RADIATION EFFECTS

The biological effects of ionizing radiation depend on factors such as the characteristics of the radiation (energy, intensity, content) and the target (structure of irradiated tissue; age, gender, general health of the person exposed to the radiation).

Characteristics of the Radiation

The potential harm to biological materials caused by their irradiation is directly proportional to the efficacy of which the radiation deposits energy in the material. Proton, neutron and alpha particles lose their energies over much shorter distances than X-rays and gamma rays with the same energy (Figure 7).

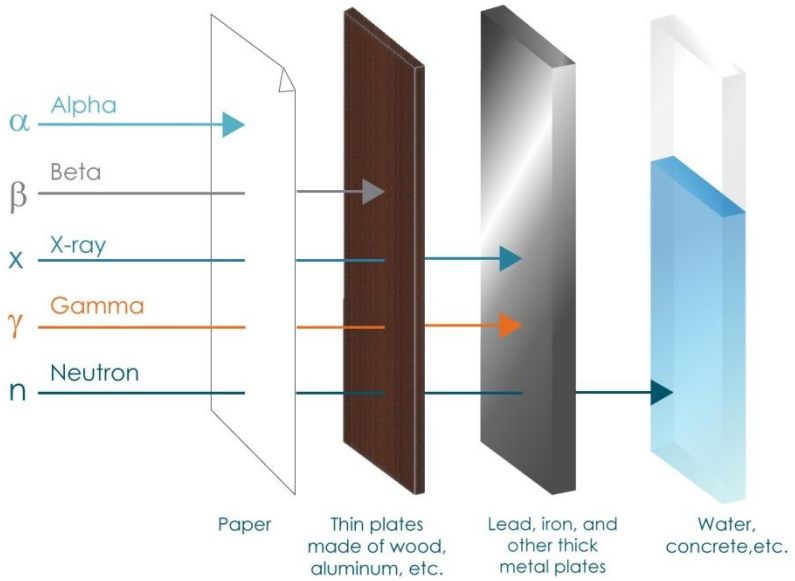

Fig 7: Penetrating power of different types of radiation.

Target Tissue Characteristics

Different tissues have different radiosensitivities. Cells that divide frequently (e.g., blood-forming cells in the bone marrow) are frequently affected by radiation more than rarely dividing cells (e.g., connective and fat tissue). Metabolic factors such as the oxygen concentration in the irradiated volume are also important.

Radiation effects on cell

Ionizing radiation injects energy into a material as it passes through it, like a microscopic bullet, until the radiation is stopped by the material due to absorption. In addition, radiation breaks the molecular bonds of the material in its path and changes the structure of the material. If the material consists of long molecular chains, the chains that are broken by the radiation form new bonds at random. In other words, radiation cuts long molecules at various positions, like a welding flame, and reconnects them in different ways. Living cells commonly consist of long protein chains, and some of these molecules can be broken by exposing the cell to radiation. The molecular fragments can then rebound in various ways, resulting in new molecules. These new molecules cannot function like the original molecules, and so they need to be repaired. Otherwise, these defective molecular structures will accumulate in the cell, changing the cell's metabolism; if the defective molecule is DNA, it can result in the formation of a cancer cell. Cells have certain repair mechanisms that they can employ for this type of damage. Cells in developed organisms can even check their molecules one by one, and they prefer to rebuild these molecules at certain intervals rather than repairing any damage. However, the capacity for cell repair is limited,

and if this limit is exceeded, the damaged molecules will start to accumulate and affect the vital survival functions of the cell. There is no such thing as a fully radioresistant cell.

Structures that form the cell, such as the nucleus, and particularly chromosomes undergoing division, are more radioresistant than the cell cytoplasm. One of the most prominent effects of radiation at the cellular level is the suppression of cell division. The growth of cells that are exposed to radiation, particularly during cell division (mitosis), is interrupted.

Ionizing radiation can cause breaking, sticking, clamping and curling in chromosomes. Broken chromosomes can reorganize, remain the same, or combine with other chromosomes. All of these events result in mutations or in eventual cell death (Figure 8).

