Effects on Tissues

Hierarchy

cell - tissue - organ - system organization.

Historical Study

- French Scientists Bergonie and Tribondeau
- Study the response of rat testis to radiation
- Developed a “Law” (a generalization)of radiation response of tissues.

The Law of Bergonié and Tribondeau

- Stem cells are radiosensitive. The more mature the cell the more sensitive.

- The older the tissue or organ, the more radiation resistant it is.

- The lower the metabolic activity, the higher the resistance.

- The radiosensitivity increases with the proliferation rate and growth rate.

Casarett’s Classification

- Casarett divides cells into four divisions by radiosensitivity.

Casarett's Classification

- I. Vegetative Intermitotic - cells which divide regularly and have no differentiation
- II. Differentiating Intermitotic - cells which divide regularly, some of which are differentiated.
- III. Reverting Postmitotic - cells which do not divide regularly.
- IV. Fixed Postmitotic - cells which do not divide and are highly differentiated.

Human Cell Radiation Sensitivity

- High
  - Lymphocytes (white blood cells)
  - Spermatogonia (sperm-producing cells)
  - Erythroblasts (immature red blood cells)
  - Intestinal crypt cells (small intestine)
- Mid
  - Spermatids (non-dividing immature sperm)
  - Osteoblasts (immature bone cells)
- Low
  - Muscle cells
  - Nerve cells

Further refined Cell Sensitivity(1)

- Most radiation-sensitive mammalian cells

  A. Erythroblasts (red blood cell precursors). These cells are primitive cells with a high mitotic future and relatively large nuclear volume.

  B. *Mature lymphocytes (one of two major classes of circulating white blood cells).*

  C. Certain spermatogonia (the most primitive cells in the spermatogenic series)

Further refined Cell Sensitivity(2)

- Second most radiation-sensitive mammalian cells

  A. Granulosa cells (cells surrounding the ovum) in developing mature ovarian follicles

  B. Myelocytes (in the bone marrow)

  C. Intestinal crypt cells

  D. Germinal cells of the epidermal layer of skin

Further refined Cell Sensitivity(3)

- Third most radiation-sensitive mammalian cells
    - A. Gastric gland cells
    - B. Endothelial (lining) cells of the small blood vessels

Further refined Cell Sensitivity(4)

- Fourth most radiation-sensitive mammalian cells
  - A. Osteoblasts (bone forming cells)
  - B. Osteoclasts (bone resorbing cells)
  - C. Chondroblasts (precursors to cartilage cells)
  - D. Granulosa cells of primitive ovarian follicles
  - E. Spermatocytes and spermatids

Further refined Cell Sensitivity(5)

- Less than moderately sensitive mammalian cells
  A. Osteocytes (bone cells)
  B. Sperm
  C. Superficial cells of the gastrointestinal tract

Further refined Cell Sensitivity(6)

- Fairly large dose of radiation necessary to alter these mammalian cells
  - A. Parencymal and duct cells of glands
  - B. Fibroblasts (these form the intercellular fibrous matrix)
  - C. Endothelial cells of the large blood vessels
  - D. Erythrocytes (red blood cells)

- Fairly radiation-resistant mammalian cells

    A. Fibrocytes (connective tissue cells)

    B. Reticular cells (fixed hematopoetic stem cells)

    C. Chondrocytes (cartilage cells)

    D. Phagocytes (scavengers)

Further refined Cell Sensitivity(8)

- Least sensitive to radiation of all mammallian cells

    A. Muscle Cells

    B. Nerve Cells (it may be that the nerve cells are sensitive, but it takes a long time to take effect)

Growth Kinetics and Radiosensitivity

- Rapid division leads to earlier radiation response.
- Slow cell division leads to a delayed radiation response.
- Latency in the radiation response may be seen in radiotherapy.
- Radioresponsiveness depends on vascular architecture of the tissue and the interaction of cell death, recovery and repopulation.

Radiosensitivity of Organs

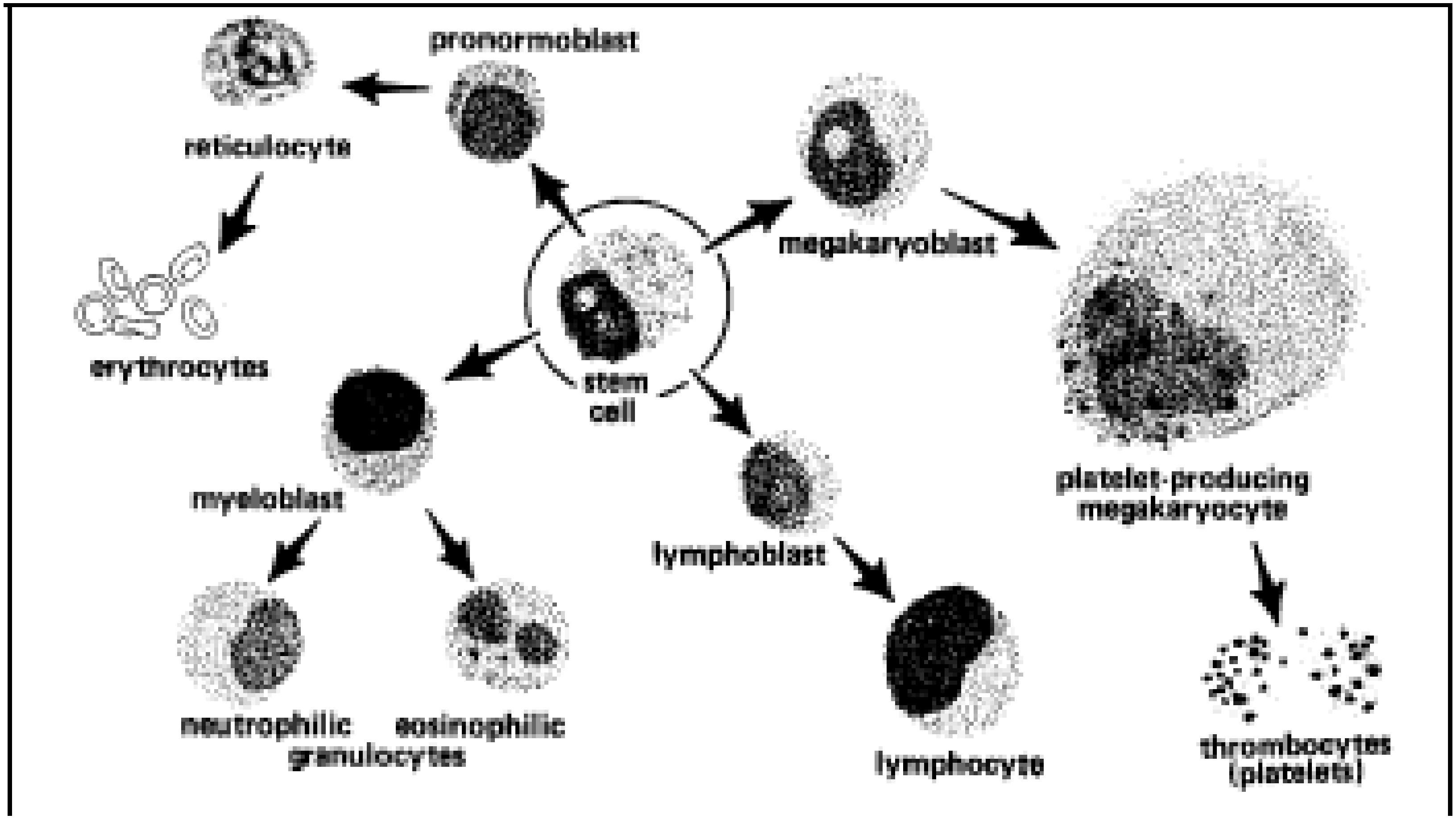
General Pattern

- inhibition of cell division in mitoticly active cells
- chromosome aberrations
- hemorrhage and edema
- removal of debris by phagocytic cells
- cell regeneration

Hematopoietic Tissue
Description

- Bone marrow (myelopoeietic)
- circulating blood (erythropoietic)
- lymphoid tissue (thrombopoietic)

Pluripotential Stem Cell
(located in the bone marrow)



Cell Function

- Lymphocytes - involved in immune response
- Granulocytes - scavenger-type cells used to fight bacteria
- Thrombocytes (platelets) - involved in blood-clotting to prevent hemorrhage
- Erythrocytes - red blood cells that transport oxygen

