TOTAL BODY RADIATION SYNDROMES (ACUTE RADIATION SYNDROMES)

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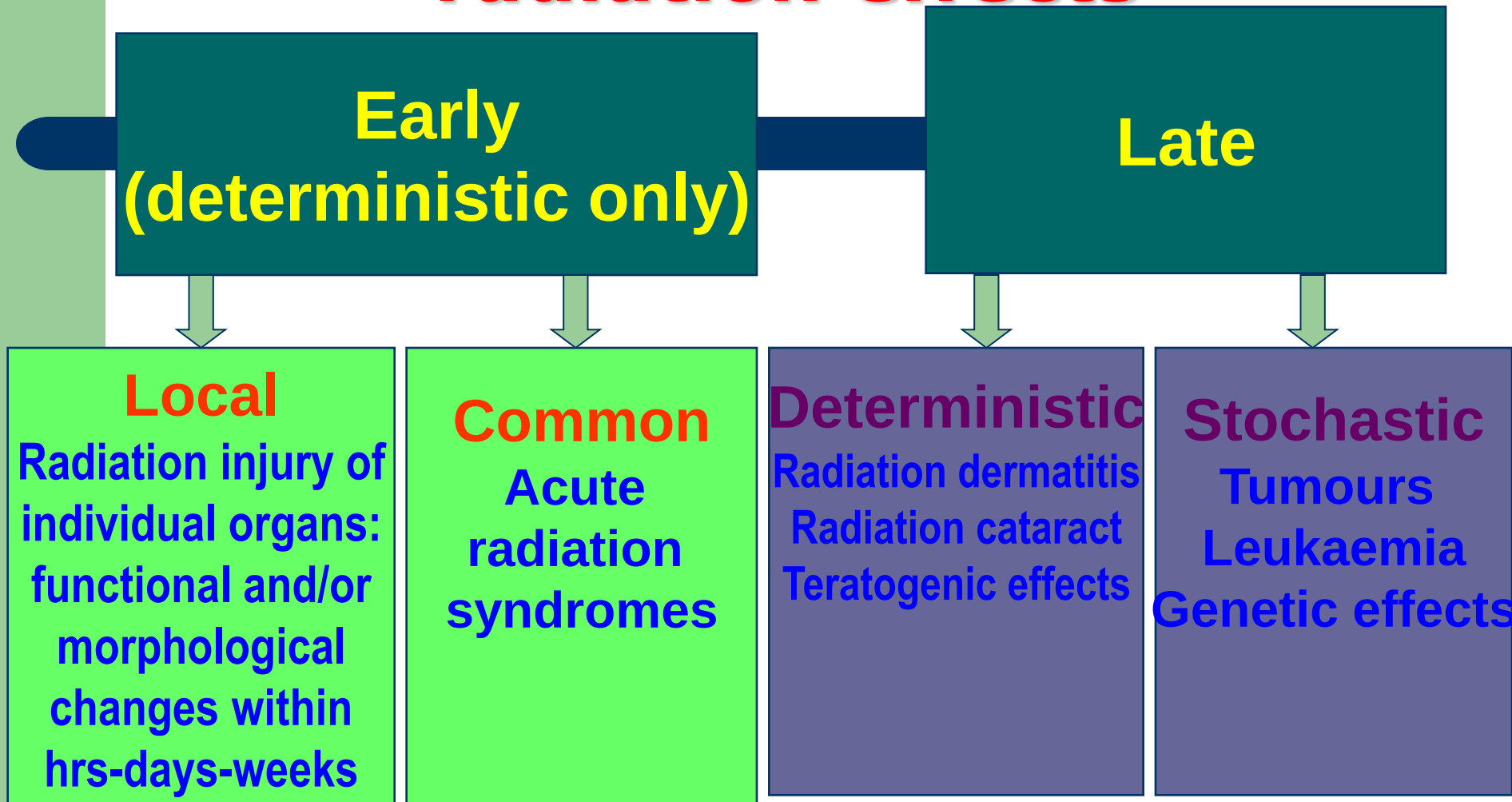
The most important radiation effects



Forms of radiation injury depending on conditions of radiation exposure

Acute total external radiation exposure	Acute radiation syndrome
Acute local external irradiation or external contamination	Local radiation injury
Acute total external radiation exposure with external or internal contamination	Acute radiation syndrome coexisting local or internal radiation injury
Combined exposure of radiation and non-radiation factors	Combined radiation injury
Chronic external or internal radiation exposure	Chronic radiation syndrome

Early deterministic effects after whole body irradiation

- **< 0.1 Gy – no detectable difference in exposed or non-exposed patients**
- **0.1–0.2 Gy – detectable increase in chromosome aberrations, but no clinical signs or symptoms**
- **0.12 Gy – sperm count decreases to minimum about day 45**
- **0.3 Gy – detectable temporary sterility for man**
- **0.5 Gy – detectable bone marrow depression with lymphopenia**

Total body radiation syndrome is observed when:

- The exposure of the organism is **acutely** in a matter of **minutes** (rather than **hours or days**).
- The area of the organism exposed to radiation is the **total-body** or **very near total-body**.
- The exposure is produced by **external penetrating source** such as **x-rays, γ-rays** and **neutrons**.

Phases of acute radiation syndrome

- Initial or prodromal phase
- Latent phase
- Manifest illness phase
- Recovery phase

- **1. Prodromal stage** is the **first phase**.
  - characterized by **nausea, vomiting and diarrhea**.

  The prodromal stage may last from **a few minutes to a few days**, depending on the dose.
- **2. Latent stage** is the **second phase**.

  The term is derived from the generally **healthy appearance** of the experimental animals during this time.

  During this stage **changes are taking place in more radiosensitive organs and systems**.

- **3. Manifest illness stage** is the **third phase**.

It follows after the latent stage when specific sings and symptoms of the damaged organs and systems become **exhibited**.

It may last **from minutes to weeks**, depending of the dose.

- ❑ **As dose increases the number of survivors and survival time decreases accordingly**.

1. Bone marrow (the hematopoietic) syndrome

(1-10 Gy)

Mild form 1-2 Gy

Moderate form 2-4 Gy

Severe form 4-6 Gy

Very Severe form 6-10 Gy

2. Gastrointestinal syndrome

(10-100 Gy)

3. Central Nervous System syndrome

(neurovascular) (CNS) - > 100 Gy

Critical organs/tissues after acute whole body radiation exposure

Doses, Gy	Critical organ/tissue	Mortality %	Mortality days
1 – 2	Bone marrow	–	–
2 – 4		5	40 – 60
4 – 6		50	30 – 40
6 – 10		95	10 – 20
10 – 30 (100)	Gastrointestinal tract	100	7 – 14
> 30 (> 50 > 100)	CNS	100	1 – 5

Health effects	Acute, Gy
Blood(number of cells)	0.5
Vomiting (treshold)	1.0
Mortality (treshold)	1.5
$LD_{50/60}$ (min/-)	3.2-3.6
$LD_{50/60}$ (treatment)	4.8-5.4
$LD_{50/60}$ (BMT)	> 5.4

Factors decreasing $LD_{50/60}$

- Coexisting trauma combined injury
- Chronic nutritional deficit
- Coexisting infection
- Contribution of high LET radiation

I. Bone marrow syndrome

(1 Gy – 10 Gy)

- **Prodromal stage**

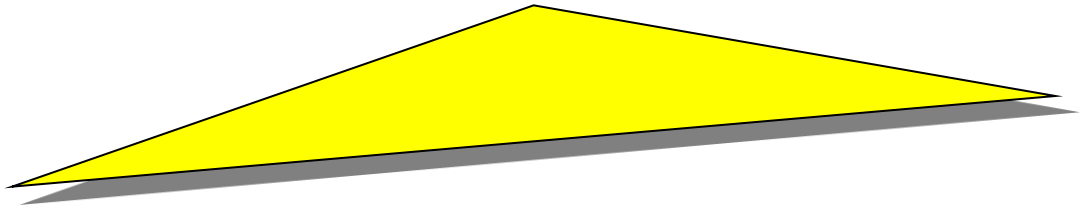
occurs a few hours post-exposure

nausea, vomiting

- **Latent stage**

a few days to 3 weeks,

the number of cells is not severely depressed.