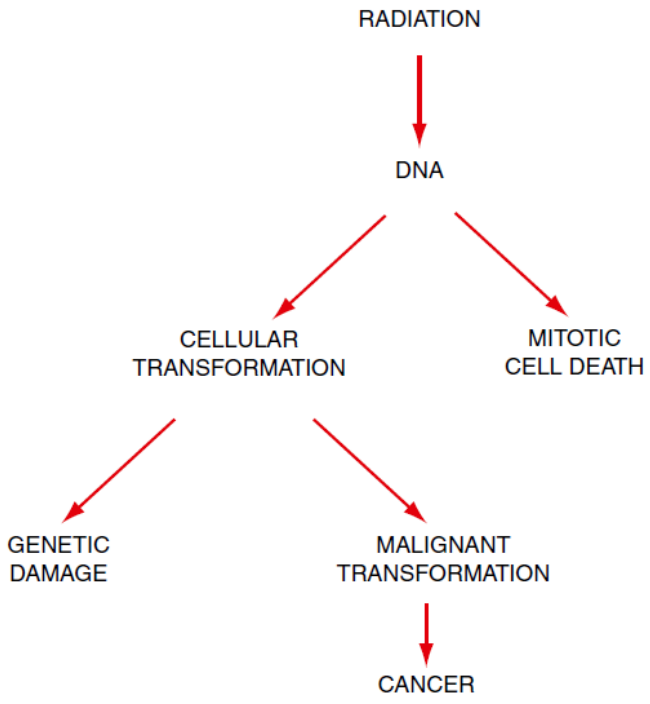

Fig 8: Radiation effects on cell

Radiation effects on tissues and organs

Most information on radiation effects on normal tissues and organs comes from observations during and after radiation therapy treatments. This is because the doses and effects of radiation cancer treatments are carefully monitored. Cancer treatments with radiation began within a few years of Roentgen's discovery. Radiation treatment of cancer is based on the fact that rapidly dividing cells are more sensitive to radiation. Cancer is made up of rapidly dividing cells, so the cancer cells are expected to be more sensitive to radiation than normal tissue. The major challenge in radiation therapy is to eradicate cancer without unduly damaging surrounding normal tissues. Even today, the amount of radiation delivered to the tumor is limited by the collateral damage to nearby normal tissues. Radiation oncologists have been observing radiation injuries to normal tissues since the birth of the field. Early treatments were limited by the poor penetrating ability of the radiation, so skin reactions limited the dose that could be safely delivered to deeper lying tumors. In the 1950s and 1960s, higher-energy radiation beams became available and data on radiation effects to internal tissues and organs became available

Skin

Skin is the most important and largest organ in the body. It usually first shows initial effects of external radiation because the radiation must pass through the skin to reach the internal organs. Radiation doses of about 2 gray can produce skin reddening. The gray (symbol: Gy) is a derived unit of

ionizing radiation dose in the International System of Units (SI). It is defined as the absorption of one joule of radiation energy per kilogram of matter.

The thin outer layer of the skin, the epidermis, is about 100 μm thick. It is made up of about 15 layers of epithelial cells, which are continuously regenerating. The epidermis is covered with a layer of protective dead cells, which are continuously sloughed off. The basal or lowest layer of the epidermis contains continually dividing stem cells, which differentiate into skin cells as they migrate up to the skin surface. This migration takes 2–6 weeks depending on the skin thickness. The epidermis layer first shows radiation damage because it is closest to the surface and is made up of rapidly dividing cells (figure 9).

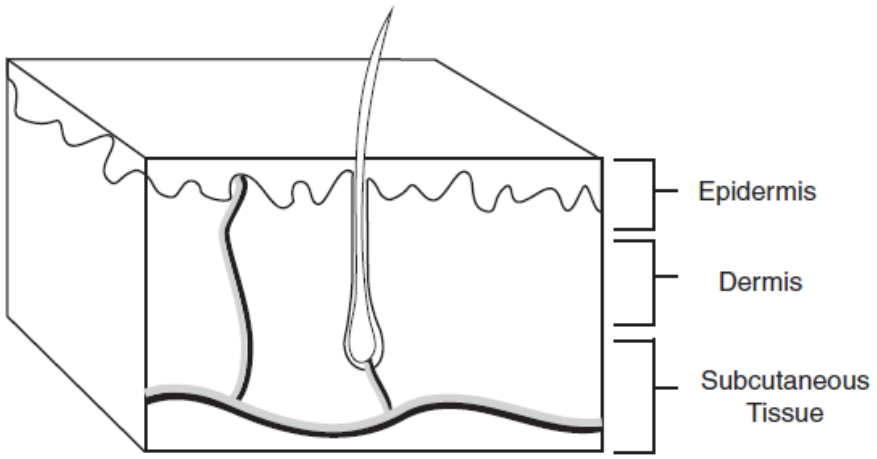

Fig 9: The layers of the skin.