Hematopoietic Tissue

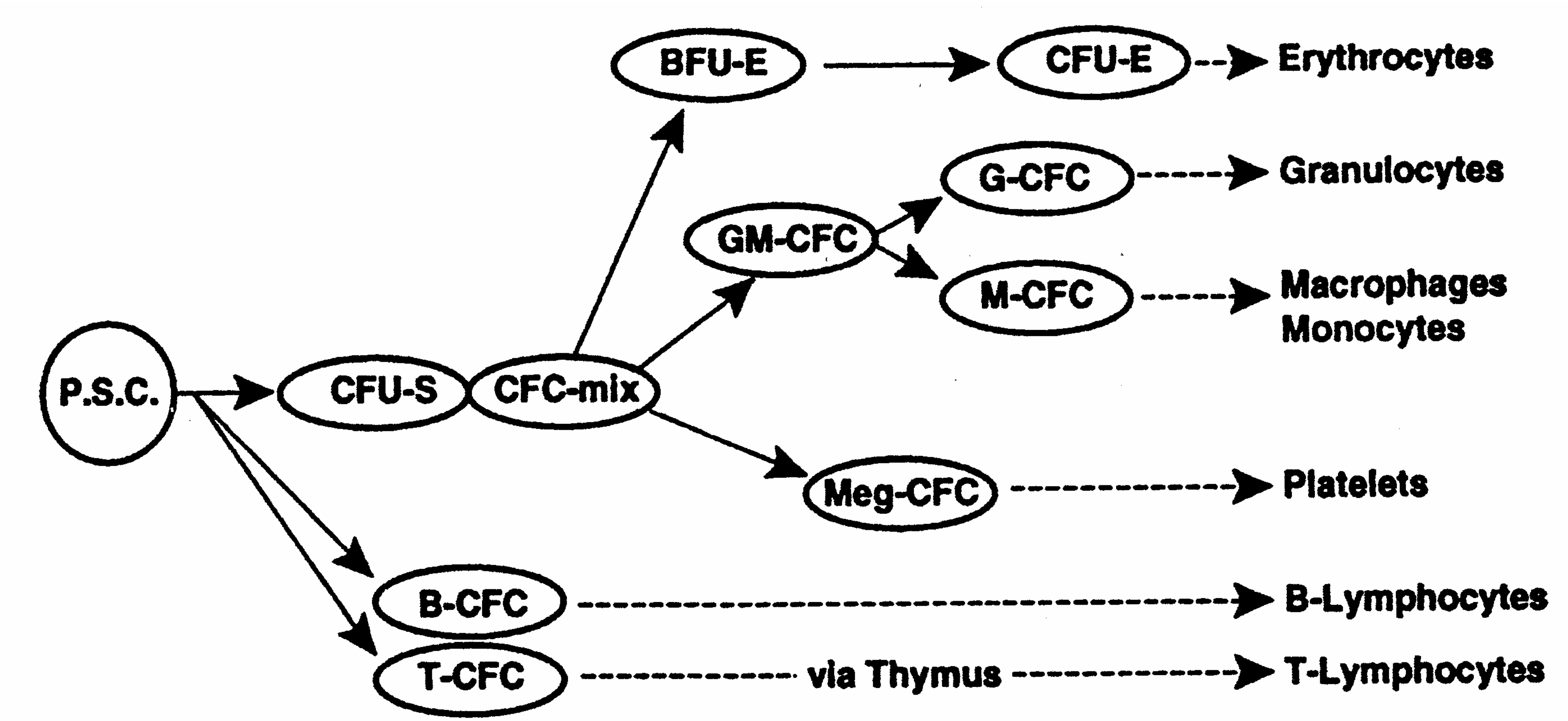
Radiation Sensitivity

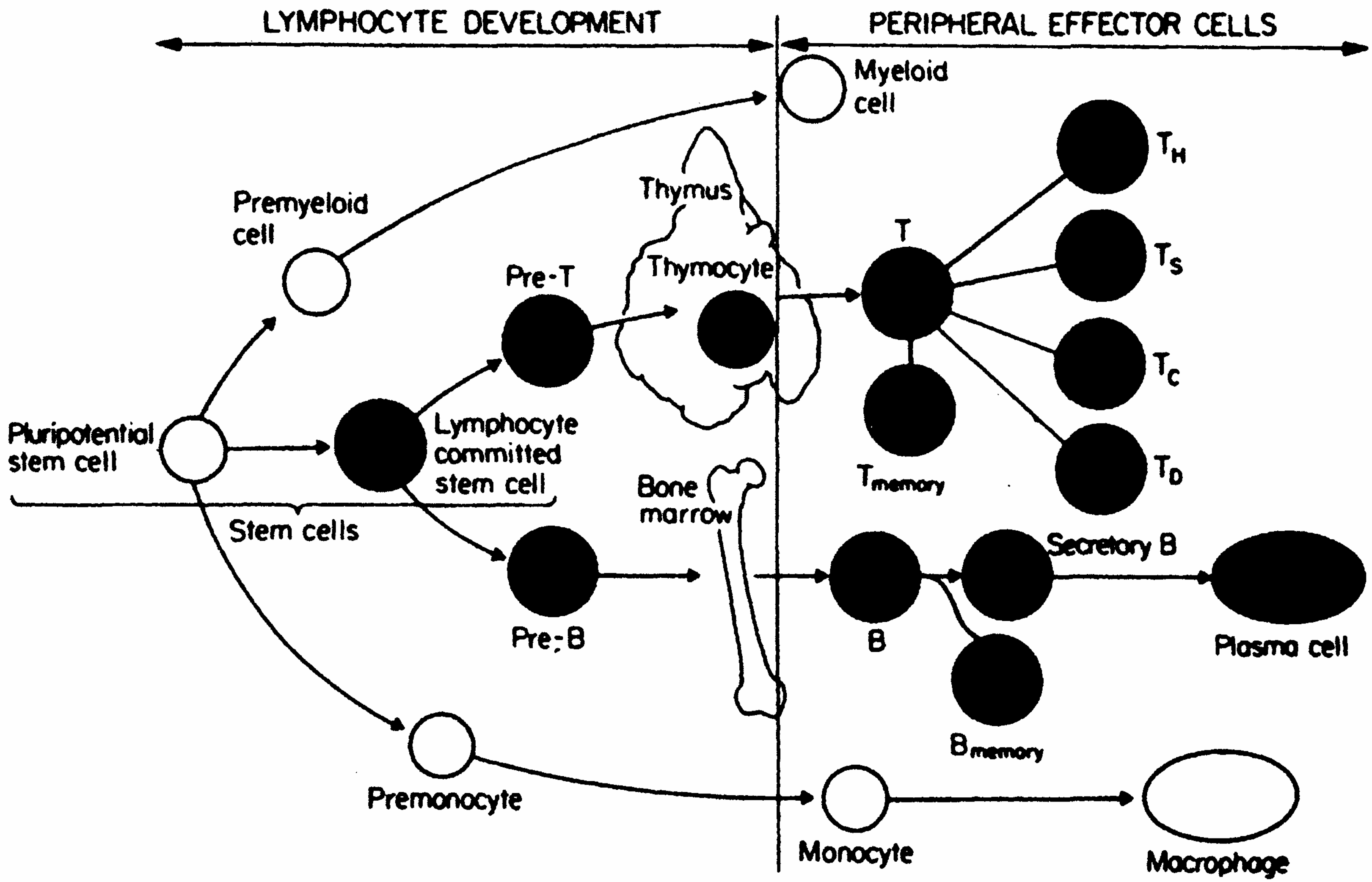
- Bone marrow irradiation results in depression of the blood cells following some time after the irradiation due to the destruction of precursor cells.

- Red blood cells recover first followed by the white blood cells.

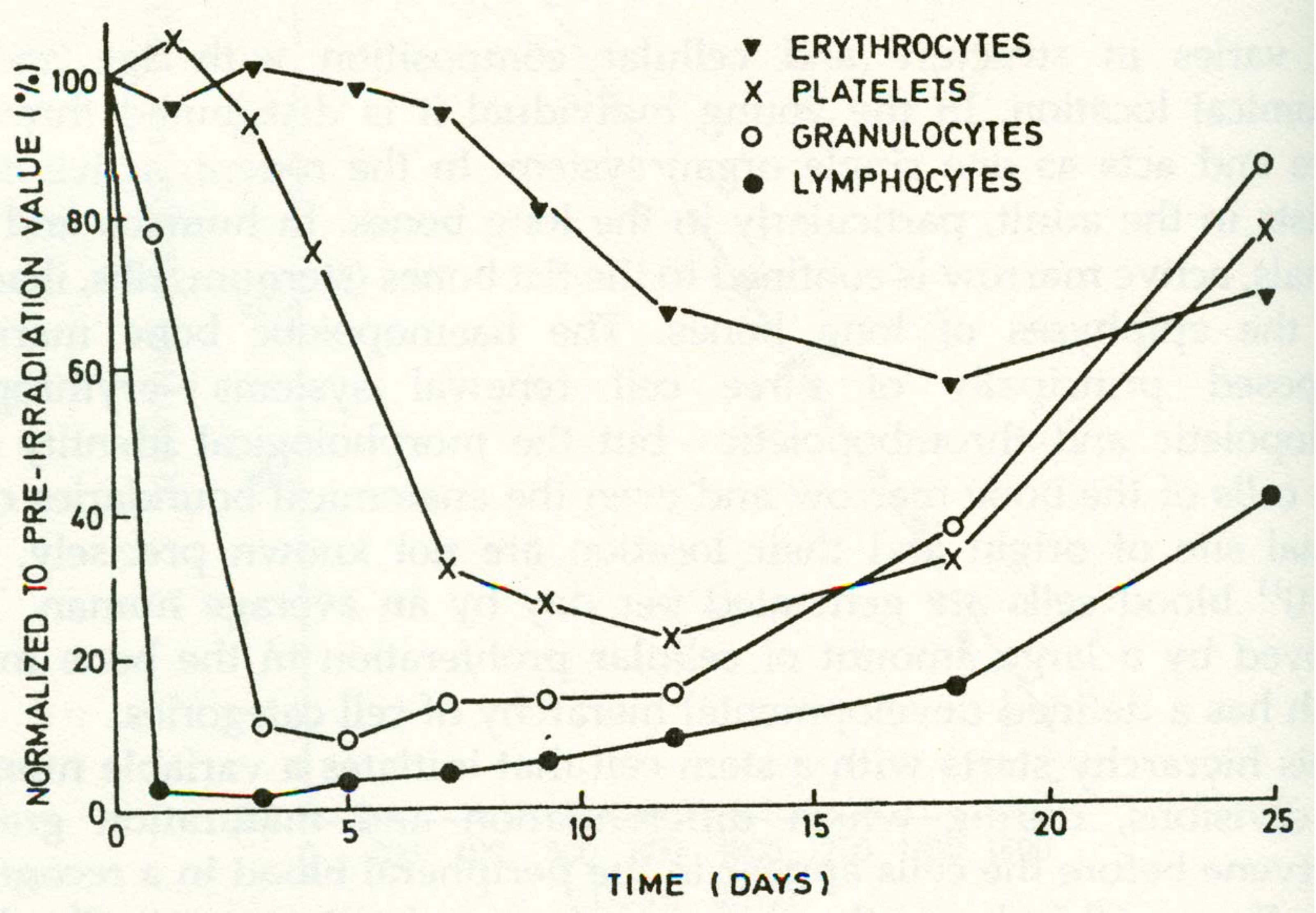
- The loss of white blood cells leads to a sensitivity to infections.

Blood Cells (1)

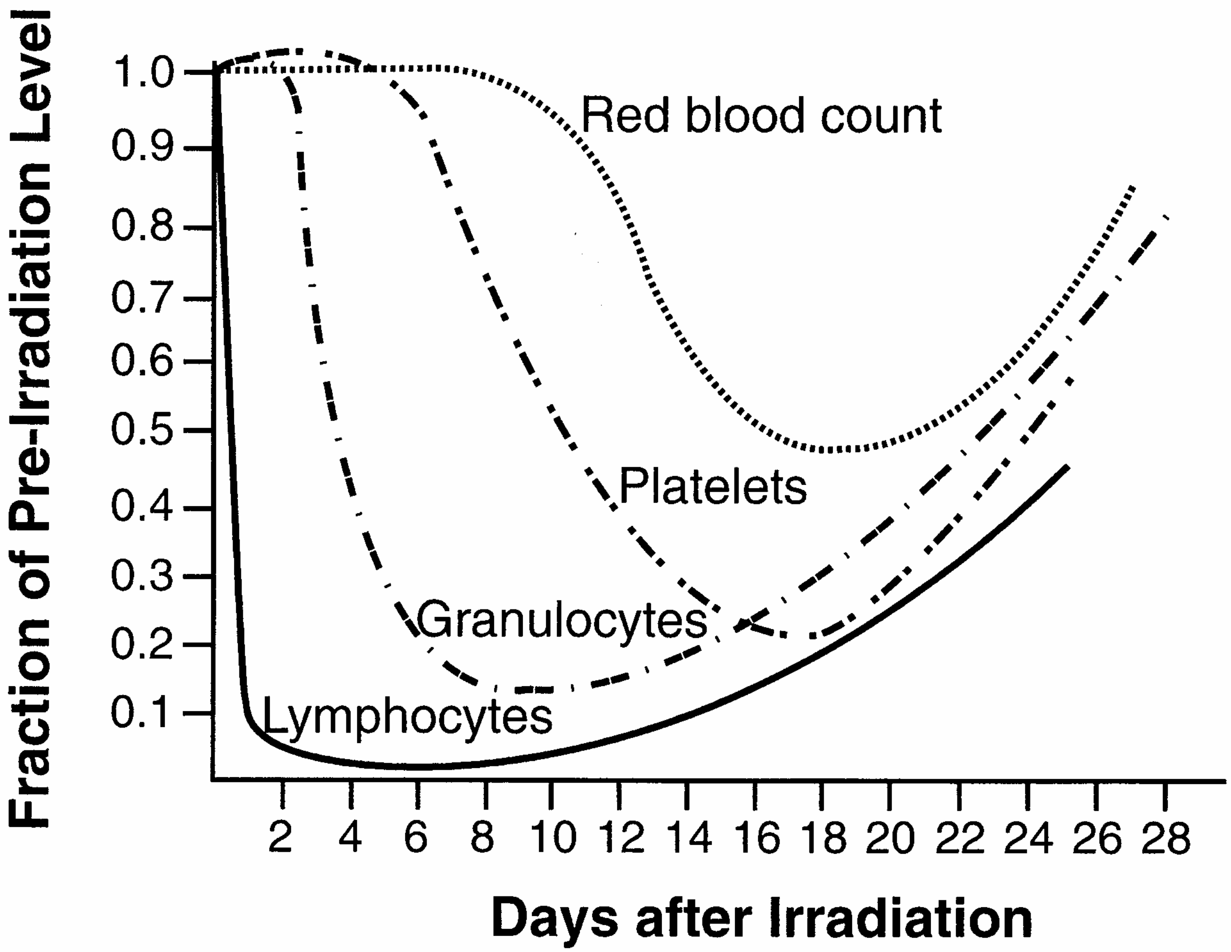



LYMPHOCYTE DEVELOPMENT
PERIPHERAL EFFECTOR CELLS
Myeloid cell
Premyeloid cell
Thymus
Thymocyte
Pre-T
T
T_H
T_S
T_C
T_D
T_{memory}
Pluripotential stem cell
Lymphocyte committed stem cell
Stem cells
Bone marrow
Secretory B
Pre-B
B
Plasma cell
B_{memory}
Premonocyte
Monocyte
Macrophage