- **Manifest illness stage**

3-5 weeks, pancytopenia anemia, hemorrhage, infections, epilation (loss of hair) – 2-6 weeks, after 6 months regrowth of the hair is complete

Laboratory findings

- initial granulocytosis 2-4 days
- leukopenia 4-5 weeks
- Lymphocytopenia (Ly↓) 3-4 days
- Tr ↓ < 50000 after 4th week

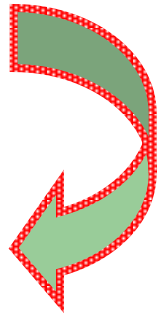
Late critical phase 4-5 weeks

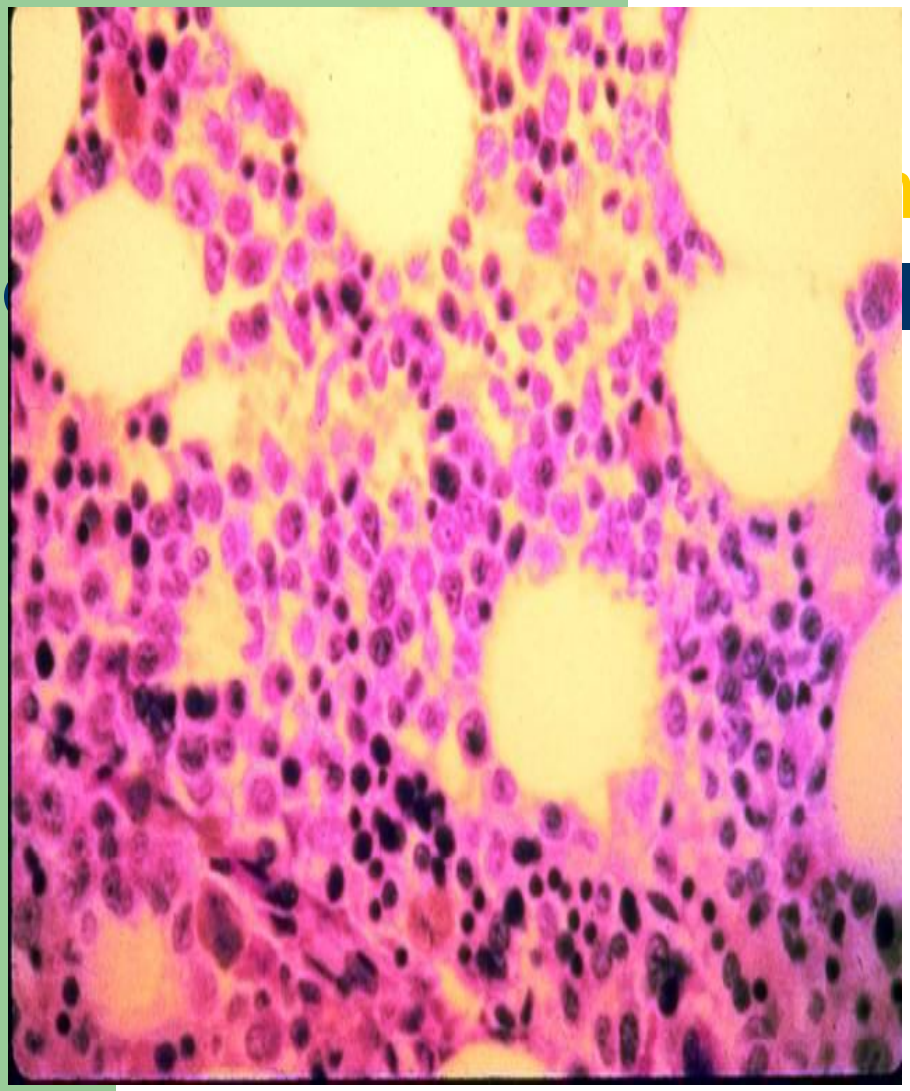
- Nausea, vomiting
- Fever
- Diarrhea
- Severe granulocytopenia and thrombocytopenia

The primary reason for death

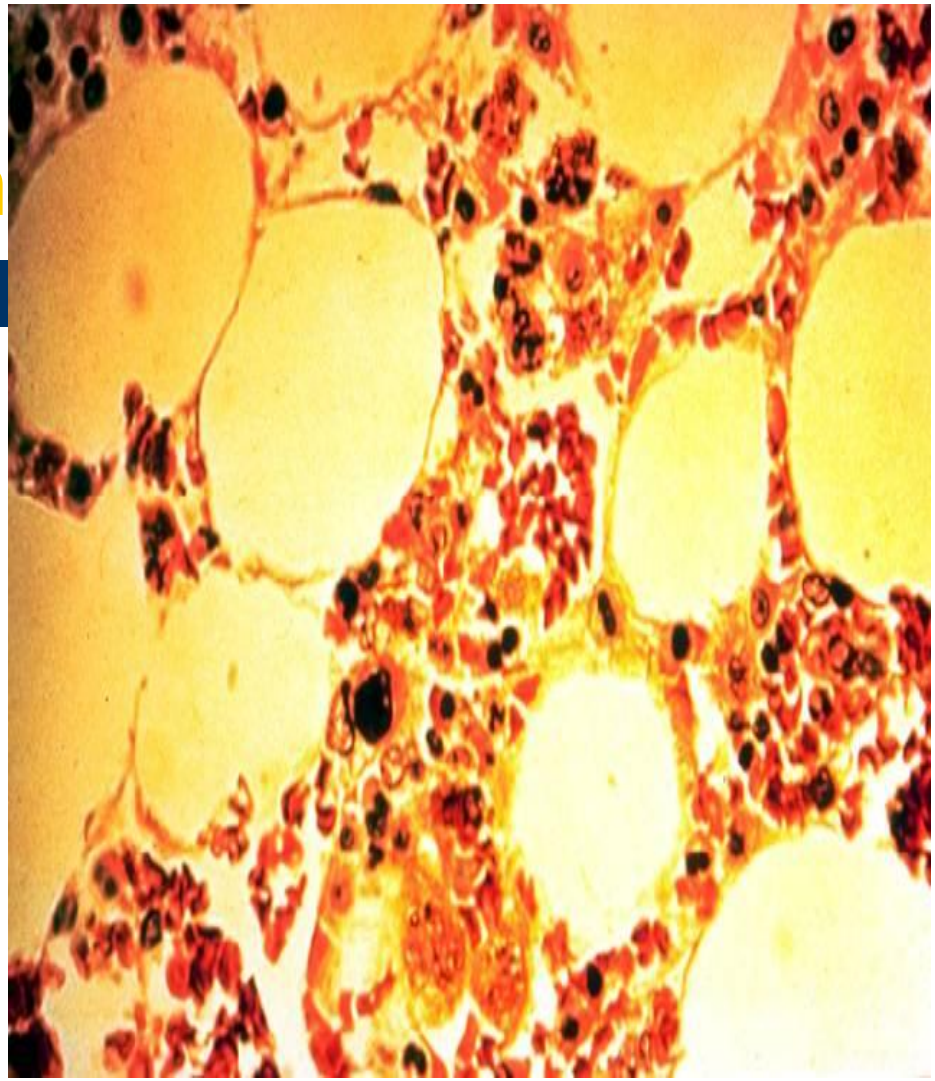
bone marrow depletion, pancytopenia

severe neutropenia – infections
platelet deficiency - bleeding





Normal bone marrow cells



Bone marrow damaged by radiation injury

Threshold doses for symptoms of the prodromal phase (ARS)

- anorexia, nausea and vomiting (1 Gy)
- diarrhea (4 – 6 Gy),
- malaise, weakness and fatigue (1 – 2 Gy),
- fever (8 – 10 Gy)

Characteristic of symptoms of prodromal phase of ARS depending on doses

	1 – 2 Gy	2 – 4 Gy	4 – 6 Gy	> 6 Gy
Initiation	2 hours	1 – 2 hours	0,5 – 1 hours	5 – 20 minutes
Vomiting	unitary	repeated	frequently repeated	unrest-rained
Diarrhea	–	–	+ –	+ + +
Duration	1 – 3 hours	to 1 day	to 2 days	more than 2 – 3 days

Pathogenesis of emetic syndrome

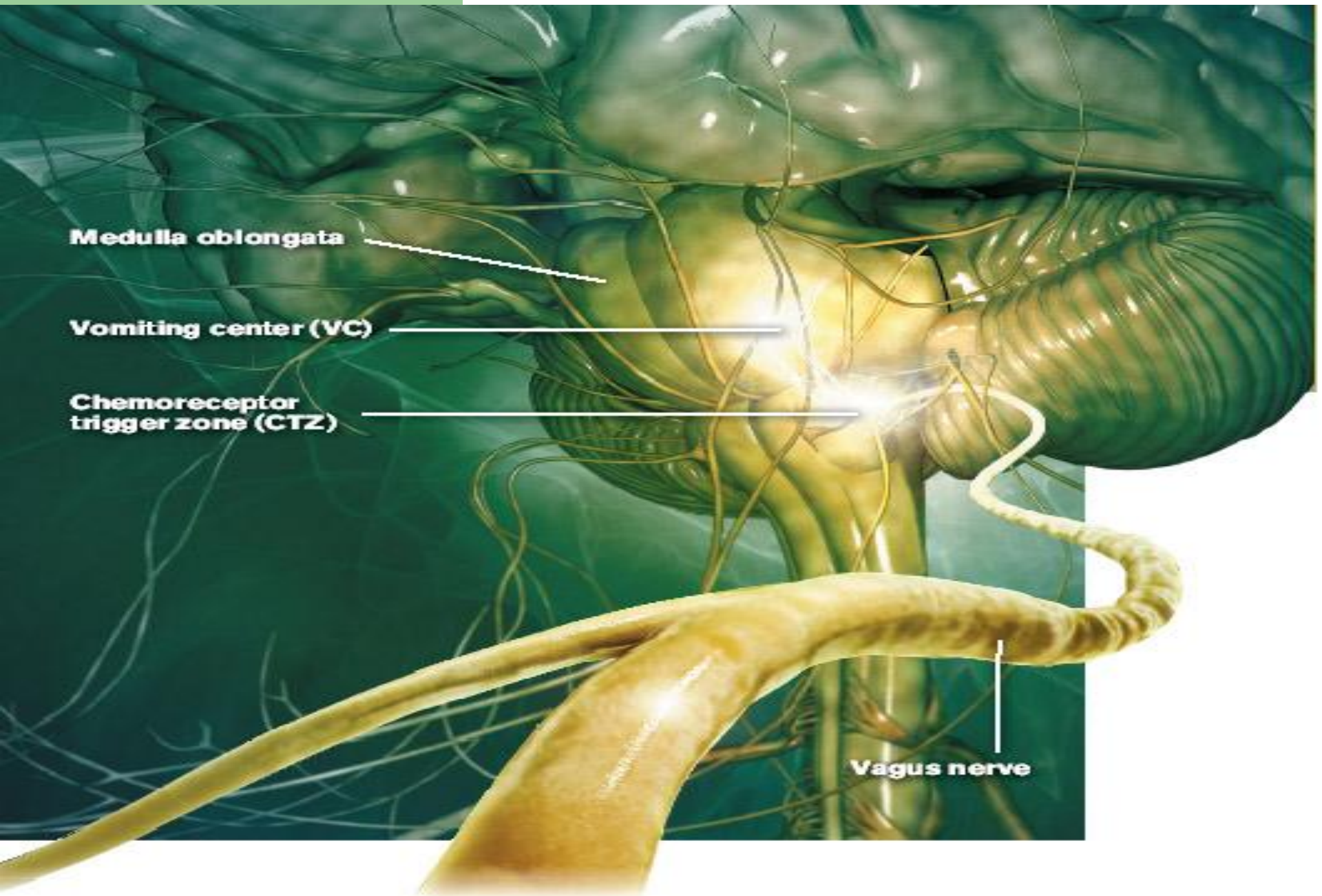
- **Central mechanism:**

  activation of chemoreceptor trigger zone of vomiting centre by biological actively substances from irradiated tissues – biogenic amines, regulatory peptides and other bioregulators