The dermis lies below the epidermis and contains muscle fibers, blood and lymph vessels, sweat glands, and hair follicles as well as nerves to respond to touch and pain. The vascular system is limited to the dermis and below.

The epidermis exhibits an early and acute radiation reaction. The underlying dermis shows delayed radiation damage long after the radiation dermatitis of the epidermis has healed. Evidence of dermal injury may not appear until 3 or 4 months later. The amount of damage may not be fully realized for some years. Late skin injuries includes chronic skin fibrosis (thickening of the skin by fibrotic tissue), skin contraction, and in rare cases dermal necrosis owing to damage to the dermal capillaries.

The deep redness and the sensitivity caused by radiation fade shortly after the exposure, similar to the effects of sunburn. The skin takes somewhat longer to return completely to its natural color following radiation exposure. In the cases of higher exposure, there may be a second more serious effect that becomes evident many months, or even a few years, after exposure. This is due to the damage to the underlying, slowly dividing cells at the lower skin layers and to the vessels supplying the deeper layers.

Some individuals may continue to have a slightly pinkish or tan hue to their skin for years after exposure. Some individuals may notice a small patch of tiny blood vessels on the skin surface of the radiated area.

Dry desquamation is a condition of itchy dry scaly patches of skin where the patches readily fall off. Dry desquamation is usually the first radiation symptom prompting a patient to seek medical attention, usually from a dermatologist. Few dermatologists consider the possibility of

radiation exposure when faced with dry itchy skin. The usual course of treatment for skin not recognized as damaged by radiation consists of trying a few creams and ointments with no improvement. Often the next step is to perform a "punch biopsy" to determine the underlying cause. This is consistent with a dermatologist's experience and training. It is also one of the most undesirable things to do because the skin's ability to repair injury has been seriously compromised by the radiation. Patients having repeated or extended interventional procedures should *always* mention this fact to the dermatologist and strongly decline a punch biopsy.

Lungs

The lung is an important site of late radiation damage and is one of the more radiosensitive organs in the body. There are two types of reactions, pneumonitis that occurs 2 to 6 months after irradiation and fibrosis which usually occurs more than 1 year after irradiation. These reactions can cause increases in tissue density on lung scans and increases in breathing rate. Measuring changes in breathing rate has been used extensively to assay the dose-response relationship for radiation-induced lung damage in rats and mice, particularly the development of pneumonitis.

Studies in rodents have documented that there is a rapid induction of inflammatory cytokines in the lung after irradiations, but the relationship between this induction and the later development of functional symptoms is unclear. Studies in lung cancer patients have related prolonged increases in transforming growth factor –beta 1 (TGF-β 1 is a polypeptide member of

the transforming growth factor beta superfamily of cytokines) levels in plasma following radiotherapy to the likelihood of developing lung fibrosis.

Pulmonary fibrosis refers to the formation of scar tissue in the lungs that can occur for many reasons, including radiation therapy for lung cancer. Symptoms include shortness of breath and a decreased ability to exercise. Pulmonary fibrosis is usually permanent.

In rodents, genetic factors can influence the development of pneumonitis and fibrosis following lung irradiation, although these factors do not affect the radiosensitivity of lung cells directly. Genetic factors may help to explain interpatient differences in response to lung irradiation. The dose required to cause a functional impairment in lung depends on the volume of (functional) lung irradiated, with small volumes being able to tolerate quite large doses. This effect is due to the functional reserve of the lung because imaging with CT scans or plane X rays films demonstrates that the irradiated region has sustained severe damage and will develop fibrosis.

Studies in rodents, using the dose required causing an increased breathing frequency in 50% of animals (median effective dose= ED50) as an endpoint, have defined a relationship between ED50 and volume irradiated which is not linear with dose and which indicates that the base of the lung is more sensitive than the apex. The underlying mechanisms may relate to the functional reserve in different regions of the lung and/or to the extent of cytokine production following irradiation of different regions of the lung. There is also (limited) evidence for regional effects following irradiation of human lung.

Breast

Radiation treatment for breast cancer is usually spread out over 6 weeks with five 2-Gy treatments per week. This results in a total dose of approximately 60 Gy.