Response to Radiation

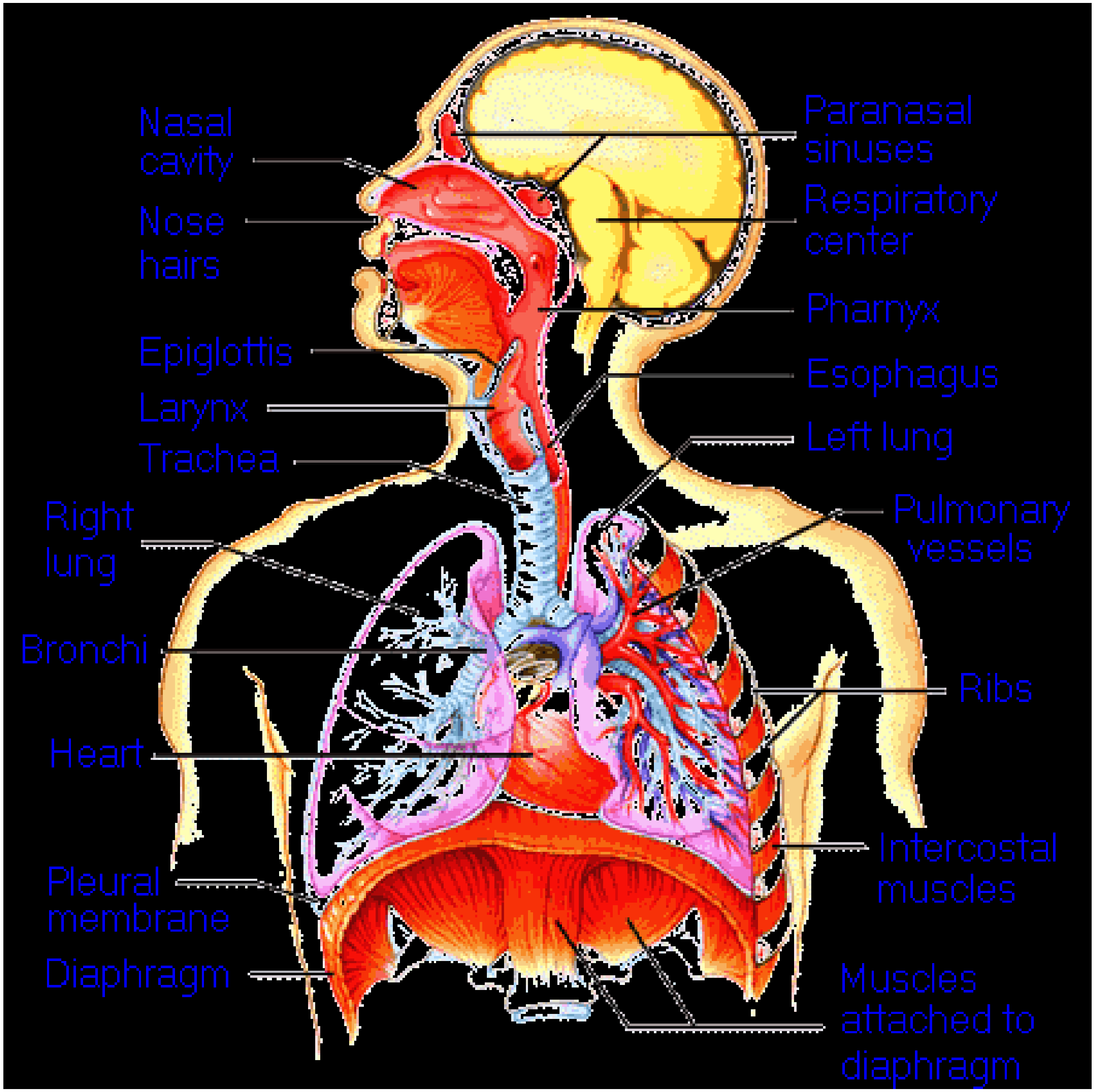


Response to Radiation



Thoracic Organs (1)

- Radiation effects appear in the esophagus before the lungs due to the ***rapid division of cells in the esophagus***.
- Radiation pneumonitis results from damage to alveolar cells (air sac cells) and capillary cells.
- Starvation cell death may also occur, which results in early esophageal damage and later lung fibrosis.

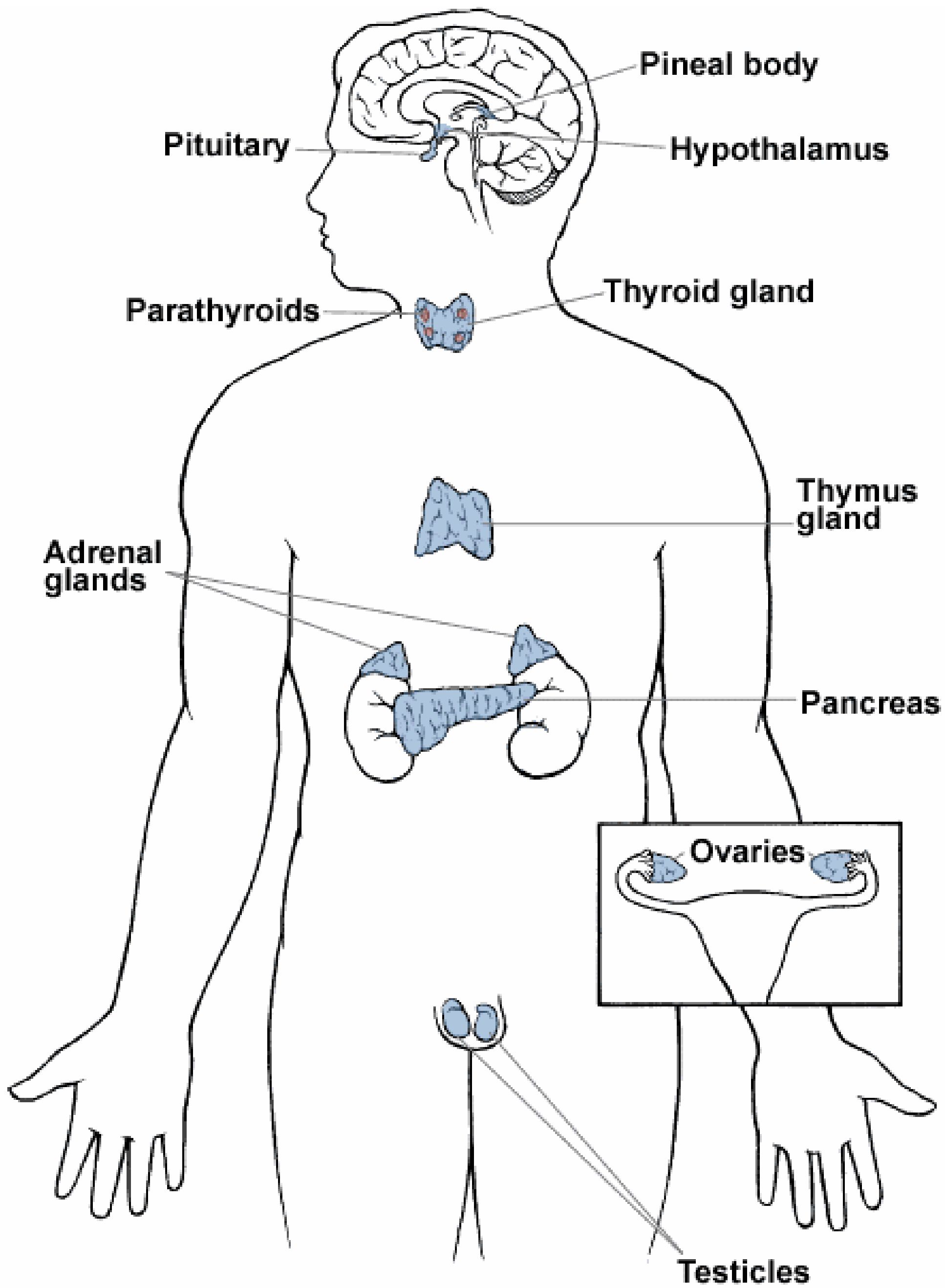

Nasal cavity
Nose hairs
Epiglottis
Larynx
Trachea
Right lung
Bronchi
Heart
Pleural membrane
Diaphragm
Paranasal sinuses
Respiratory center
Pharnyx
Esophagus
Left lung
Pulmonary vessels
Ribs
Intercostal muscles
Muscles attached to diaphragm

Thoracic Organs (1)

- The heart, large artery, and large veins are less affected by radiation than the capillaries, which are affected by occlusions.
- **Capillary tissue** is the *most important limiting tissue* in irradiation of a radiation therapy patient.

Thyroid

- The normal thyroid is more radioresistant than the hyperactive thyroid.
- High doses of radiation can permanently damage normal thyroid tissue, leading to hypothyroidism.
- Hyperthyroidism is typically treated by radioiodine which concentrates in the thyroid.