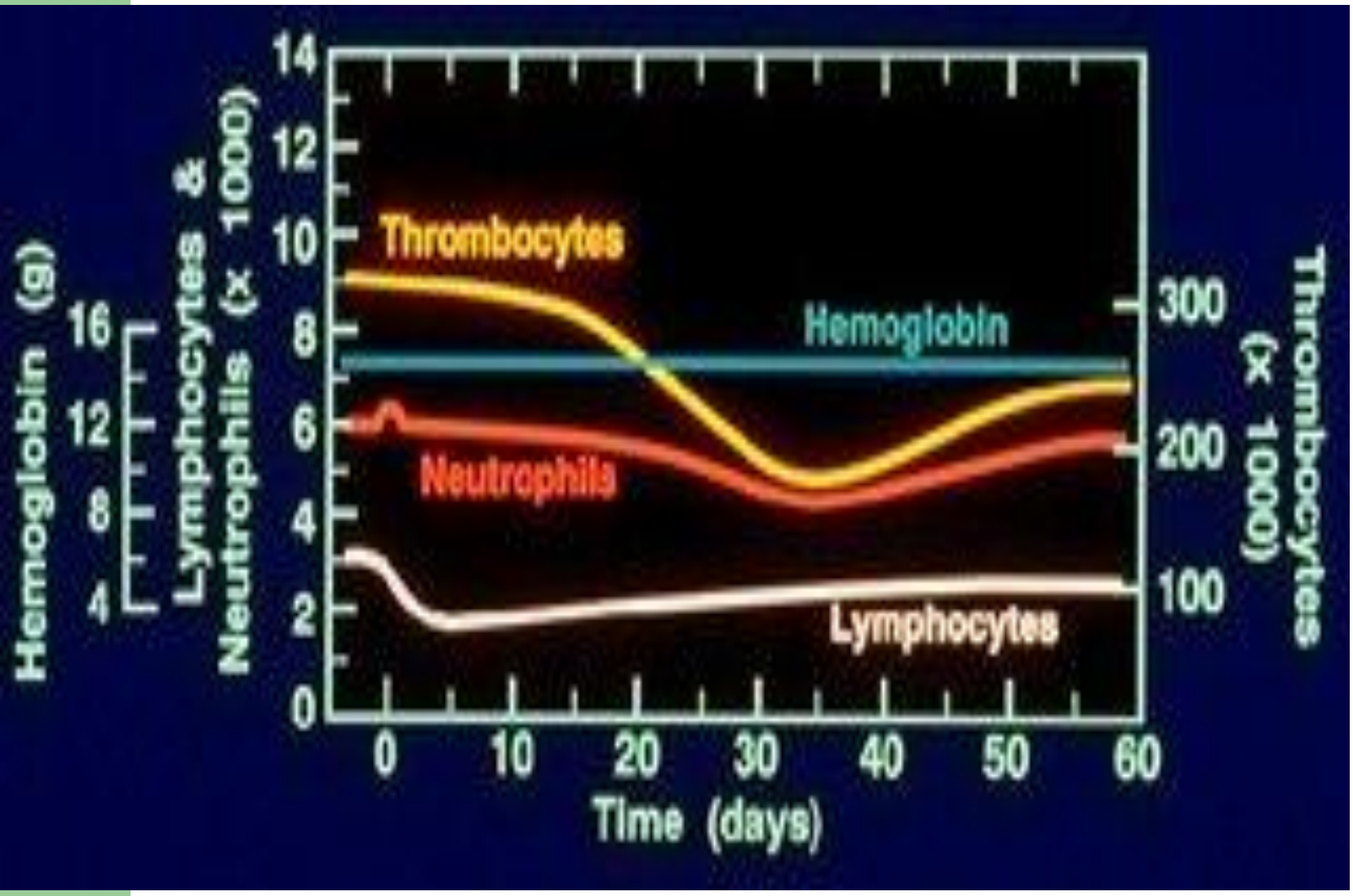
- **Peripheral or reflex mechanism:**

  irritation of peripheral emetic receptors from peripheral zones located, mainly, in digestive tract

