms appear soon after irradiation and last for a limited period of time. The classic symptoms for this stage are nausea, vomiting, as well as anorexia and possibly diarrhea (depending on dose), which occur from minutes to days following exposure. The symptoms may last (episodically) for minutes up to several days.

2. **Latent stage**: In this stage, the patient looks and feels generally healthy for a few hours or even up to a few weeks.

3. **Manifest illness stage**: In this stage the symptoms depend on the specific syndrome and last from hours up to several months.

4. **Recovery or death**: Most patients who do not recover will die within several months of exposure. The recovery process lasts from several weeks up to two years.

The time of onset, severity and duration of symptoms, and the survival time and ultimate mode of death depend on the total radiation dose. In mammals three distinct modes of death can be identified although overlap frequently occurs. **The three classic ARS Syndromes:**

Early Lethal Effects: Acute Radiation Syndrome (cont)

Cerebrovascular Syndrome (Cardiovascular (CV)/ Central Nervous System (CNS))

At very high radiation doses, (>100 Gy), death occurs in a matter of hours and appears to result from neurological and cardiovascular breakdown.

At these doses all organ systems in the body, including the gastrointestinal and haematological, will be seriously damaged and would fail if the individual lived long enough.

For doses >20 Gy, severe nausea and vomiting occur within minutes followed by disorientation, loss of coordination, respiratory distress, diarrhea, convulsions, coma and finally death.

The exact cause of death is not fully understood. Although death is a result of events in the central nervous system, much higher doses are required to produce death if the head alone is irradiated rather than the entire body.

It is believed that death results from build- up of pressure within the skull as a result of an increase in fluid content of the brain due to leakage from small vessels.

Gastrointestinal Syndrome

At radiation doses between 5 and 12 Gy, death occurs in a matter of days (usually 3 to 10) and is associated with extensive bloody diarrhea and destruction of the gastrointestinal mucosa.

Symptoms are nausea, vomiting, lack of appetite and prolonged diarrhea. After a few days, these lead to dehydration, weight loss, emaciation, complete exhaustion and ultimate death.

No human has survived a total-body dose in excess of 10 Gy.

Early Lethal Effects: Acute Radiation Syndrome (cont)

Death is due to the depletion of the stem cells of the epithelial lining of the gastrointestinal tract. The normal lining of the intestines is an example of a self- renewing tissue. Dividing cells are confined to the crypts which provide a continuous supply of new cells which move up the villi that line the intestine.

The cells at the top of the folds of villi are continuously sloughed off and cells that originate from mitosis in the crypts continuously replace the villi. The radiation kills large proportions of the dividing cells and eventually the surface lining of the intestine will be completely denuded of villi.

Radiation doses large enough to cause death as a result of the gastrointestinal syndrome will be already much larger than that required to produce haematopoietic death. However, death will occur before the full effect of radiation on the blood-forming organs has been expressed.

Haematopoietic Syndrome

At lower radiation dose levels (2.5-5.0 Gy) death, if it occurs, is due to effects on the blood-forming organs.

Actively dividing precursor cells in the bone marrow are sterilised by the radiation and the subsequent supply of mature red cells, white cells, and platelets is diminished. The critical time when the number of circulating cells in the blood reaches a minimum value occurs some weeks after the radiation dose.

A concept used to measure death from this cause is the 50 percent lethal dose (LD50) which is the dose that causes a mortality of 50 percent in the population (humans or animals) within a specified period of time.

Mean Lethal Dose

Humans develop signs of haematological damage and recover from it much more slowly than all other mammals.

Consequently, the LD50 estimates for haematopoietic death for humans are expressed as LD50/60, in contrast to the LD50/30 for animals.

Many attempts have been made to estimate LD50/60 for man based on the experience of Hiroshima and Nagasaki, the total-body irradiation of patients with malignant disease, and nuclear accidents.

The LD50 for humans (that is, the dose that would be lethal to 50 percent of the population) is found to be 3 to 4 Gy for young adults without medical intervention. It may be less for the young or the old.

Bone marrow transplantation techniques are used routinely to ‘rescue’ patients given supra-lethal doses of radiation for the treatment of leukemia or in preparation for organ transplants. In such cases, the dosimetry is accurate and the doses are just enough to suppress the immunological response. Typically, doses are 12 Gy in six fractions over three days, the two daily fractions being given about eight hours apart.

In the case of accidental exposure, however, the absorbed radiation is usually non- uniform and the dose level unknown, making it difficult to assess the severity of its effect.

This in turn makes it difficult to provide optimum treatment. Patient management is usually conservative and treatment is instituted only in response to specific symptoms, that is, antibiotics for infection, intravenous fluids for dehydration and platelet infusion for bleeding.

The important thing is to avoid infection, bleeding and trauma when blood elements are at their minimum. The patients do not require special isolation or barrier nursing. The use of bone marrow transplants in these patients is controversial and usually unsuccessful.