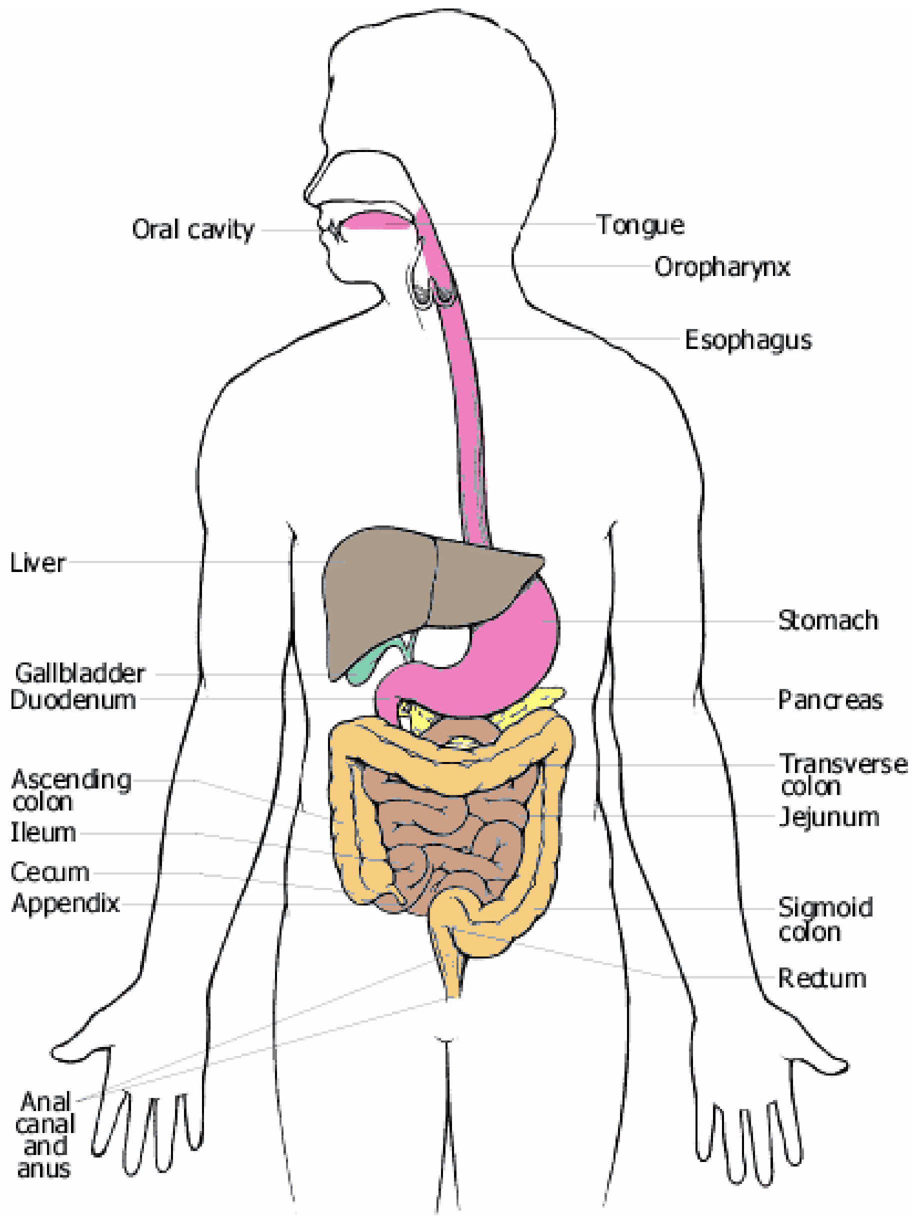

Pineal body
Pituitary
Hypothalamus
Parathyroids
Thyroid gland
Thymus gland
Adrenal glands
Pancreas
Ovaries
Testicles

Kidney

- Due to slow cell turnover, it takes several months for radiation injury to occur in the kidney.
- Acute radiation **nephritis** may cause up to 30% mortality.
- Even those who recover will have chronic radiation nephritis.
- ***Nephritis*** is a general term for inflammatory diseases of the kidney.

Digestive System

- High levels of radiation causes ulcerations in the esophagus, mouth and stomach.
- The salivary glands and the pancreas are fairly radioresistant.
- The liver is extremely radioresistant due to its post-mitotic state.
- The small intestine is the most important site of radiation injury.


Oral cavity
Tongue
Oropharynx
Esophagus
Liver
Stomach
Gallbladder
Duodenum
Pancreas
Ascending colon
Transverse colon
Jejunum
Ileum
Cecum
Appendix
Sigmoid colon
Rectum
Anal canal and anus

Small Intestine (1)

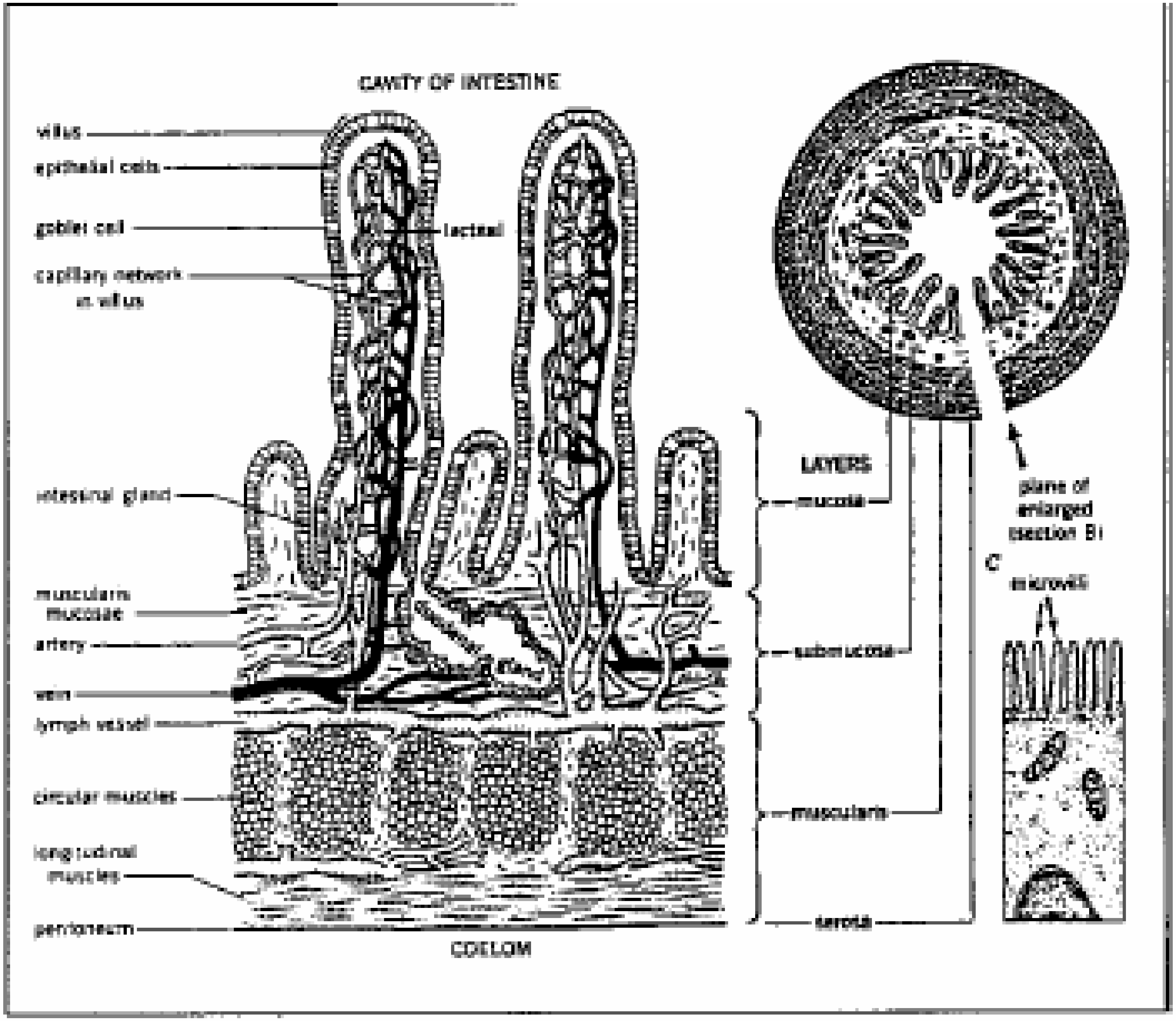
- duodenum (with connection to the stomach and pancreas)
- jejunum (the main part of the intestine)
- ileum (where the small intestine changes to join the large intestine)

Small Intestine (2)

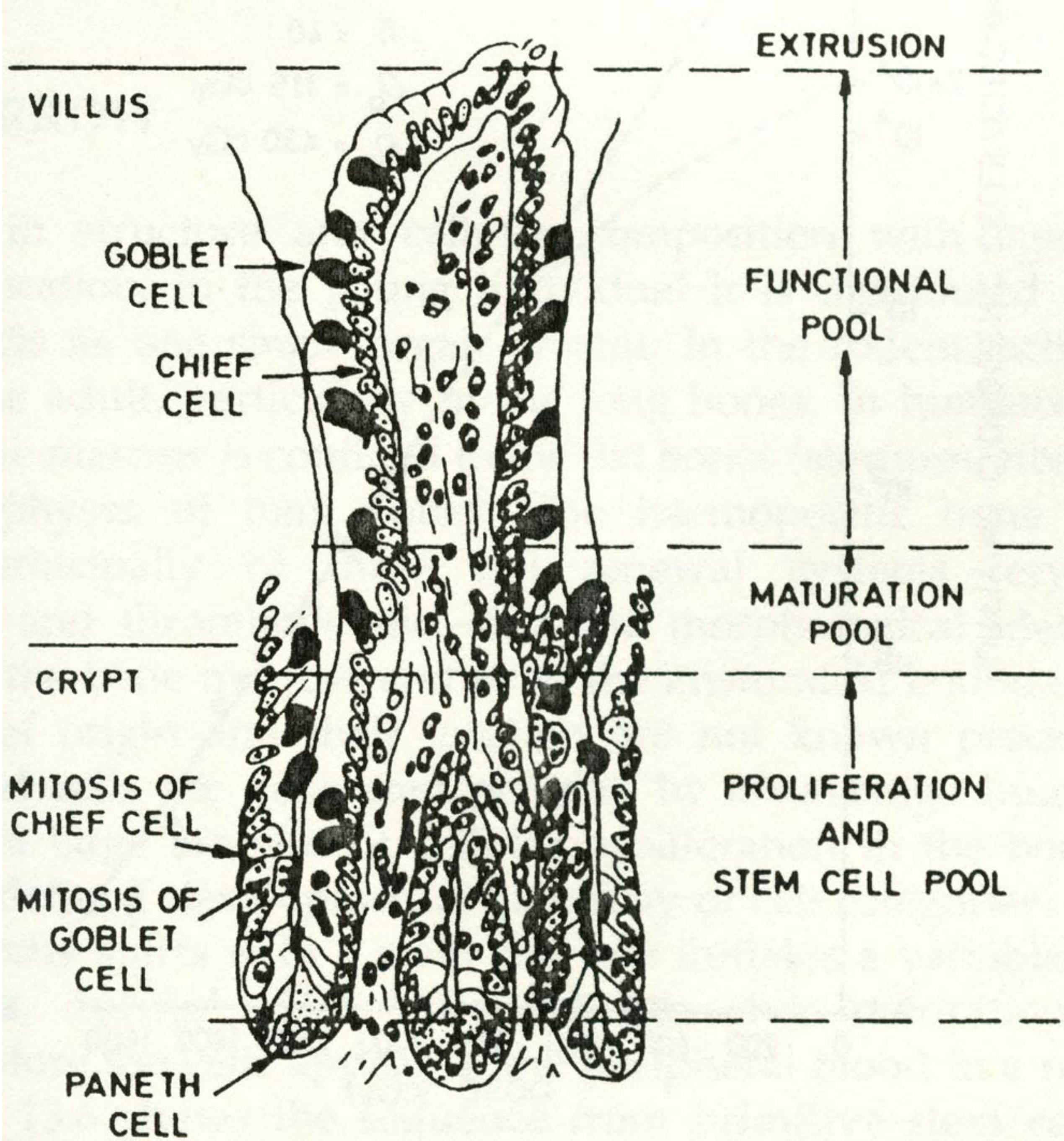
- The ileum is the principal site for absorption of digestive products from the gastrointestinal tract.

- Digestion and absorption is enhanced by the large surface area of the intestine due to its length, intestinal folds, **vill**i, and **microvill**i. Proteins, carbohydrates, and lipids are absorbed into the blood stream at this location.

- In contrast, the large intestine functions to recover water from the waste and propel the mass to the rectum.