Late side effects from breast irradiation usually appear one or more years after treatment. The two major long-term complications of breast radiation treatments are fibrosis and lymphedema. Fibrosis is a hardening or stiffening of the tissues due to loss of elasticity due to a diffuse scarring. Lymphedema is a swelling due to localized fluid retention caused by damage to the lymphatic system. The complications are the result of the blood vessel and connective tissue damage that were in the radiation field. Studies have shown that there is no increase in thyroid cancer following radiation treatment for breast cancer.

Kidneys

Major complication includes clinical nephritis and kidney failure. A single dose of 6 Gy to kidneys shows early (within 48 hours) damage. A single dose of 10 Gy results in protein spilling into the urine indicating inadequate filtration by the irradiated kidney. Radiation nephritis usually does not occur until months after the kidneys are exposed.

Circulatory system

Blood and Blood Vessels

After a significant (>1 Gy) radiation dose from exposure to the whole body, all blood elements are adversely affected. Increases in dose result in an increased effect, and the effects are seen earlier. In the case of a whole body exposure from a radiation accident, the loss of white blood cells means the body's defenses against infection are diminished. Damage to the skin and intestine make the body particularly vulnerable to bacterial infection during the first few weeks following exposures greater than 1 Gy.

A person exposed to 1 Gy has their lymphocyte cell count reduced. He or she will be more susceptible to infection. Early symptoms of such exposures mimic the flu, that is, loss of appetite, nausea, diarrhea, and vomiting. The chapter on whole body radiation treats the effects of decreased white blood cells following radiation exposure more completely.

Most of the long-term, late effects on tissues and organs are the result of injury to blood vessels, especially to those making up the microvasculature. Damage to the capillaries bringing oxygen and nutrients to the cells of an organ will inevitably affect its function.

The interior surface of blood and lymphatic vessels is lined with a thin layer of endothelial cells which form a barrier between the circulating blood or lymph inside the vessel and the vessel wall. Damage to the endothelial cells allows white blood cells and fluids to pass through the vessel. Radiation at lower doses can cause damage to the capillary vessels. Such changes can include less flexibility and greater vessel stiffness leading to

decreased perfusion. This is especially important in the blood vessels, brain, and skin.

Heart

Radiation damages the heart by damaging the heart muscle, the valves, or the coronary arteries. A significant complication of heart irradiation is pericarditis. Pericarditis is inflammation of the sac surrounding the heart. The most common symptom of pericarditis is a stabbing, sharp pain in the chest, which becomes stronger when exercising or taking a deep breath.

Damage to the heart muscle, called cardiomyopathy, most often results in a stiff left ventricle, which does not respond to signals to pump more blood. During strenuous physical exercise activity, the stiff left ventricle may not be capable of increased pumping action. When this happens, the blood that is being pumped through the left side of the heart is not pumped out fast enough, and some of the blood backs up in the small blood vessels of the lungs. The oxygen in the lungs is supposed to be transferred to these small blood vessels. When these vessels become engorged with the backlogged blood, the oxygen cannot be transferred to the heart, resulting in congestive heart failure.

Damage to the heart valves is a second problem resulting from radiation exposure. The heart valves lose flexibility and become stiff following radiation exposure. The stiffened valves do not seal properly and leak blood back into the heart chambers, which should be sending blood throughout the body. The amount of blood ejected from the heart during each heartbeat decreases.

Radiation can also cause coronary artery disease. Radiation can damage the small blood vessels, which supply the heart with oxygen and nutrition. The interior lining of healthy blood vessels is smooth. Radiation can roughen the inside of blood vessels. These rough spots provide a site for fatty deposits (plaques) to develop in coronary arteries and other arteries and veins. Calcium deposits can harden the plaques resulting in atherosclerosis (hardening of the arteries). Coronary artery disease occurs when one of the heart vessels is clogged with plaque. If this happens, the heart muscle may begin to weaken and die because it cannot get enough oxygen and nutrition.

If the heart tries to beat faster but is deprived of enough oxygen or nutrition, chest pain (angina) results. Angina may last a few minutes until the oxygen gets through the partially clogged artery. If the heart vessel is completely blocked, that section of the heart muscle may die. If the muscle section is small, then the result is a minor heart attack. Blockage of a larger coronary artery supplying a larger amount of heart muscle is damaged; the heart attack is serious and can be life-threatening. The left anterior descending coronary artery is known as the “widow maker” because sudden blockage of it often leads to a fatal heart attack.