Radiation-Induced Cancer

Late effects of radiation are due to damage to cells that survive but retain some legacy of the radiation exposure which remains unapparent for prolonged periods of time.

Irradiation of a germ cell (a sexual reproductive cell in any stage of development) may result in the expression of a genetic mutation in a further generation.

On the other hand, irradiation of a somatic cell (any cell that has the diploid number of chromosomes) may result in leukemia or cancer in the exposed individual.

Classification of Biological Effects

Following cellular damage, two different outcomes are possible. These are known as either stochastic effects or deterministic effects.

Stochastic Effects

Genetic effects and carcinogenesis are said to be stochastic effects. In this case, there is no dose threshold and the effect is all or nothing.

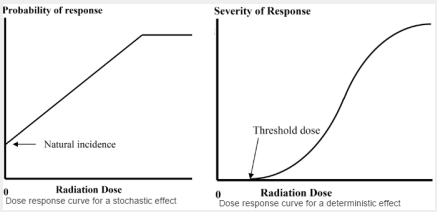
These are essentially random occurrences and the severity of the biological response is not dose related, but the probability of a response occurring is. There is also a natural incidence of these effects in the general population even in the absence of radiation.

Deterministic Effects

A somatic effect that increases in severity with increasing dose is a deterministic effect (formally non-stochastic effect).

The effects include cataracts, organ atrophy and fibrosis. There is a dose threshold and above this the severity of the biological response in the individual increases as the dose increases.

Stochastic effects and deterministic effects.



Dose response curve for a stochastic effect

Dose response curve for a deterministic effect

Carcinogenesis in Humans

Cancer induction is generally considered the most important effect of low to intermediate doses of radiation in human populations.

Historical examples of radiation carcinogenesis include the following:

Leukemia and cancer

Pioneer radiation workers, for example, Marie Curie, often died from radiation induced diseases.

Other examples include the Japanese survivors from Hiroshima and Nagasaki, and patients given radiotherapy to the spine for ankylosing spondylitis (a chronic inflammatory disease affecting the spine with eventual fusion - ankylosis- of the involved joints).

Skin cancer

Physicists and engineers who worked around linear accelerators before radiation safety standards were introduced suffered horrendous damage to their skin. Children who were given radiotherapy for scalp epilation so that ringworm could be treated with drugs also developed skin cancer. This arose only in white children and involved areas of the face and scalp which were also subjected to sunlight.

Lung cancer

Pitchblende and uranium miners developed lung cancer from inhalation of radon gas (α-emitter, high LET radiation) which became permanently deposited in the lung.

Bone cancer

The luminous-dial painters of the early 20th century ingested radium (α-emitter) by pointing their brushes with their lips. The radium substituted for calcium in areas of growing bone and ultimately produced cancer in this site. Similarly, patients injected with radium salts for the treatment of either tuberculosis (a chronic granulomatous infection usually affecting the lungs) or ankylosing spondylitis also developed bone cancer.

Liver tumours

Carcinogenesis in Humans (cont)

In the past, patients were given the contrast material 'Thorotrast' which contained thorium (α-emitter) and deposited in the liver producing tumours in this organ.

Thyroid cancer

In children given radiotherapy for suspected enlarged thymus, the treatment field included the thyroid area and so thyroid cancer often resulted from these procedures. Both malignant and benign thyroid tumours were observed. Thyroid cancer also resulted from radiotherapy of children for scalp epilation (see skin cancer above).

Breast cancer

When tuberculosis was widespread, patients often underwent fluoroscopy many hundreds of times during artificial pneumothorax. Pneumothorax is a collection of air or gas in the pleural space causing the lung to collapse and past therapeutic methods for TB. patients included induced pneumothorax in an attempt to kill the infection through lack of oxygen. An increase in breast cancer in female patients was observed as a result of this technique. Also, patients who received radiotherapy for postpartum mastitis (breast infection after child-birth) also showed an increase in breast cancer.

'One Cell' Theory of Cancer Induction

Cancer formation is believed to be initiated by a somatic mutation produced in a single cell by ionising radiation or chemical carcinogens.

If this mutation is not repaired, the cell can be promoted to divide. Eventually, the resulting transformed cells invade the host tissue and develop into a tumour.

'One Cell' Theory of Cancer Induction (cont)

Tissue typically contains 10^9 cells per gram. Therefore, if the cells divide at regular intervals then it will take 30 **'doubling times'** to produce a mass of one cubic centimetre containing approximately 1000 million cells ($230 = 1.07 \times 10^9$). The doubling time is, as it implies, the time taken to double the number of cells present and takes into consideration the cell cycle time and the natural programmed death of cells.

A mass of one cubic centimetre would generally be considered an early lesion and perhaps the smallest size that could be routinely detected by a diagnostic imaging investigation.