CAVITY OF INTESTINE
villus
epithelial cells
goblet cell
lacteal
capillary network in villus
intestinal gland
muscularis mucosae
artery
vein
lymph vessel
circular muscles
longitudinal muscles
peritoneum
COELOM
LAYERS
mucosa
submucosa
muscularis
serosa
plane of enlarged section B)
C
microvilli



EXTRUSION
VILLUS
GOBLET CELL
CHIEF CELL
FUNCTIONAL POOL
MATURATION POOL
CRYPT
MITOSIS OF CHIEF CELL
MITOSIS OF GOBLET CELL
PROLIFERATION AND STEM CELL POOL
PANETH CELL

Small Intestine Radiosensitivity (1)

- The small intestine cell turnover rate (1.4 days) is much greater than other areas of the digestive system, such as lip (15 days), colon (10 days), stomach (3 days), and esophagus (10 days).

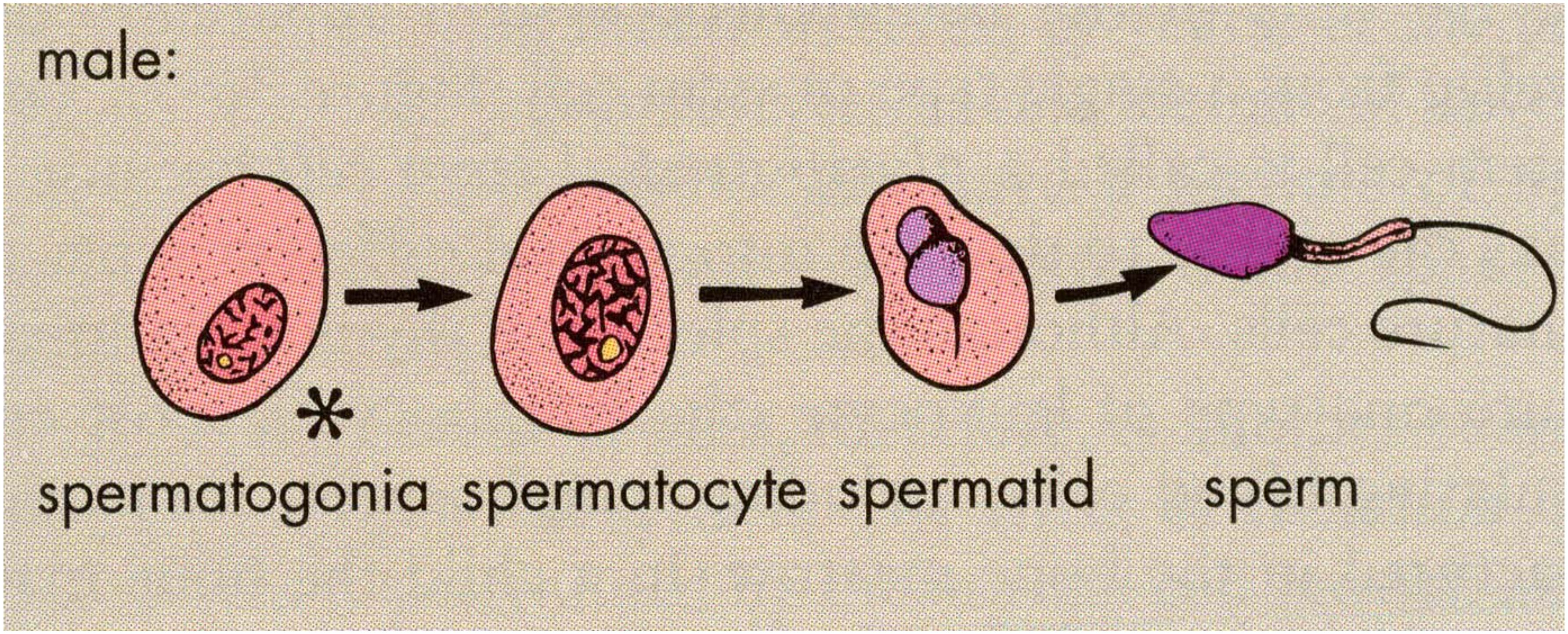
- This increased sensitivity to radiation is due to the rapid rate of cell division in the cells of the crypt and of the related villi.

- Cells are produced rapidly on the sides of the villus and migrate to the tip.

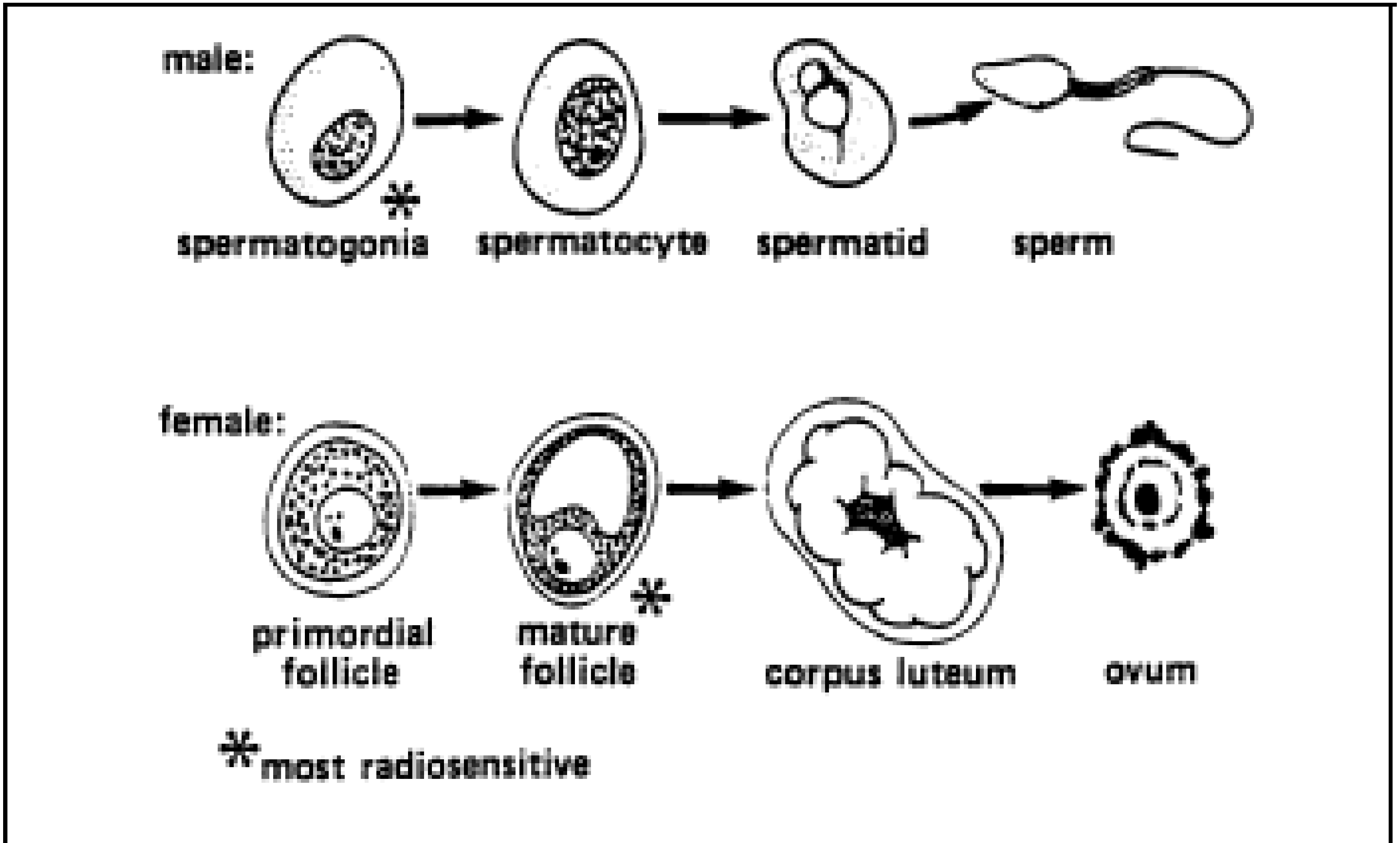
Small Intestine Radiosensitivity (2)

- If the radiation dose is high enough, there is rapid cell loss in the crypts and the villi become short and blunted.
- Radiosensitivity is exhibited as a loss of fluids and electrolytes.
- Poor absorption of nutrients leads to a high bacterial content in the small intestine.
- The bacteria cause diarrhea, which results in a loss of fluid and electrolytes, a central feature of acute radiation syndrome.

Male Gametes



Human Sex Cells



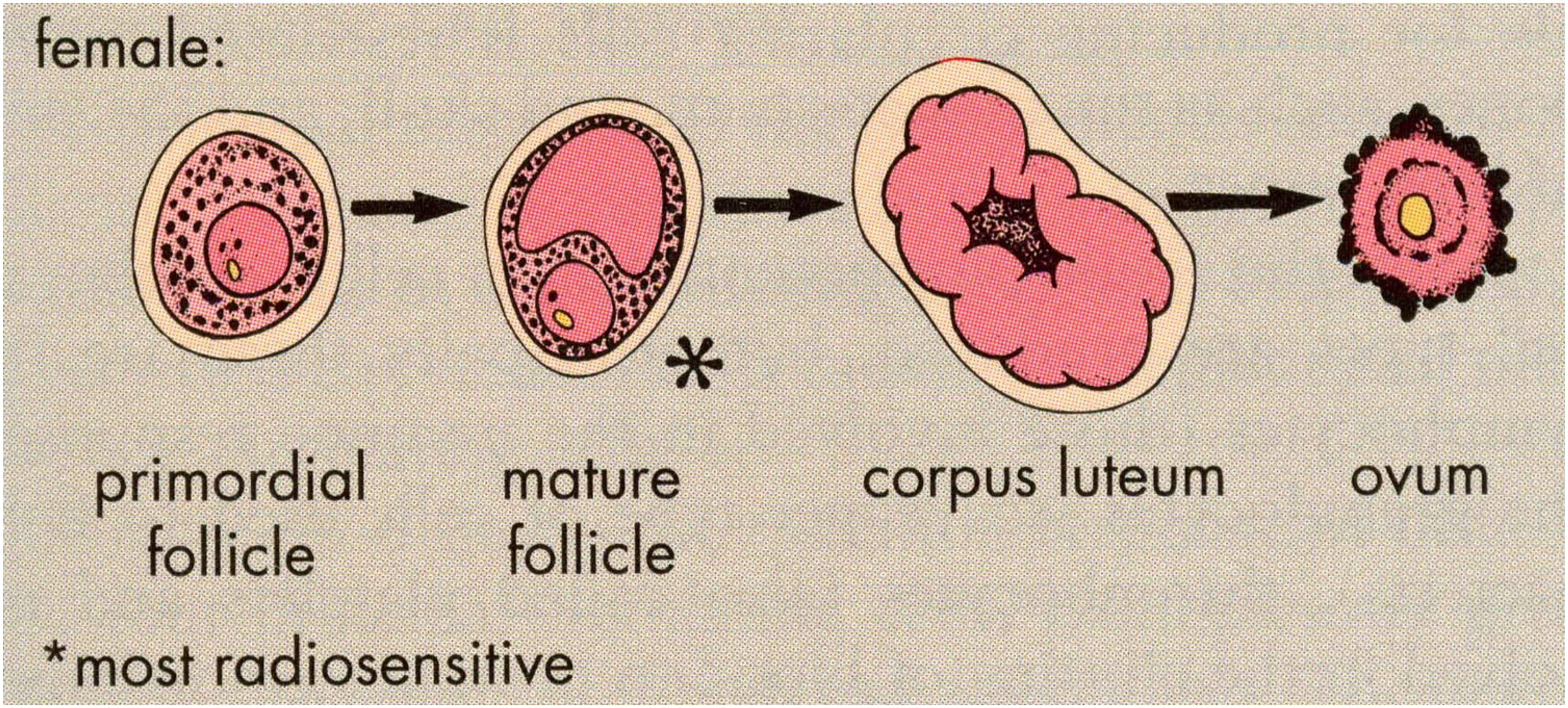
Male Reproductive System(1)

- Spermatogenesis or formation of sperm from spermatogonial cells, is extremely sensitive to radiation.
- The process of sperm formation, which occurs over 60 days, is primarily sensitive in the intermediate stages.
- The latter stages of sperm maturation, involving changes from a spermatid to a sperm, are fairly resistant due to the lack of division.
- The supporting cells of the testes (Leydig and Sertoli cells) are much more radioresistant than the sensitive spermatogonia cells.
- The effects of radiation on fertility is not apparent immediately due to the postspermatogonial cells being relatively resistant compared with stem cells.