The central nervous system

The central nervous system radiation reactions mostly occur at 6 months or later. At the early times, demyelination may occur in the white matter leading to somnolence (brain irradiation) or parathesia (spinal cord irradiation) but these early effects are usually reversible and do not

necessarily predict the development of more serious late brain necrosis or myelopathy. At later times (1-2 years) more permanent demyelination and necrosis of the white matter is seen but the damage may also be observed in the grey matter associated with vascular lesions. The risk of late effects is very dependent on dose per fraction with lower fraction sizes reducing the risk. However, repair of sublethal radiation damage in CNS is slow relative to most other tissues with a component which appears to have a half-life of about 4 hrs. This means that multiple fractions per day must be widely spaced to maximize repair.

Brain

Because brain cells do not reproduce, they are not significantly damaged unless their blood supply is compromised. Complications are necrosis and an infarction. An infarction is a group of tissue that dies because of a lack of oxygen caused by an obstruction of the tissue's blood supply.

Spinal Cord

Complications include myelitis, necrosis, and paralysis. The complications increase with the length of cord irradiated. These data are for radiation of 20-cm cord length.

Eye

The major complication of radiation to the eye is cataract formation, which is classified as a tissue reaction/deterministic effect with a threshold. Radiation cataracts begin as opacity near the posterior pole of the eye and progress forward. For many years, the threshold for cataract induction was believed to be about 2 Gy from chronic exposures over many years. Fractionated doses can cause the formation of cataracts after a latent period of 2 years or more depending on the age of the individual and the time period of exposure. Recent studies, however, have shown that the threshold for cataract formation may be significantly lower. Interventional physicians with exposures spread over many years have shown cataract formation at cumulative doses as low as 0.8 Gy.

The current regulatory limit is set at 150 mGy/year. This limit was established to reduce the risk of radiation-induced cataracts. Recently, in 2011, the International Commission on Radiation Protection (ICRP) has issued a statement that the threshold in the absorbed dose for the lens of the eye is now considered to be 0.5 Gy. For occupational exposures, the ICRP now recommends an equivalent dose limit for the lens of the eye of 20 mSv in any 1 year. Although this recommendation does not have the force of law, the recommendation of this international body probably will influence on what is considered good medical practice.

Digestive system

Esophagus

Major complications include necrosis of the lining of the esophagus. The esophagus, the tube leading from the mouth to the stomach, is located between the lungs in the chest. During radiation to lungs to treat lung cancer, the esophagus is often included in the radiation field. Pain or difficulty with swallowing, heartburn, and a sensation of a lump in the throat are side effects of the radiation. Symptoms usually occur 2–3 weeks into therapy and subside a few weeks after completing treatments.

Intestinal

The major complications of intestinal include obstruction and/or perforation leading to massive infection. Radiation damage to the intestinal tract lining will cause nausea, bloody vomiting, and diarrhea. This occurs when the intestine receives an exposure greater than about 2 Gy.

The radiation will begin to destroy the rapidly dividing intestinal cells. The most radiation-sensitive cells in the intestine are the immature stem cells. These immature stem cells are located at the base of the villi (the crypts) in the intestine. They maintain the supply of stem cells for development into mature functioning intestinal cells. The stem cells in the crypts of the intestine develop into intermediate cells, which differentiate into mature cells as they migrate up to the top of the villi. During this migration, they receive signals directing them to develop into specialized cells designed to function as part of an organ. In the mature stage, they actively perform their specialized functions. These functions include

absorption of nutrients from the gut and the discharge of waste products into the intestine. This development and migration require about 14 days. The mature gut cells at the top of the villi are soughed off at the end of their life cycle. Thus, the effects of intestinal radiation become evident about 2 weeks after exposure. The intestine is no longer able to maintain the barrier between the body waste inside the intestine and the bloodstream. This occurs just as the white blood cell population, essential for fighting infection, is dropping. The subsequent infection is often fatal.

Rectum

Exposure to the rectum comes primarily from the treatment of prostate cancer because the rectum and bladder are almost always partially included in external beam therapy of the prostate. Major complications include diarrhea, severe proctitis, necrosis, stenosis, and the formation of a fistula. A rectal fistula is an opening between the rectum and the external skin, which can be very painful and often requires corrective surgery.