Pathogenesis of emetic syndrome

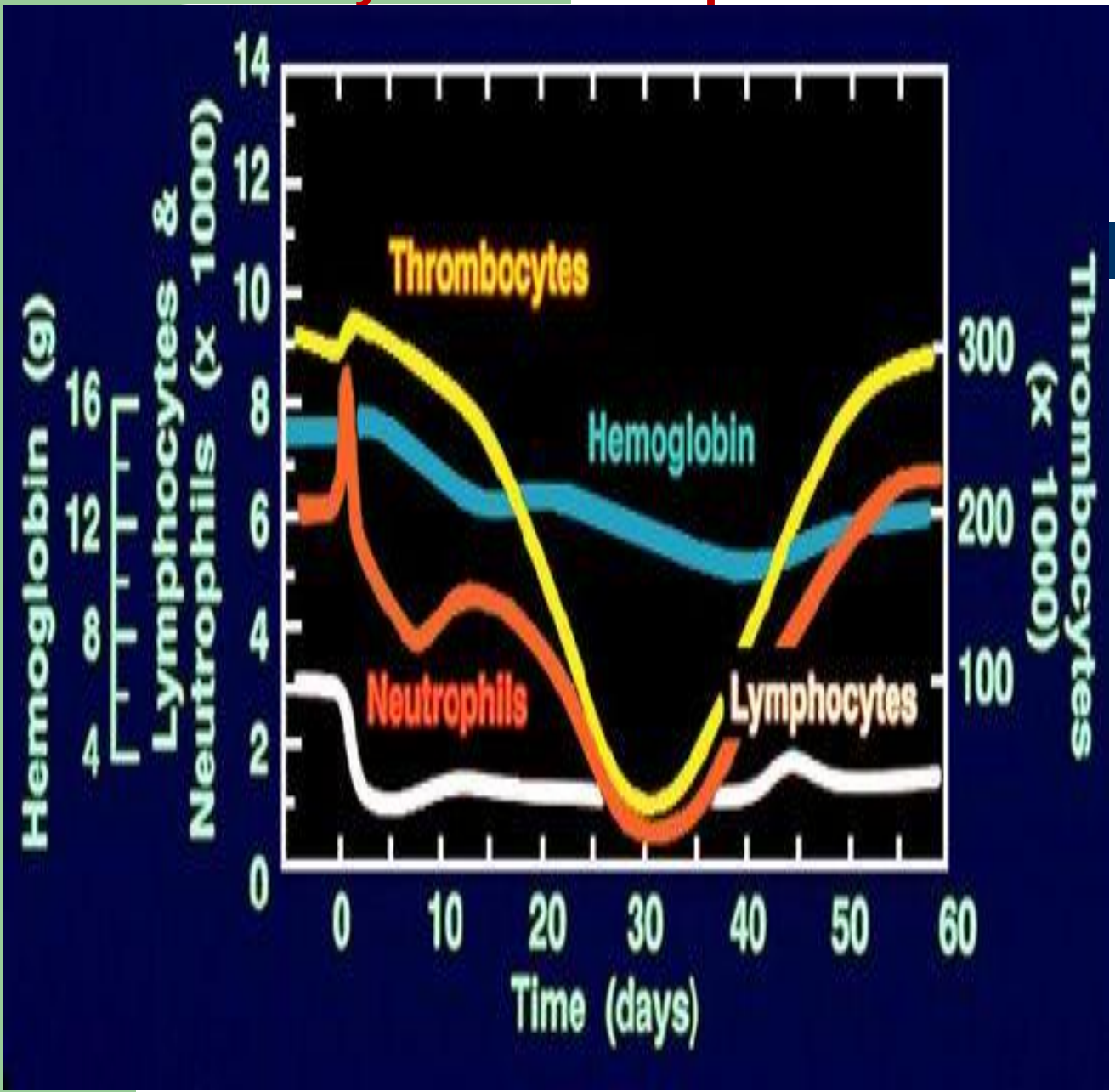


Haematological response to 1 Gy whole body radiation exposure



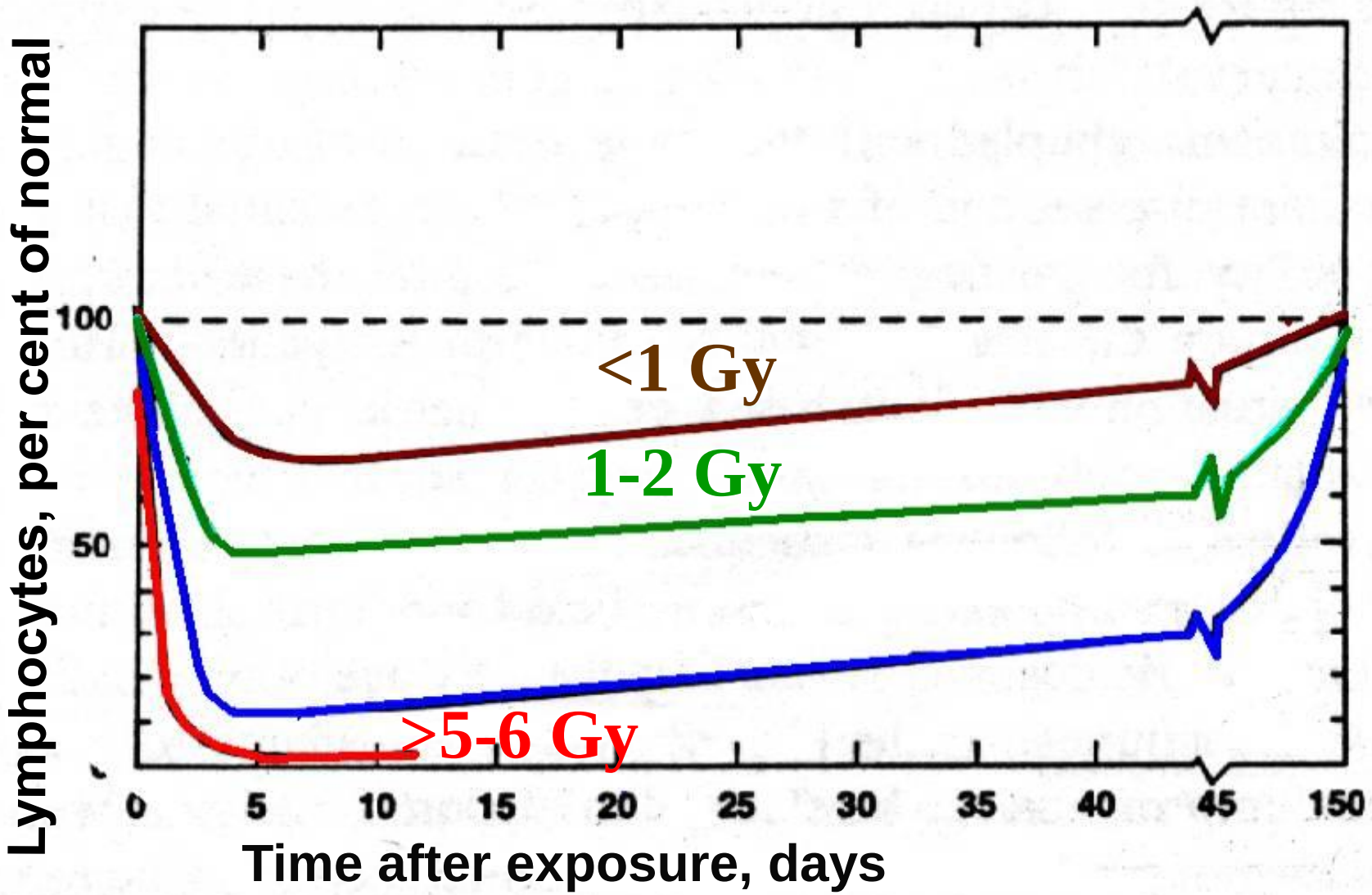
PI counts generally drop in concert with Ne counts, but an abortive count rise is not observed

Haematological response to 3 Gy whole body radiation exposure

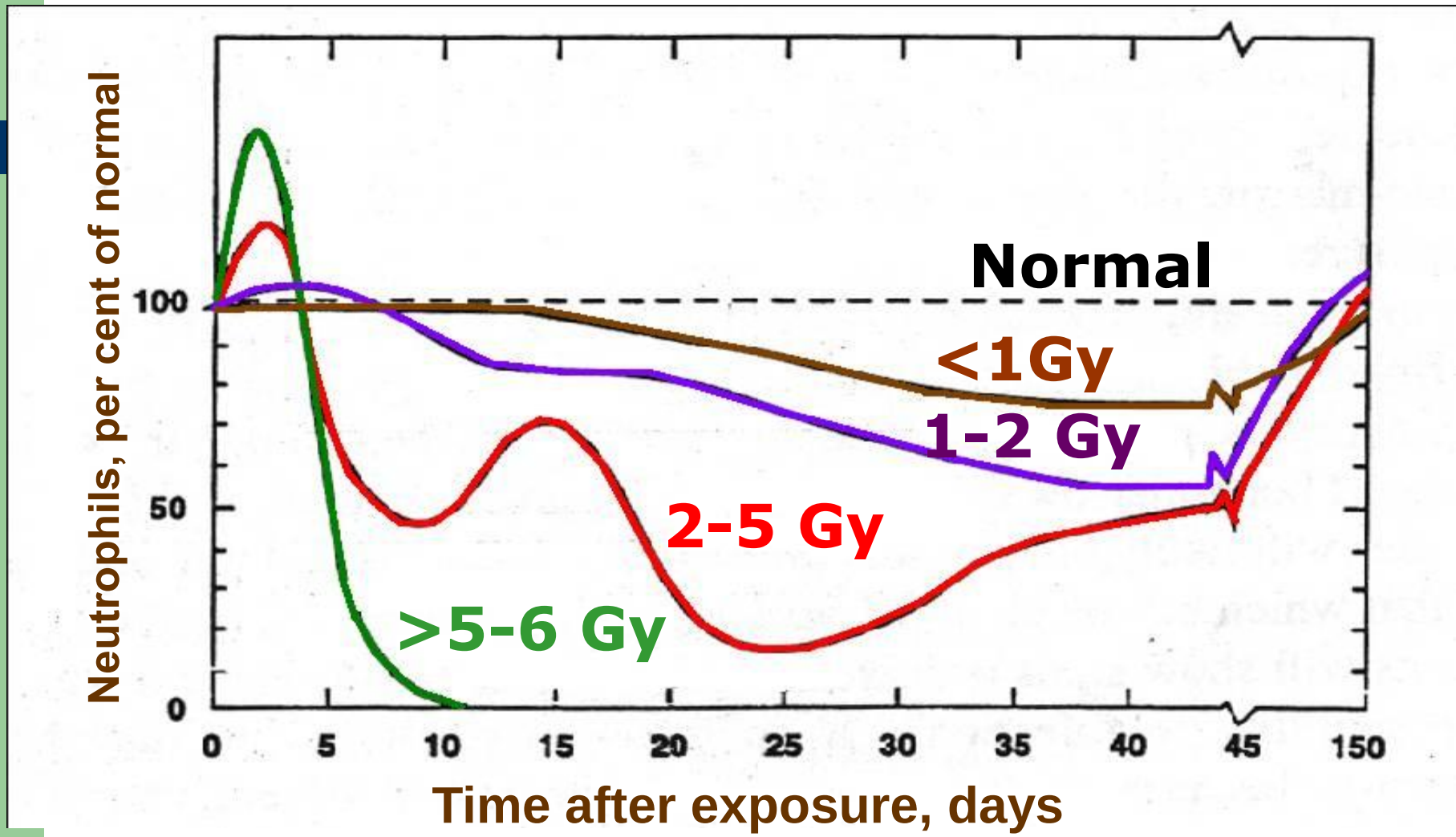


Doses greater than 2 Gy cause an initial paradoxical rise in counts that lasts only hours or days and is followed by a drop. This is caused by prompt demargination of white cells into the circulation. Any blood cell count taken during this paradoxical rise may be misinterpreted as evidence of infection. Doses of 2 to 5 Gy cause a second abortive rise (several days or a week). This second abortive rise is caused by the products of final differentiation and entry into circulation of marrow PMN (polymorphic nucleated) precursor cells, which do not need to undergo further mitotic divisions. The extent and duration of this second rise lasts for approximately a week with a rise from about 50% to about 75% of normal. Then the neutrophil count continues dropping to 20% of normal at around 25-35 days after exposure.