After 40 doubling times, the mass would be about one kilogram and significant clinical changes would be apparent.

If the patient could survive another 5 doubling times (an unlikely event) the mass would be in excess of 30 kg.

Therefore, the time from one cell to one gram is at least twice the length of time from one gram to death. This means that the tumour may have spent two-thirds of its history before being detected.

Latent period

The 'One Cell' Theory helps us to explain the existence of a 'latent period' which is the time between the irradiation and the appearance of a tumour.

Leukemia has the shortest latent period.

In the survivors of Hiroshima and Nagasaki, leukemia cases appeared within a few years, peaked between 7-12 years and essentially disappeared after 20 years.

On the other hand, solid tumours show a longer latency of from 20 to 50 years.

'One Cell' Theory of Cancer Induction (cont)

For example, if the doubling time for a tumour is 100 days, it will take over eight years to grow to a diagnosable mass of one gram. The cancer can, of course, spread to a secondary site at any stage during this period. If this metastasis grows at a similar rate, it too would take over eight years to be detected, and this would also help to explain how secondaries sometimes appear many years after the apparently successful removal of a primary tumour.

Factors Effecting Risk of Radiation Carcinogenesis

Dose is an important factor in carcinogenesis.

As dose increases, there is a linear increase in the relative risk of malignancy. At low effective doses (under 0.5 Sv) there appears to be a region of supralinearity where the relative risk is higher at these doses compared with higher doses.

High doses: The doses used in radiotherapy are a special case. There are conflicting reports of cancer risk, compounded by the higher second cancer risk expected in the population due to their genetic and environmental factors.

Recent studies have suggested that there is an elevated risk of malignancy. This includes analysis of cancer populations and comparisons between patients treated with and without radiation. The risk appears to plateau at about a factor of three, at doses approaching 10-20 Gy. Some studies suggest that the relative risk in certain tissues may be even higher.

There is some evidence that **lower dose rates**, or **fractionated doses**, may cause less carcinogenesis than a single dose at a high dose rate. This effectively halves the risk for lower dose rates when compared with high dose rates.

Factors Effecting Risk of Radiation Carcinogenesis (cont)

There is strong evidence from the atomic bomb survivors that the **age of the person** has a significant effect on the development of malignancy. Females under the age of 15 seem to have the highest risk. Women over 50 have minimal excess risk. Middle aged individuals are also at a much lower risk than the young.

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Assessing the Risk of Radiation Exposure

Most data on carcinogenesis in humans involve relatively small numbers of individuals who received relatively large doses of radiation.

It is difficult, therefore, to deduce from these results the form or shape of the dose-response relationship

Various models can be used to extrapolate high dose data on cancer incidence to the low dose region, so that risk estimates can be made.

In the **linear-no-threshold (LNT)** relationship, the excess cancer incidence is assumed to be proportional to the dose, that is, the rate of risk (the slope of the graph) is the same at high and low doses.

In the alternative **linear-quadratic relationship**, the excess cancer incidence is proportional to the dose and the dose squared. You can see that this implies a smaller risk at low doses compared to the linear relationship.

Nnote that both models depict the risk of cancer in excess of the normal incidence expected at zero radiation dose.

Estimates are usually expressed as the number of excess (radiation-induced) cases of cancer in an exposed population per unit dose. The radiation dose can be the result of exposure to x-rays, neutrons, α-particles and as we have seen earlier, the relative biological effectiveness (RBE) of various radiations are often quite different.

Assessing the Risk of Radiation Exposure (cont)

In fact, the complexities of RBE are too difficult in specifying dose limits in radiological protection. It is necessary, therefore, to have a simpler way to consider differences in the biological effectiveness of different radiations. One Gray of neutrons, for example, is more hazardous than one Gray of x-rays.

The term **Radiation Weighting Factor (WR)** has been introduced for this purpose and the equivalent dose is obtained by multiplying the absorbed dose by WR. When the absorbed dose is in Grays (Gy), equivalent dose is in Sieverts (Sv).

WR for all low-LET radiations (x-rays, gamma-rays, and electrons) is unity, while high- LET radiations have WR values between 5 and 20. Using this system, an absorbed dose of 10 mGy of a radiation with a WR of 20 would result in an equivalent dose of 200 mSv.

For the purposes of radiation protection in radiotherapy, diagnostic radiology and nuclear medicine, the radiation weighting factor WR is unity since the radiations involved are generally only x-rays, gamma-rays and electrons. In these circumstances, an absorbed dose of 10 mGy will result in an equivalent dose of 10 mSv.

The currently accepted risk estimate for radiation-induced cancer is based on the linear- no-threshold model.

For low dose radiation accumulated at low dose rate, the numerical risk is estimated to be:

4.0×10^{-2} Sv-1 for adult workers and

5.0×10^{-2} Sv-1 for the whole population

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