Bladder

The complications are bladder contraction, volume loss, and difficulty in completely emptying or leaking from the bladder. These are extremely high-radiation doses and will be encountered only in radiation oncology cancer treatments or very serious radiation accidents.

Liver

Major complications include jaundice and liver failure. Jaundice results in a yellow tint of the skin and the whites of the eyes.

Glands

Thyroid

Radiation-induced cancer can come from either external exposure or ingestion of radioactive iodine, which is concentrated by the thyroid. This is especially true of exposure during childhood.

In routine thyroid testing, iodine-131 (written I-131) is given as a capsule swallowed by the patient. The I-131 in the bloodstream can pass through the placental barrier, so exposure to the mother can result in exposure to the fetus. Fetal exposure to I-131 is a hazard only after the 12th week of pregnancy because the fetal thyroid is not developed before then.

Potassium iodide, KI, given to the patient before taking the iodine capsule will diminish the uptake by the thyroid. The KI occupies the iodine receptors in the thyroid so the radioactive iodine is not taken up by the gland. Unfortunately, the KI must be given before, or within a few hours of exposure to radioactive iodine, so its protective effects are primarily limited to planned medical exposures. KI does not protect against external radiation.

An individual whose thyroid is exposed to 1 Gy of external radiation is eight times more likely to develop thyroid cancer than a unexposed person. These data come primarily from external medical exposures during

the 1930s and 1940s when radiation was used to treat many childhood problems. Medical reasons for exposing children in the 1930s and 1940s included tinea capitis infections (scalp ringworm), enlarged tonsils and thymus glands, and cutaneous hemangiomas. The greatest risk of developing thyroid cancer is between 5 and 29 years after radiation exposure. After this period, the risk decreases.

Reproductive Organs

Temporary sterility in women occurs at doses of about 1.5 Gy. Doses in excess of 6.0 Gy will permanently sterilize a woman. Prior to the introduction of birth control pills, it was not uncommon for women to request radiation for sterilization as an alternate to surgical sterilization.

Temporary sterility occurs in men at doses above 2.5 Gy and permanent sterility at doses above 5.0 Gy.

Fetus

Cells most susceptible to radiation damage are those engaged in rapid division and growth. This makes unborn babies particularly sensitive to radiation exposure. There are many possible biological effects of radiation on embryos and fetuses including miscarriage, developmental delays such as smaller head size, mental retardation, and childhood cancer. Fetal doses less than 100 mGy are considered below the level of concern for radiation damage to the fetus. Radiation dose to the fetus is about 25% of the entrance skin dose. Fetal effects from radiation are somatic.

Miscarriage The effect of a pregnant woman's exposure to radiation depends on the gestational age of the fetus. Radiation exposure during later stages of pregnancy can produce developmental delays and increased incidence of cancer. The newly fertilized conceptus is especially sensitive to radiation damage because each of the cells in the conceptus is vital to the proper development of the fetus. Any significant radiation damage during the first 2 weeks of pregnancy will lead to miscarriage. That is, in utero exposure during the first 2 weeks of pregnancy radiation damage is an "all-or-nothing" effect.

Radiation damage to the fetus can lead to delayed growth and development of the fetus. The damage may persist as a developmental delay well into childhood. In particular, radiation-exposed fetuses may have smaller than average head, may have brain sizes that are small for their gestational age, and may display cognitive deficits associated with delayed brain development.

One of the most disturbing effects of fetal radiation exposure is either retarded brain growth or mental retardation or both as a result of underdevelopment of brain cells. The fetus is most sensitive to mental retardation due to radiation exposure during the 8–16 weeks of pregnancy. This is when the brain is most rapidly developing. The decrease in mental acuity has been noted only in doses above 100 mGy. During the 8- to 16-week period, the decrease is estimated to be about 30 IQ points per gray.

Childhood

Childhood cancers are more likely in babies who were exposed to radiation in utero or infancy. During this time, their cells are rapidly replicating and are more sensitive to radiation. The rate of cancer deaths from radiation is 5%/Sv for adults and may be as much as twice high for infants and young children.

The consensus of experts has been that abortion due to fear of radiation effects on the fetus should not be considered at radiation doses *to the fetus* of 100 mGy or less. A reasonable estimate of fetal dose from diagnostic plane imaging is one quarter (25%) of the entrance skin dose. The fetal dose from computed tomography (CT) examinations is equal to the computed tomography dose index (CTDI).

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