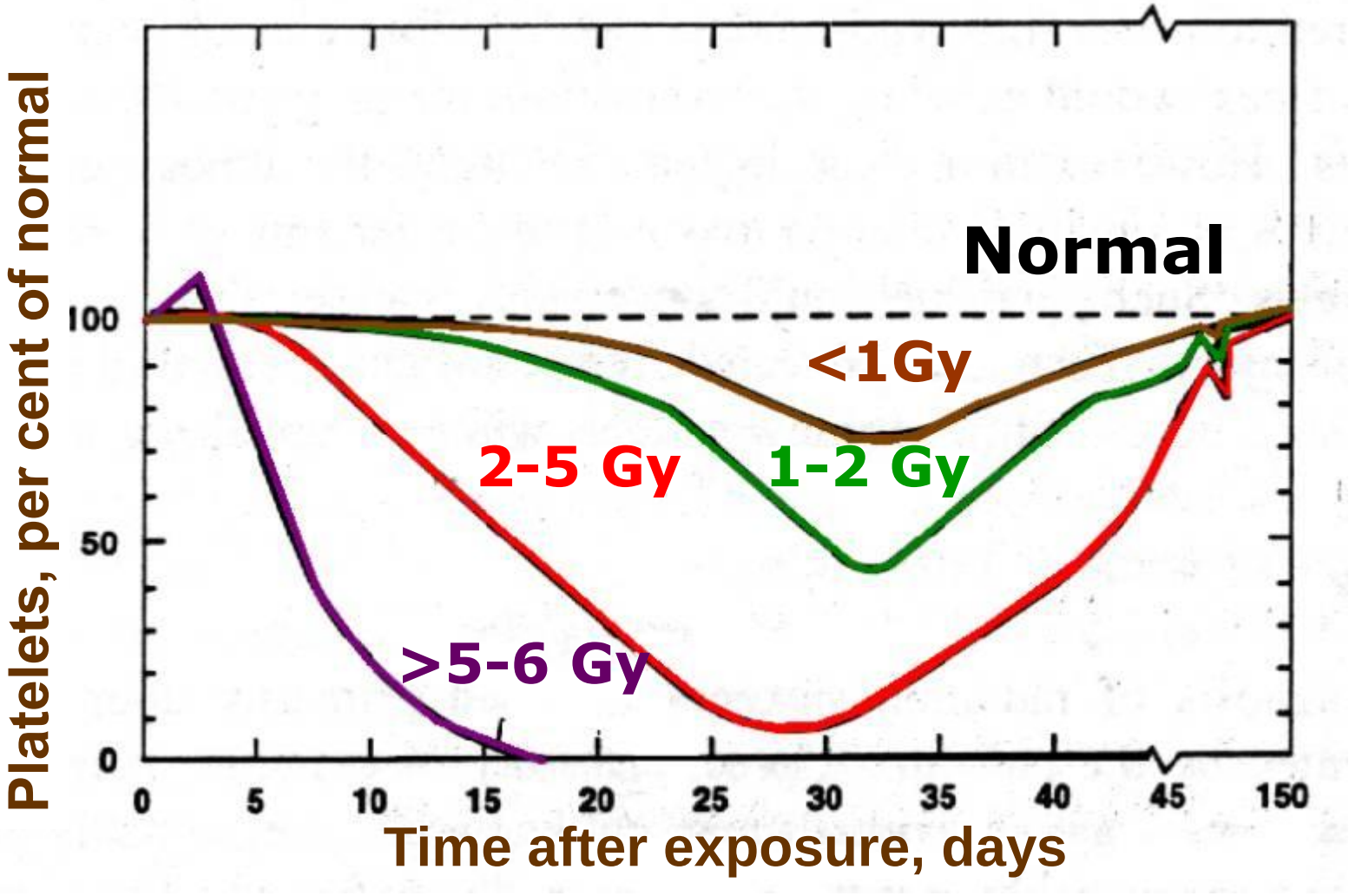
Lymphocyte changes



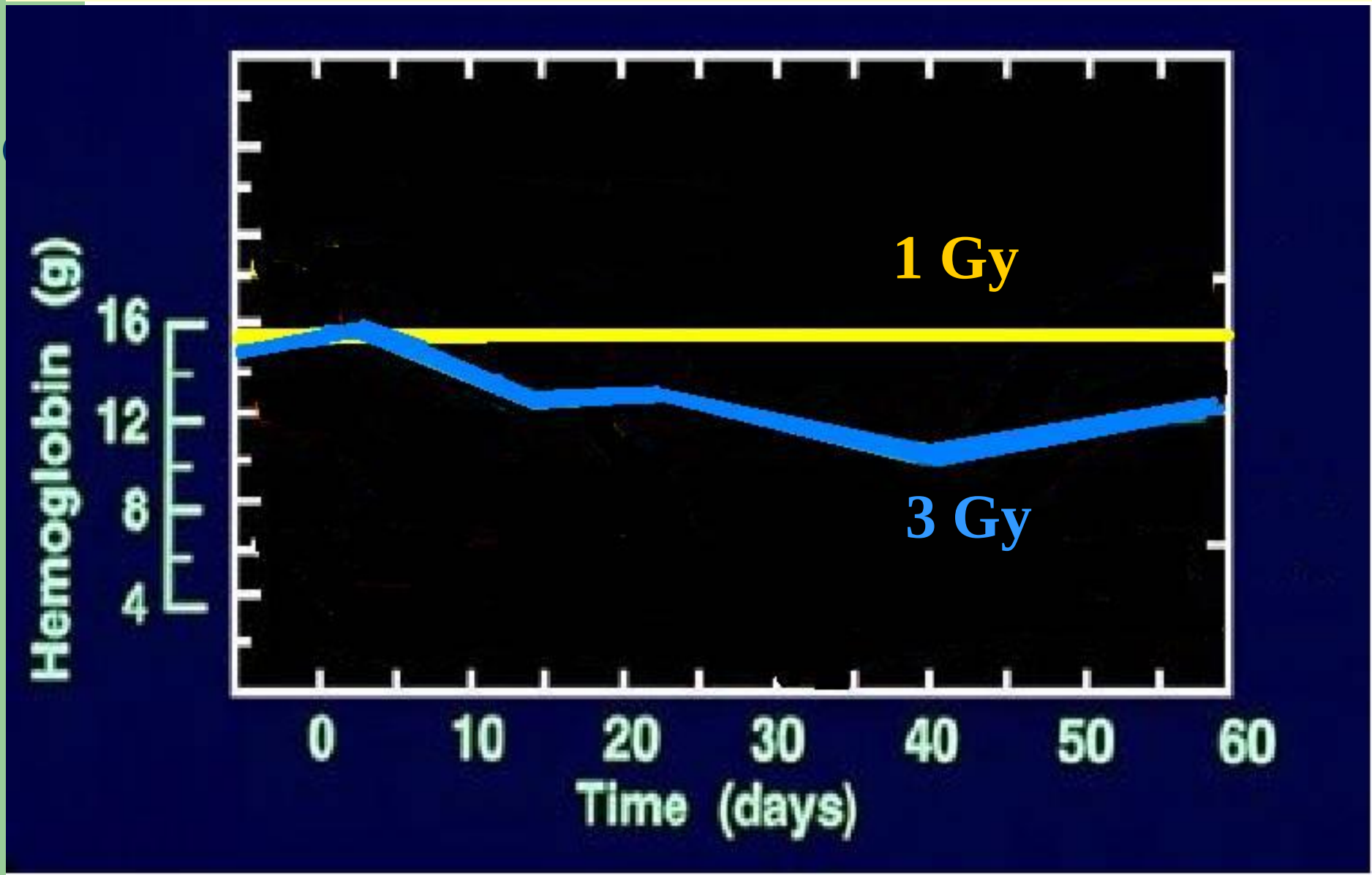
Leukocyte changes



Thrombocyte changes

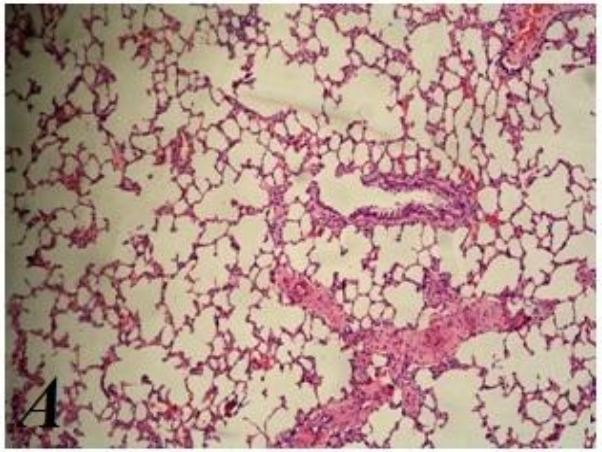


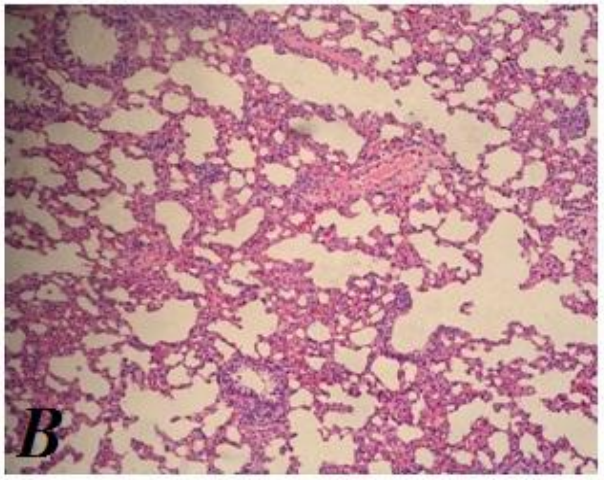
Erythrocyte changes

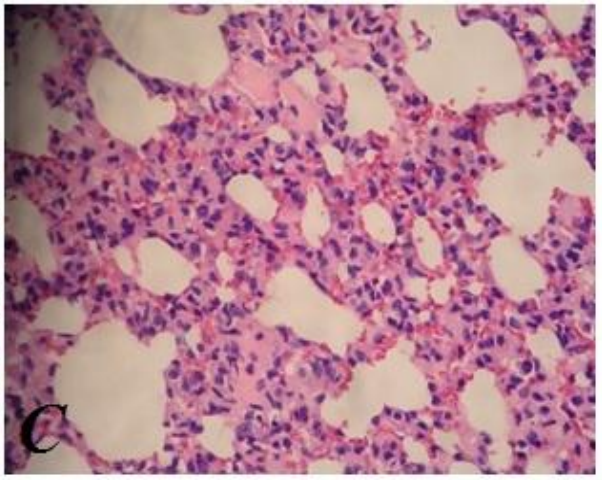


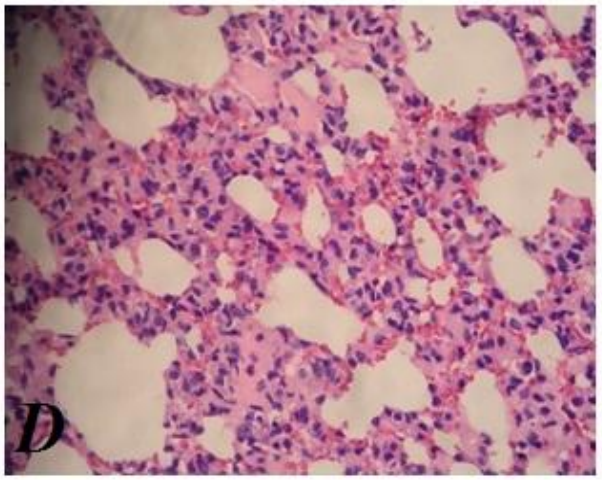
Basic syndromes of manifest illness phase