Male Reproductive System(2)

- The exposed mature sperm cells usually disappear in 2-4 weeks.
- Sterility follows when these mature cells are depleted and lasts until spermatogonia can repopulate by division.
- Radiation-induced sterility is not accompanied by changes in hormone balance or libido. Fifteen rads is the threshold that will produce temporary sterility, beginning two months after irradiation and lasting up to twelve months.
- Roughly five hundred rads (350-600) to the testes will produce permanent sterility.
- Since male gametogenesis is a self-renewing system, evidence suggests that genetic mutations induced in postspermatogonial cells are the most

Female Gamete



Female Reproductive System

- As is true for the male, the female gamete (ovum) is radiosensitive.
- Unlike the male, the ovaries may atrophy after irradiation, resulting in permanent or temporary sterility.
- The intermediate follicles of oogenesis are the most sensitive.
- Massive doses (250-600 rads) may lead to permanent sterility.
- Hormonal changes, similar to menopause, accompany this radiation induced sterility.
- Due to the reduced number of oocytes in an older female, *the older ovary is more sensitive* to radiation than the younger ovary.

Epidermis (1)

- The skin, or epidermis, is also radiosensitive due to the rapid division of the basal cells, which are essentially stem cells.
- The length of the cell cycle and the transit time depend largely on the anatomical site, age, species, and the function.
- These cells migrate outward, keratinize, and are sloughed off, to be replaced by new cells formed by the basal layer.
- Damage to these cells produces the earliest evidence of radiation damage—*erythema*.

Epidermis (2)

- Early erythema is a sunburn-like reddening of the skin, which reaches its peak during the first week.

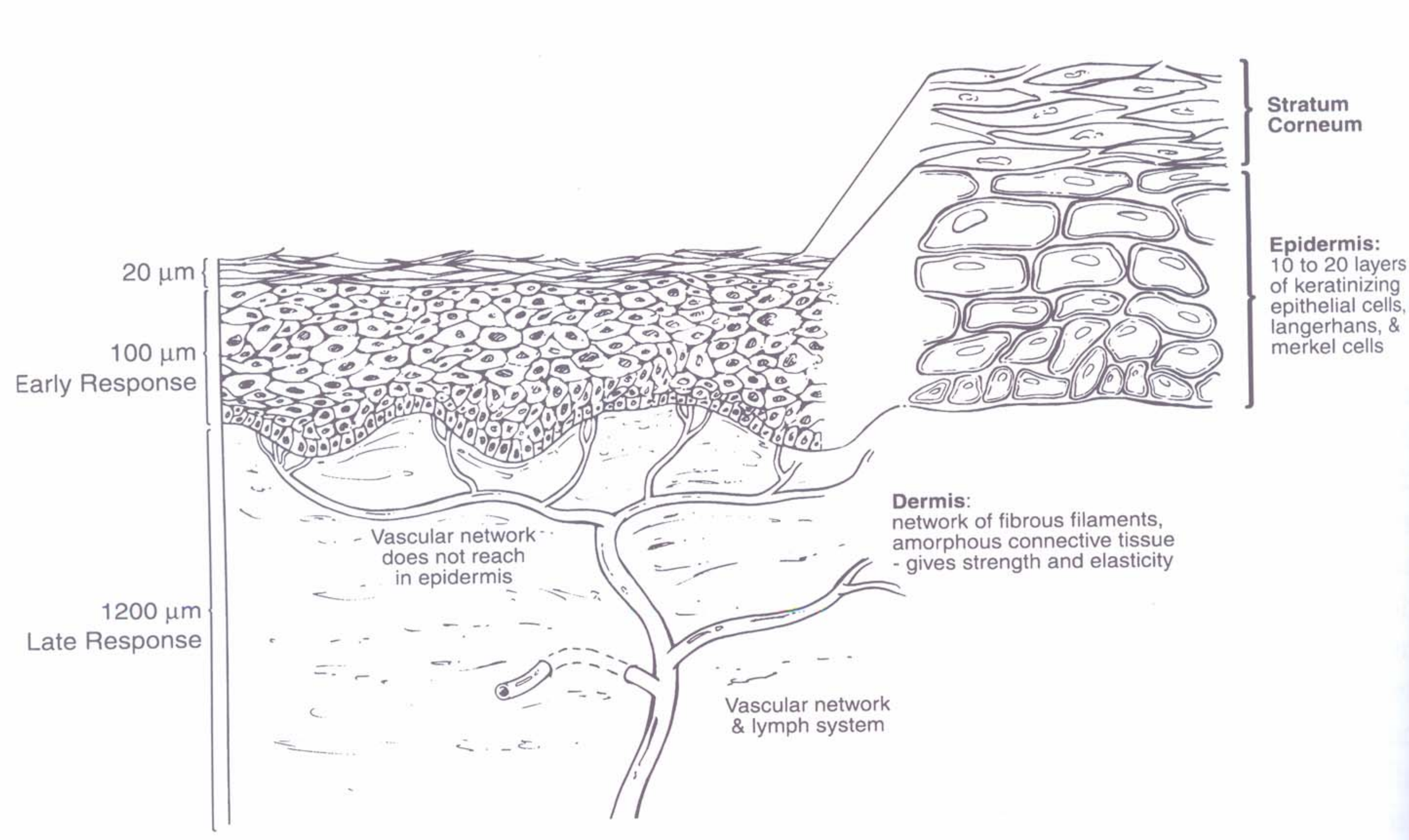
- This state is followed by desquamation of the tissues, basically ulceration of the skin.

- The main erythema reaction involves not only the epidermis, but the dermis and the subcutaneous layers, especially the blood vessels.

Epidermis (cont.)

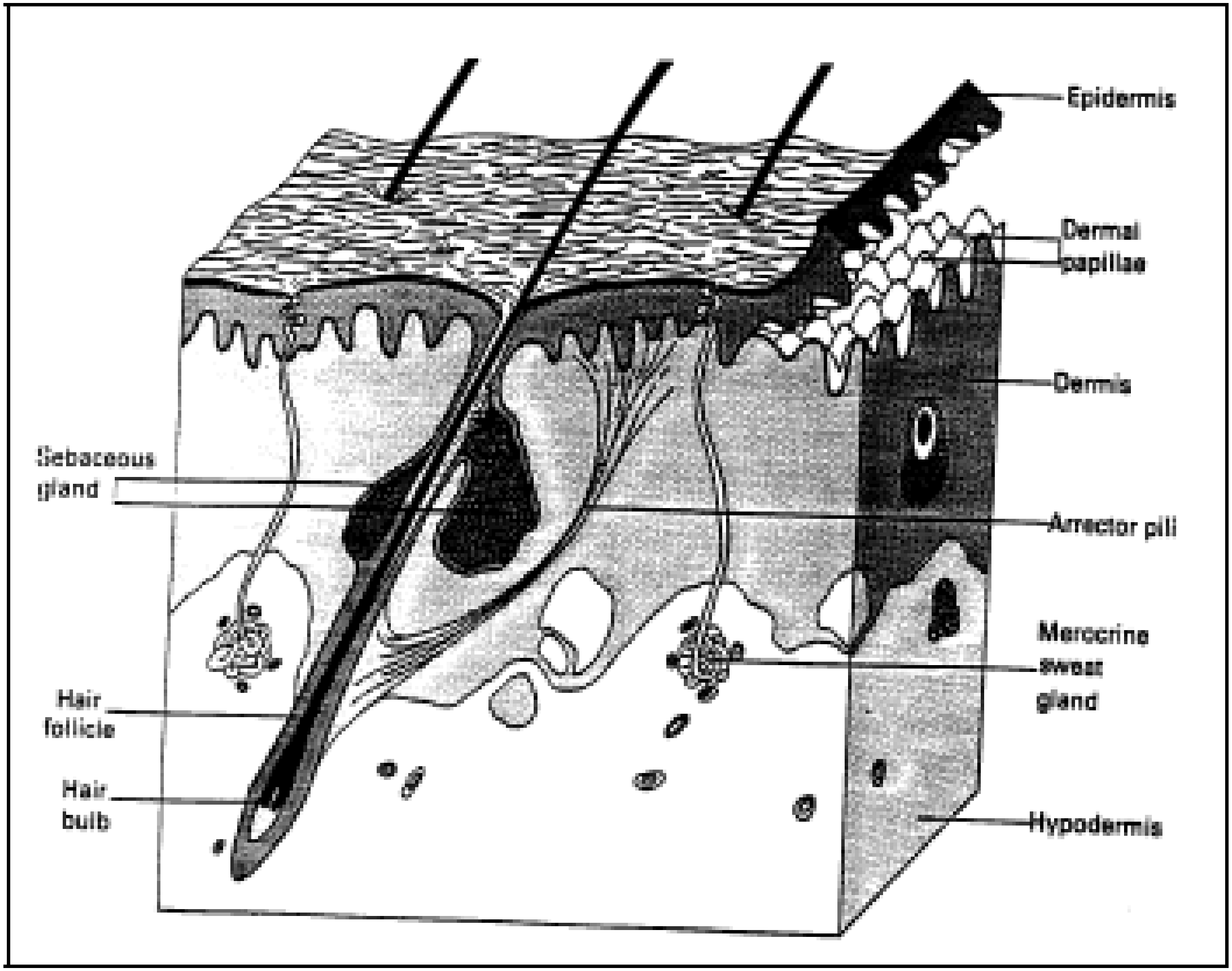
- This appears in a wave-like manner and may lead to dry or moist desquamation.
- Moist desquamation is the clinical tolerance for radiation therapy. At extreme levels of radiation, necrosis of tissues occur with degeneration extending to the bone tissue.
- It is the normal transit time of the basal layer of the epithelium that determines the pattern of radioresponsiveness.
- As for the hair follicles, the fastest growing hair is the most sensitive to radiation.
- This is again due to the rate of cell division being greater in faster growing hair.
- Therefore the list of hair affected from most to least rapid growing, is: beard, scalp, armpit, chest, and pubic.
- At a higher dose of radiation, hair loss ceases being temporary and is permanent.
- Hair will often turn white after a moderate dose.
- The sweat glands will also cease to function at high doses of radiation.