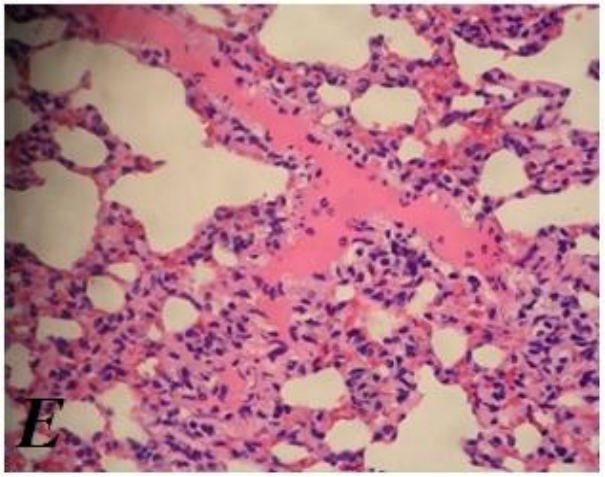
- Pancytopenia
- Haemorrhage (petechial haemorrhages/skin, massive haemorrhages/internal organs)
- Systemic and localized infections (sepsis, fever, toxemia)
- Gastrointestinal syndrome (vomiting, diarrhea, radiation kaheksia)
- Skin (atrophy, epilation)











A no morphological changes in the lungs

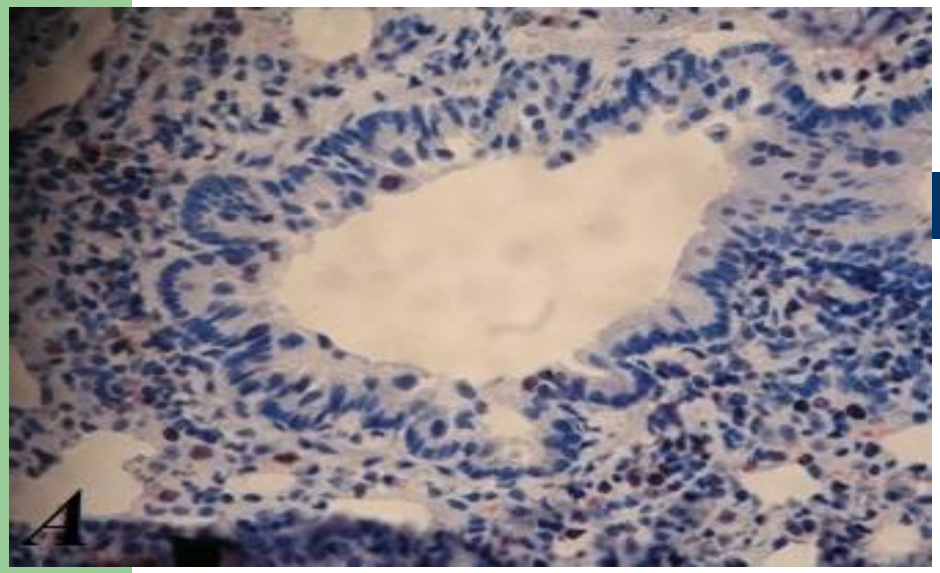
B Severe circulatory damage of small blood vessels, marked congestion

C Perivascular and interstitial hemorrhages

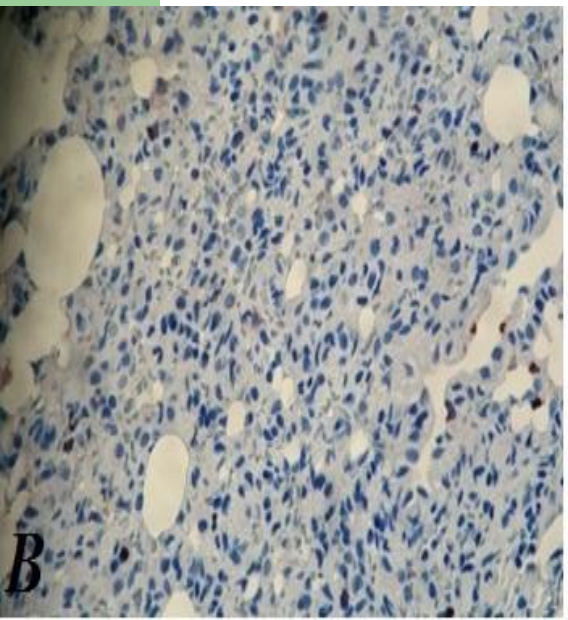
D Perivascular edema

E Perivascular edema, Perivascular and interstitial hemorrhages

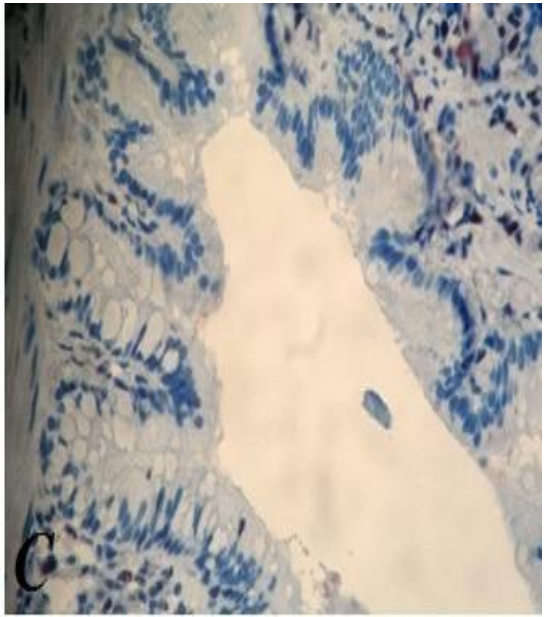
Immunohistochemistry (Ki-67 – marker of proliferative activity, 6 Gy ionizing radiation)



A Controls – proliferative index (bronchial epithelium 4%)



B Severe decrease in the proliferative activity (single positive cells in the intra-alveolar septa)



C Total absence of proliferative activity in the bronchial epithelium

II. Gastrointestinal syndrome

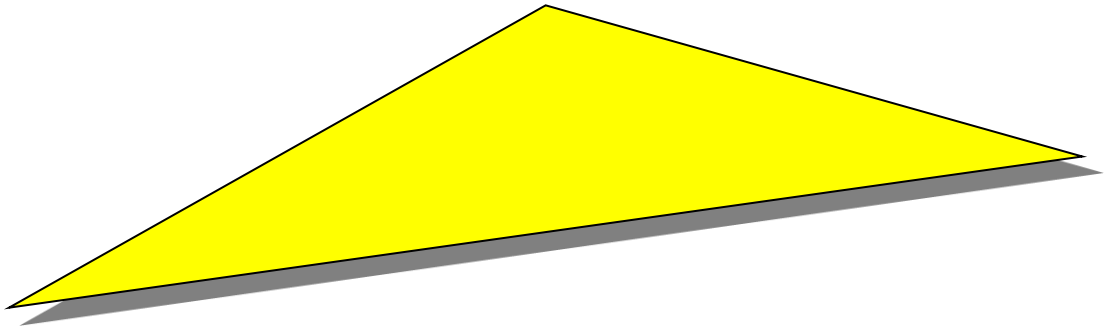
(≥ 10 Gy; ≥ 6 Gy – 100 Gy)

- **Prodromal stage – (within hours)**

The initial symptoms resemble airsickness or seasickness, watery diarrhea, nausea, vomiting, cramps

- **Latent stage/lack**

(asymptomatic for several hours), astheno – vegetative syndrome (tiredness, weakness}

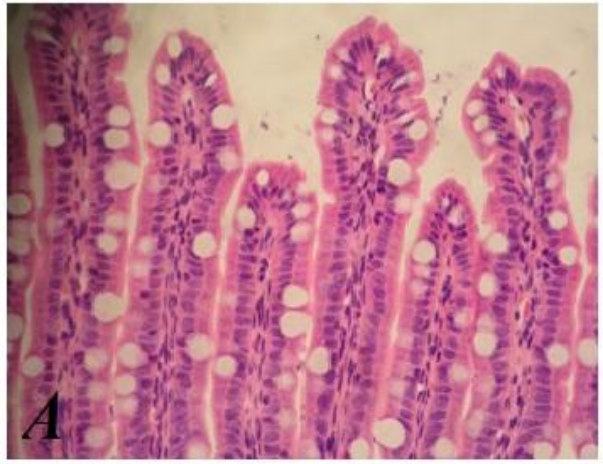


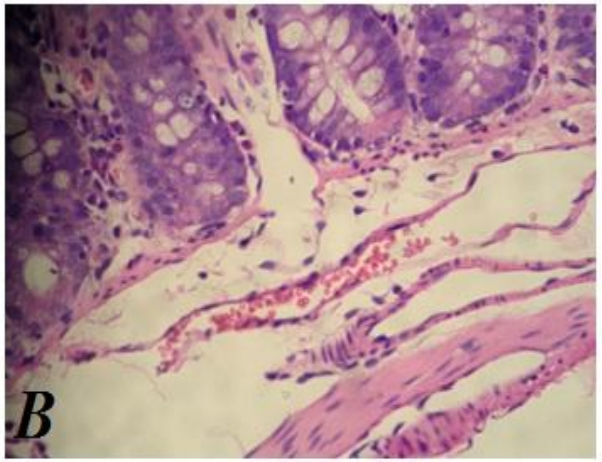
- **Manifest illness stage**

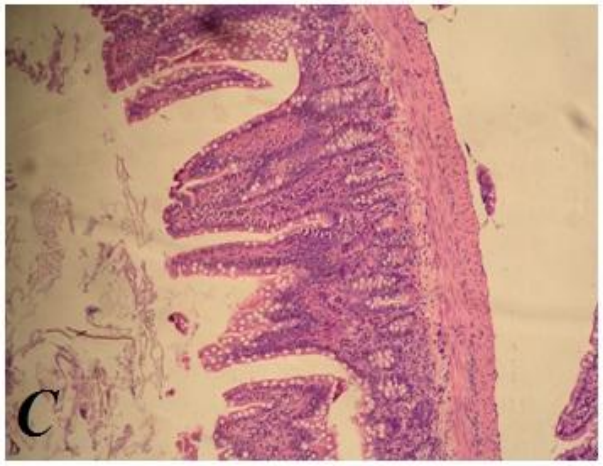
Profuse vomiting
High fever
Malaise, anorexia
Persistent diarrhea (bloody)
Dehydration
Circulating collapse

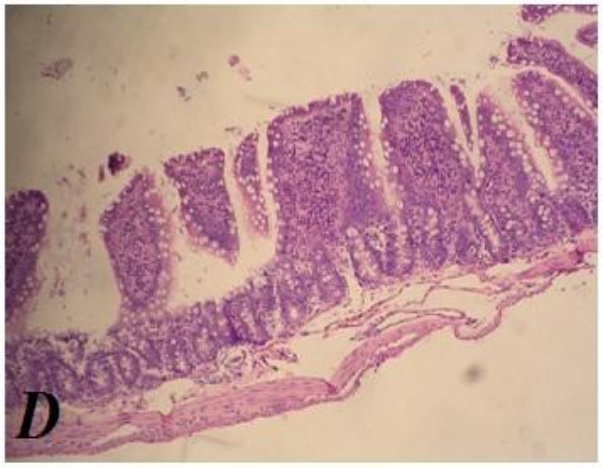
Laboratory findings

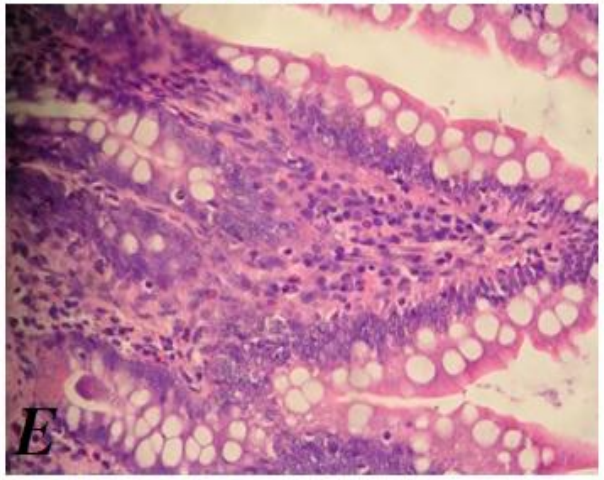
A marked decrease in granulocyte, lymphocyte and platelet counts

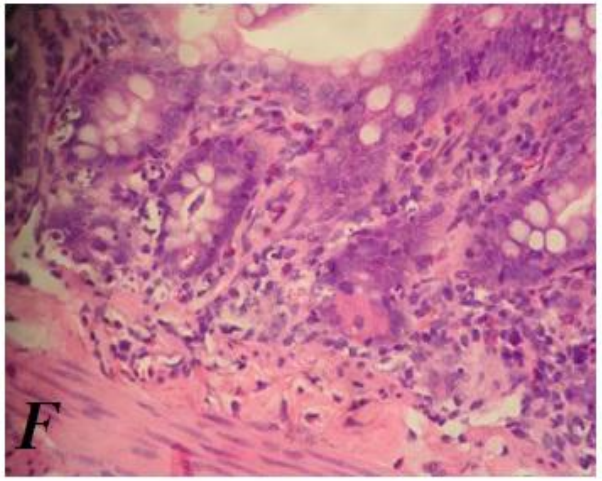












A no morphological changes in the small intestines

B hemorrhages in the submucosa and subserosa, venous hyperemia, perivascular edema

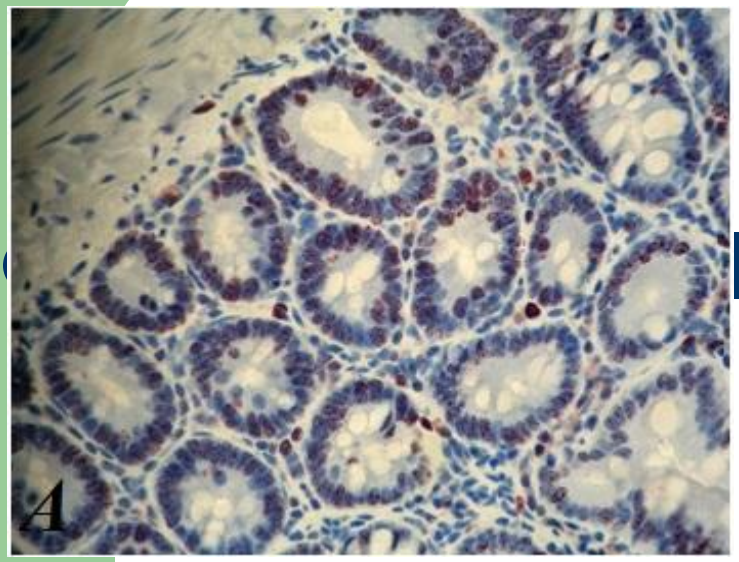
C Marked atrophy (the villi are shortened)

D thickened, deformed, flattened villi (areas of adhesions between them)

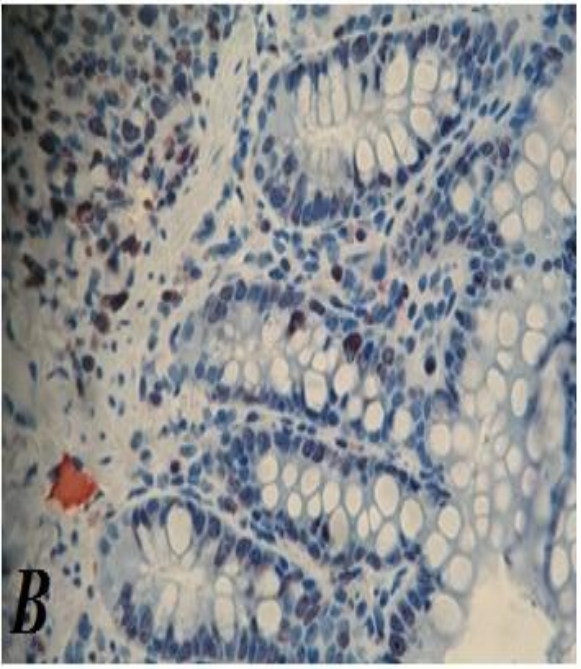
E Marked edema and inflammatory infiltrates in the chorion

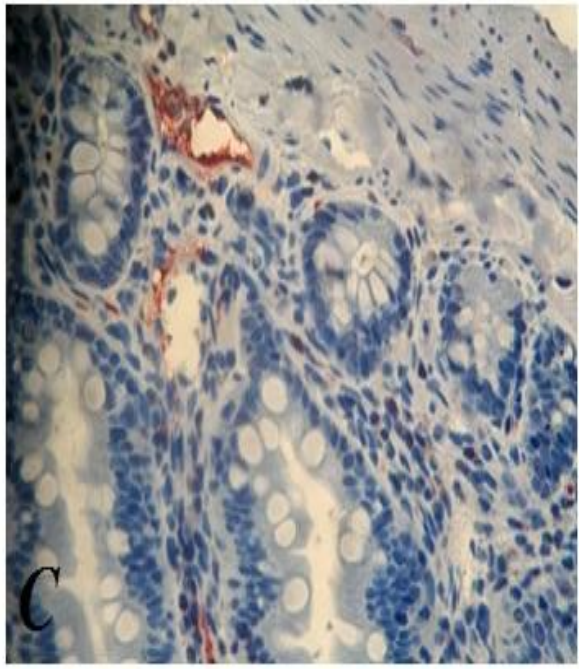
F Atrophy of the crypts, single abortive crypts 3-7 days

Immunohistochemistry (small intestine) 6 Gy ionizing radiation



A Controls – proliferative index in basal cells of small intestine (85%)