Skin

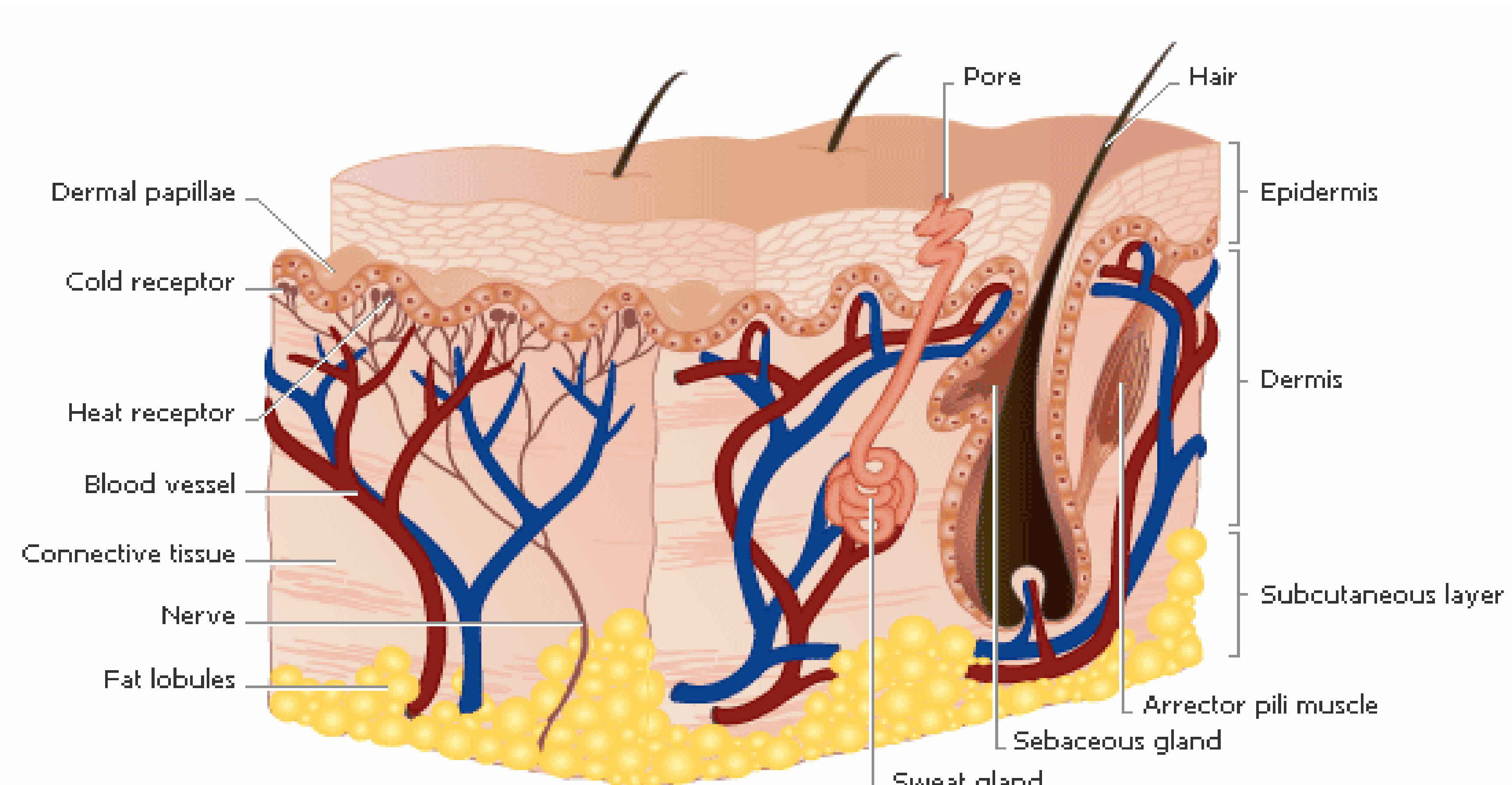


20 µm
100 µm
Early Response
1200 µm
Late Response
Stratum Corneum
Epidermis:
10 to 20 layers of keratinizing epithelial cells, langerhans, & merkel cells
Dermis:
network of fibrous filaments, amorphous connective tissue - gives strength and elasticity
Vascular network does not reach in epidermis
Vascular network & lymph system

Skin Structure



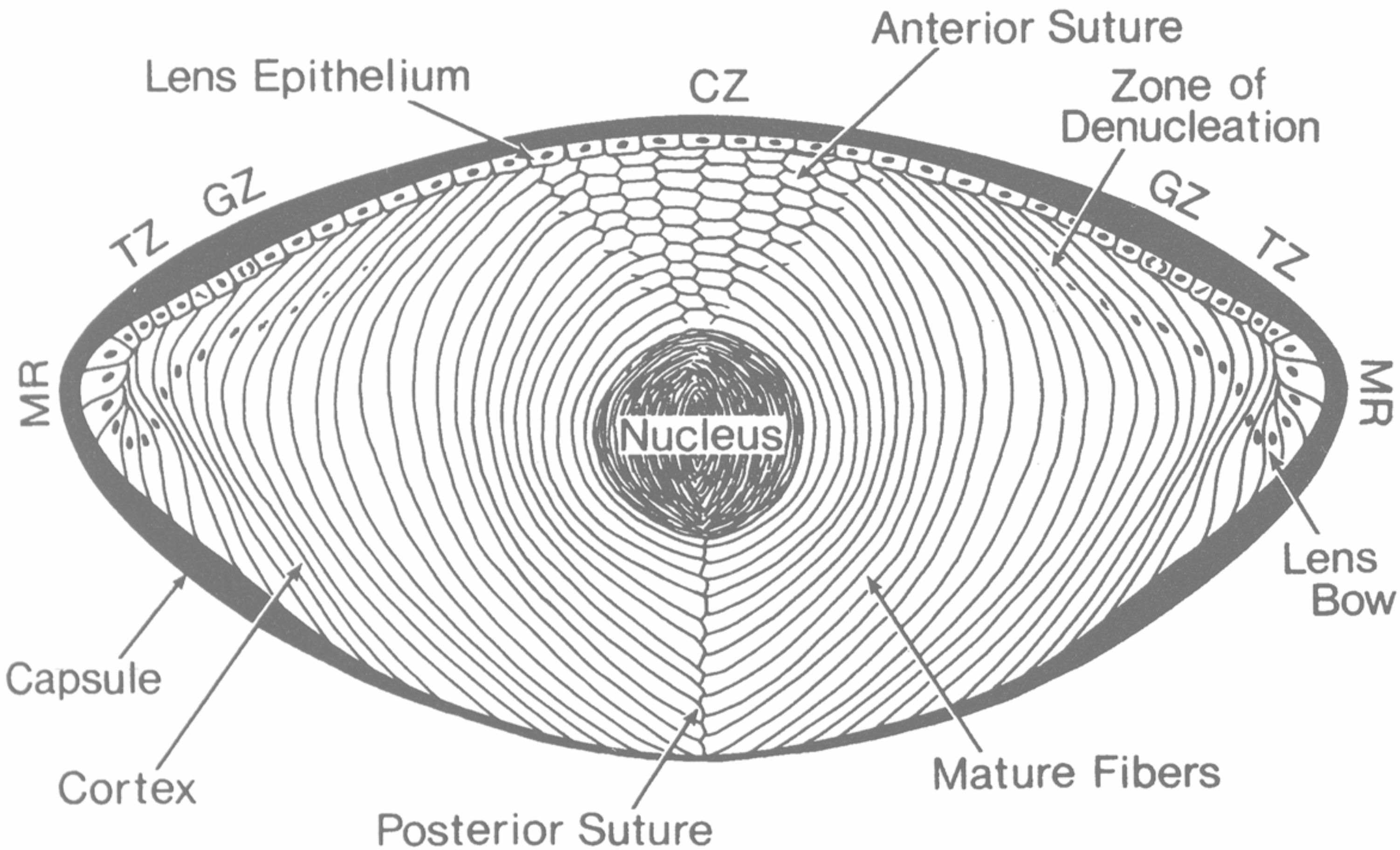
Epidermis (Skin)



Eye - Cataractogenesis

- Of all the eye components, only the lens is radiosensitive.
- This is due to the turnover of the lens cells.
- The sensitivity of the lens is species-dependent and age-dependent.
- Neutrons are particularly effective in forming cataracts.
- Cataracts result from the opacification of these cells.
- The average latency period for cataracts is 2-3 years.

Anatomy of the Lens



Central Nervous System

- This system was ***once thought extremely radioresistant*** because of the low rate of cell division of the neurons; however, this false belief was due to the late manifestation of radiation damage.
- The spinal cord is much more sensitive than the brain.
- Upon irradiation, the brain suffers from brain edema.
- The earlier mode of injury affects white matter through damage to the supporting glia cells. The later mode of injury is vascular in nature.
- When the brain is exposed to high doses of radiation in radiotherapy, there is a risk of late brain necrosis.
- Chronic radiation encephalopathy may occur 3-4 months after radiotherapy.
- A single very high dose may lead to acute meningoencephalopathy.

Fetal and Embryonic Tissue

- The neoplastic tissue of an embryo or fetus is composed of rapidly dividing cells that are extremely radiosensitive.

- The three different periods of intrauterine development—preimplantation, organogenesis, and fetal development and growth—are each affected differently by radiation.

- The classic effects of irradiation during pregnancy are the following:

❖ Lethal effects, induced by radiation before or immediately after embryo implantation or at high doses during the other stages, expressed as prenatal or neonatal death.

❖ Malformations during major organogenesis, when the main body structures are formed.

❖ Growth disturbances, induced at all stages of development but especially in the latter part of pregnancy.

❖ Carcinogenic effects of radiation are high in utero.

Preimplantation

- During *preimplantation (0-9 days in man)*, there are several cell divisions before the fertilized ovum reaches the uterus.
- The loss of several cells due to irradiation causes death of the organism. Losses at this stage are not detectable in humans.
- This is the most sensitive stage to lethal effects of radiation.
- Growth retardation is not observed at this stage, because this is an "all or nothing" effect of radiation due to the small number of and the general nature of the cells.

Organogenesis (1)

- *Organogenesis*, running from 10 days to six weeks after fertilization in humans, is the stage in which organs and systems are formed.
- Radiation administered early in this period would affect the nervous system early and the skeletal system later in the stage, due to the production of a specific defect during the period of organogenesis. Death or malformation can occur from irradiation.
- This is the most disastrous period for irradiation.

Organogenesis(2)

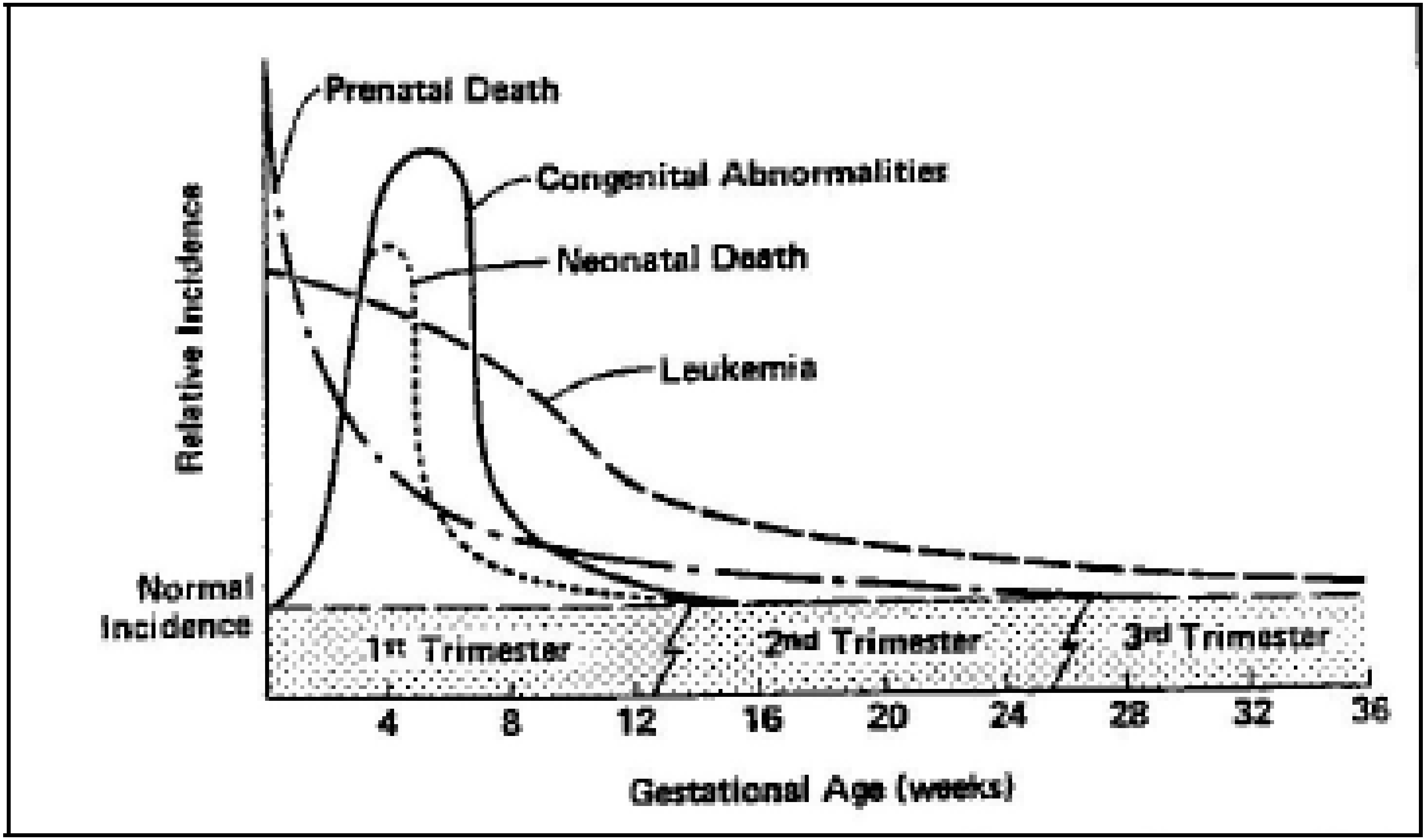
- The loss of a system, such as gastrointestinal, could be fatal for the organism. If death occurs as a result of irradiation in this sage, it is likely to be neonatal death, occurring at or about the time of birth.

- Embryos also exhibit the greatest intrauterine growth retardation. This is a weight reduction which is due to cell depletion.

- Therefore, there is an association between growth retardation and teratogenesis.

- The malformation of body structures, which is expected due to irradiation during organogenesis, is rare in the Japanese survivors

Embryonic Tissue Response



Fetal stage

- The *fetal stage* in humans runs from six weeks to term.
- Higher doses of radiation are needed to cause death in the fetal stage—smaller head size is a common result in this stage.
- Most organs are formed and growth is occurring in this period.
- Irradiation in this stage can cause effects on the hematopoietic system, liver, kidney, and developing gonads.
- Much higher doses of radiation are required to cause lethality in this period.
- Irradiation during the fetal stage exhibits the largest degree of permanent growth retardation.
- According to data from both medical exposure and Hiroshima/Nagasaki, the most common effects of in utero irradiation are microcephaly (sometimes combined with mental retardation), other central nervous system defects, and growth retardation.

Pregnant Mothers X-Rays

- A great deal of data concerning radiation effects have come from X-ray exposure in expectant mothers. Exposure to medical radiation has led to the following conclusions:

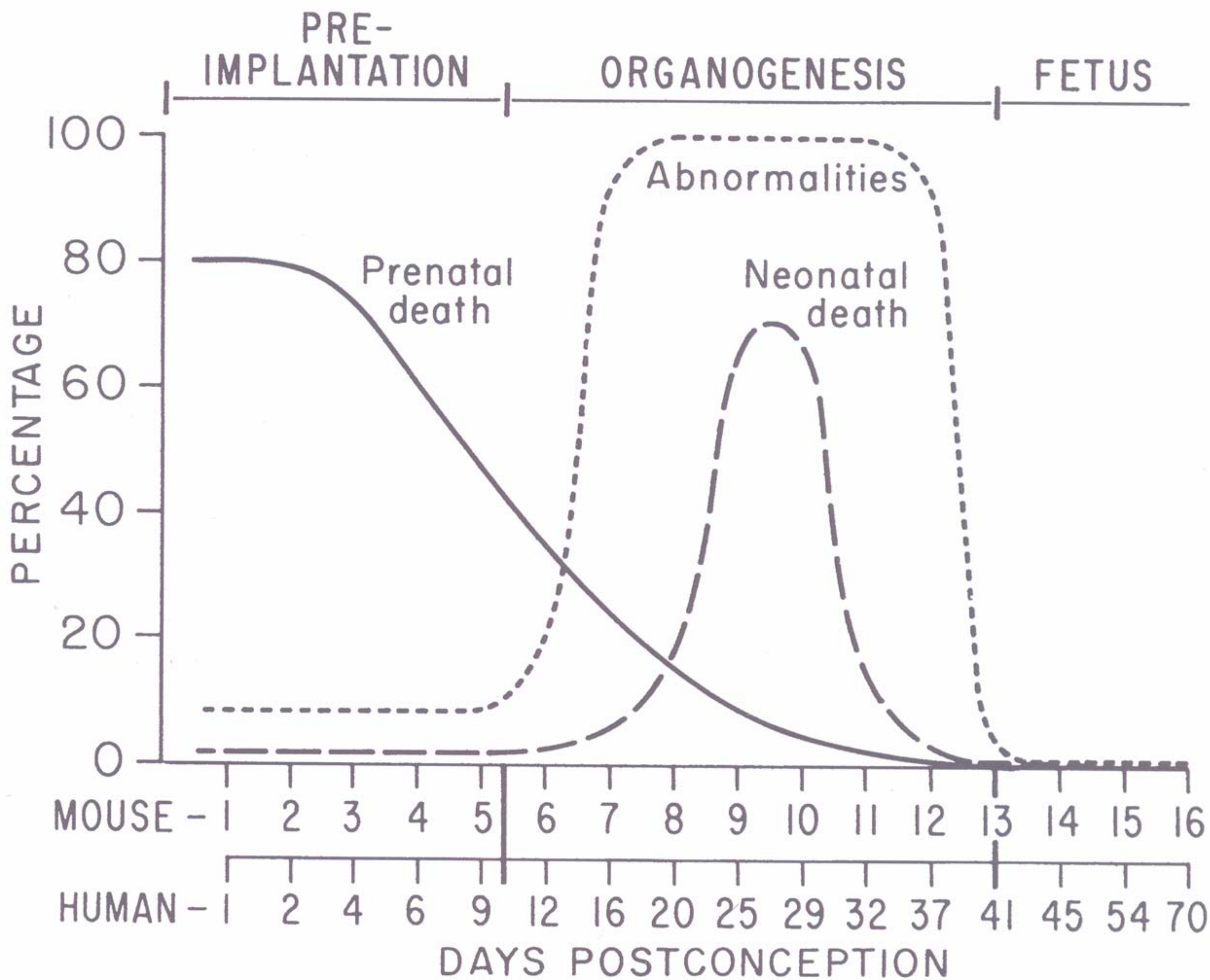
    - ❖ Large doses of radiation (250 rads) at 2-3 weeks of gestation do not produce severe abnormalities in most children although many embryos are aborted.

    - ❖ Irradiation at 4-11 weeks of gestation leads to severe abnormalities of major organs in most children.

    - ❖ Irradiation at 11-16 weeks produces stunted growth, microcephaly, mental retardation, eye, skeletal, and genital organ abnormalities.

    - ❖ Irradiation at thirty weeks leads to functional disabilities.

    - ❖ Susceptibility to carcinogenic effects of radiation is high during the in utero period. Diagnostic exposure increases the natural cancer incidence by a factor of 1.5 to 2.



PRE-
IMPLANTATION
ORGANOGENESIS
FETUS
100
80
60
40
20
0
PERCENTAGE
Abnormalities
Prenatal
death
Neonatal
death
MOUSE - 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
HUMAN - 1 2 4 6 9 12 16 20 25 29 32 37 41 45 54 70
DAYS POSTCONCEPTION

Permissible Dose to Fetus

- Overall, the maximum permissible dose to the fetus during gestation is 5 mSv, with a monthly limit of 0.5 mSv. A dose of 10 rads to the embryo during the sensitive period of gestation (10 days - 26 weeks) is regarded as the cut-off point, above which a therapeutic abortion may be considered.
- The “10-day” rule refers to the fact that X-ray examinations of the lower abdomen in women should *only be carried out in the first ten days following the first day of the menstrual cycle.*
- Since 1984, it is believed the risk of radiation injury could be greater in the seven weeks before the mother becomes pregnant than in the first two weeks of pregnancy.

Stochastic and Nonstochastic Effects

- *Nonstochastic* effects are those which have a dose threshold and have a dose-response relationship.
- Nonstochastic effects have a severity scale associated with dose. Increasing the dose is expected to increase the severity of the outcome.
- These effects require reduced function of a class of cells essential to maintaining an activity.
- If a reduction occurs in a cell population, such as epidermal cells, a loss of function will occur.
- The effects of radiation mentioned in this lesson are nonstochastic.
- *Stochastic* effects are those for which there is no known threshold dose.
- Stochastic effects would be the production of cancer or genetic defects in egg or sperm.
- The severity of the response is independent of dose.
- A stochastic effect signals an event in a single cell that ultimately leads to its irreversible alteration.

Nonstochastic Effects (1)

- Radiologists look at the effects of radiation as *early* or *late effects*. Protraction and fractionation can affect the appearance of early and late effects.
- The early effects of radiation are based on the proliferation of cells (division), as evidenced by the effect on testes and intestines.
- The esophagus, small intestine, large intestine, and stomach all suffer the same late nonstochastic effects.
- Irradiation of the organs leads to stricture of the organ (*stenosis*). Stenosis can then lead to blockage of the organ.
- Fiberatrophy of the tissues also occurs. These late effects are due not to interference with division but to changes in the microvasculature of the cell or cellular DNA.
- The liver is radioresistant due to lack of cell division in the mature cells. However, radiation-induced hepatitis can occur. Irradiation of the kidneys results in arteriolar nephrosclerosis.

Nonstochastic Effects (2)

- Nonstochastic late effects on the lungs includes radiation-induced pneumonitis.
- Whereas little is known about the effect on the brain, irradiation of the spinal cord can lead to paralysis.
- Irradiation of the lens of the eye results in cataracts.
- As for stochastic effects, the primary early effect is acute radiation syndrome.
- The primary importance of late stochastic effects lies in radiation-induced malignancy and genetic effects.
- Both of these effects, early and late, will be studied in the next lesson.

Summary

- The effects of radiation on a tissue are due primarily to the rate of division of the cells making up the tissue.
- The effects of radiation on the sperm and ovaries are especially important because of the possibility of effects on future generations due to genetic mutations.
- Radiation has an aging effect on kidneys and eyes.
- The effect of radiation on the skin can be used to estimate the effects of radiation on the body cell division.
- Irradiation of the embryo can lead to death, organ malformation, or growth deficits.
- Stochastic and nonstochastic effects differ in dose threshold and dose response relationship.