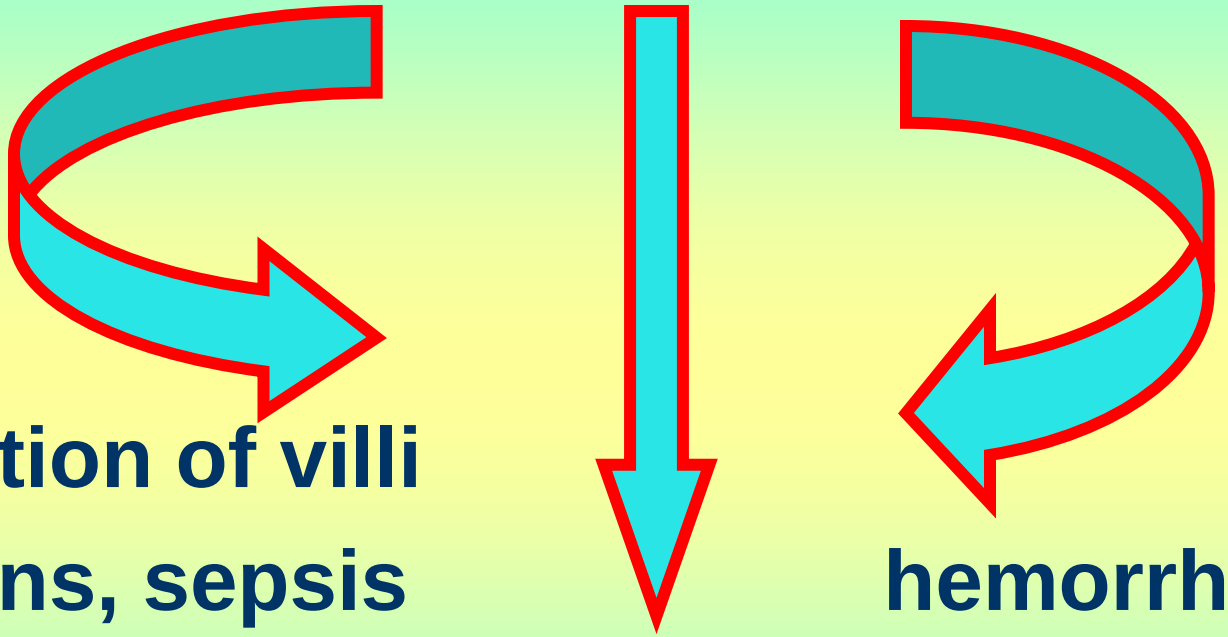




B total suppression of the proliferative activity (< 10%) in the epithelium of the crypts; single positive cells

C zones with total absence of expression of Ki-67 antigen

Lethal outcome



denudation of villi

infections, sepsis

hemorrhages

fluid and electrolyte imbalance

Systemic effects of gastrointestinal syndrome

- Malabsorption → malnutrition
- Fluid and electrolyte shifts → dehydration, acute renal failure, cardiovascular collapse
- Gastrointestinal bleeding → anaemia
- Gastrointestinal infectious → sepsis
- Paralytic ileus → vomiting, abdominal distention

III. Central nervous system (CNS) syndrome

≥ 50 Gy; ≥ 100 Gy

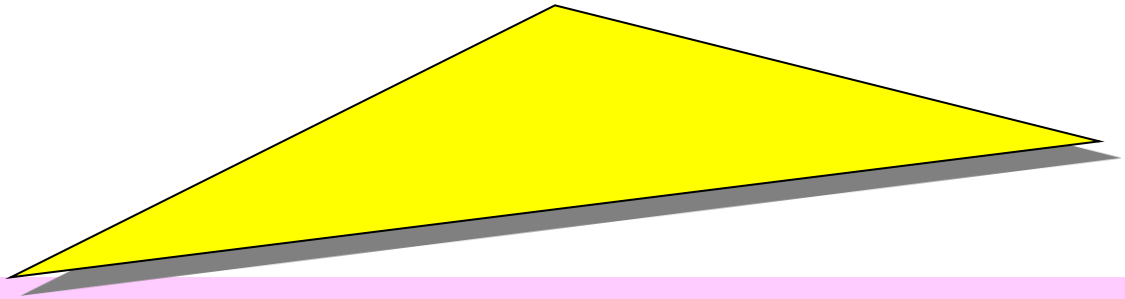
- **Prodromal stage**

(a few min to a few hours)

confusion, profuse vomiting, loss of consciousness, lethal outcome 2-3 days

- **Latent stage**

(may last minutes, hours, or missing)



Manifest illness stage

(5-6 hours)

disorientation, ataxia, watery diarrhea, respiratory distress

cerebral oedema

meningitis (2 hours)

convulsions, coma

Morphological changes

- **Perivascular and parrenchymal granulocytic infiltration** in the meninges, choroid plexuses and brain
- **Vasculitis** is a common observation. Veins and arteries of all size are equally involved.
- The cerebellum brain stem and spinal cord are less involved.
- The lesions appear earlier in **the gray matter**, but eventually **the white matter** becomes more severely involved.

Meningitis appears as early as 2 hours after exposure. The choroid plexuses are also involved with a maximum peak of edema and leukocytic infiltration occurring 8 hours after exposure. The local brain damage probably results from the damage of cells as well as the injury of blood capillaries.

Vascular changes

- Hemorrhage
- capillary endothelium vacuolization
- Increased capillary permeability

Lethal outcome

cerebral oedema **neuronal changes (pyknotic and lytic)**

Treatment of acute radiation syndromes

- **The therapy** of the radiation syndrome **should not be based** on the **absorbed radiation dose**.
- It should be guided only by the **daily appraisal of clinical and laboratory findings**.
- First, it is necessary to establish whether the individual has been exposed to **x-rays or neutrons**.
- Neutron exposure may **induce radioactivity** in the human body. Therefore, the **hair, nails** and **blood will emit radiation**.
- For this reason the **neutron-irradiated persons should be isolated** from those who have exposure to x- or gamma radiation.

- An **early dosimetry** should be made to obtain accurate dose estimation. However, such **dose estimations are of limited value** in patient management for the following reasons:
  - **suitable dose** - measuring **apparatus may be absent** when accident occurs.
  - **two or more kinds of radiation** usually are involved, which effectiveness is not known

Patients with acute, whole body irradiation will fall into one of **three groups**:

a) those who recover with minimal intervention;

b) those who require aggressive supportive care, up to and including bone marrow stem cell transplantation;

c) those who, die due to the dose they received, concomitant physical trauma, or inadequate clinical resources, will be triaged to receive palliative care.

<1 Gy Exposure >10 Gy

LD50/60 → 3.5 Gy (min treatment)

4 – 5 Gy (antibiotics, transfusion, CSFs)

Treatment

- transfusion of blood products
- antibiotics and antiviral drugs
- hematopoietic growth factors (CSFs)
- bone marrow transplantation (BMT)

Obtaining a history and physical examination, **removal of external contamination, dose estimation, supportive care, symptomatic treatment, and replacement of fluids and electrolytes** should be **the earliest goals** of medical management. Reverse isolation is needed for patients with whole body doses greater than **2-3 Gy**. Surgical intervention, when required, should be carried out **within 36 h**, and not **later than 48 h** after exposure. Additional surgery, if required, should not be performed until at least **6 weeks** post-exposure, in order to assure recovery from the period of **cytopenia and immunosuppresion.**

The prodromal symptoms of **nausea and emesis** will be particularly troublesome to patients.

Selective 5-HT3 (**serotonin**) receptor antagonists are recommended for radiation-induced **emesis**. They block the vomiting reflex by inhibiting 5-HT3 receptors in the vomiting center, the hemoreceptor trigger zone and in the small intestine.

Prodromal symptoms - Emesis

Selective 5-HT3 (serotonin) receptor antagonists

- Ondansetron
- Granisetron
- Dolasetron
- Tropisetron

Diarrhea

- Anticholinergics
- Loperamide (Imodium)

(opioid receptor agonist similary to morphine); ↓ the activity of the myentericus pl. ↓ the tone of smooth muscles of the intestine ↑ absorption of fluids and nutrients

- Metamucil (Psyllium) –

absorbs water in the dygestive system, regulation of perystalsis

- Amphogel (Al hydroxide) antiacid

Hematopoietic growth factors (Cytokines, CSFs)

Cytokines are a unique family of growth factors. Secreted primarily from leukocytes, cytokines stimulate both the humoral and cellular immune response, as well as the activation of phagocytic cells. Cytokines that are secreted from lymphocytes are termed **lymphokines**, whereas those secreted from monocytes or macrophages are termed **monokines**. Many of the lymphokines are also known as **interleukins** (**ILs**), since they are not only secreted by leukocytes but also able to affect the cellular responses of leukocytes.

Specifically interleukins are **growth factors**, targeted to cells of hematopoietic origin. **Colony-stimulating factors** (**CSFs)** are cytokines that stimulate the proliferation of specific stem cells of the bone marrow.

The following cytokines are choices available for patients expected for experience severe **neutropenia**:

Hematopoietic growth factors (Cytokines, CSFs)

- **Filgrastim (G-CSF, Neupogen R), granulocyte colony-stimulating factor;**
- **Pegfilgrastim, pegylated form of Filgrastim**
- **Sargramostim (GM-CSF, Leukine R), granulocyte macrophage colony-stimulating factor;**
- **Macrophage colony-stimulating factor (M-CSF);**
- **Stem cell factor (SCF).**

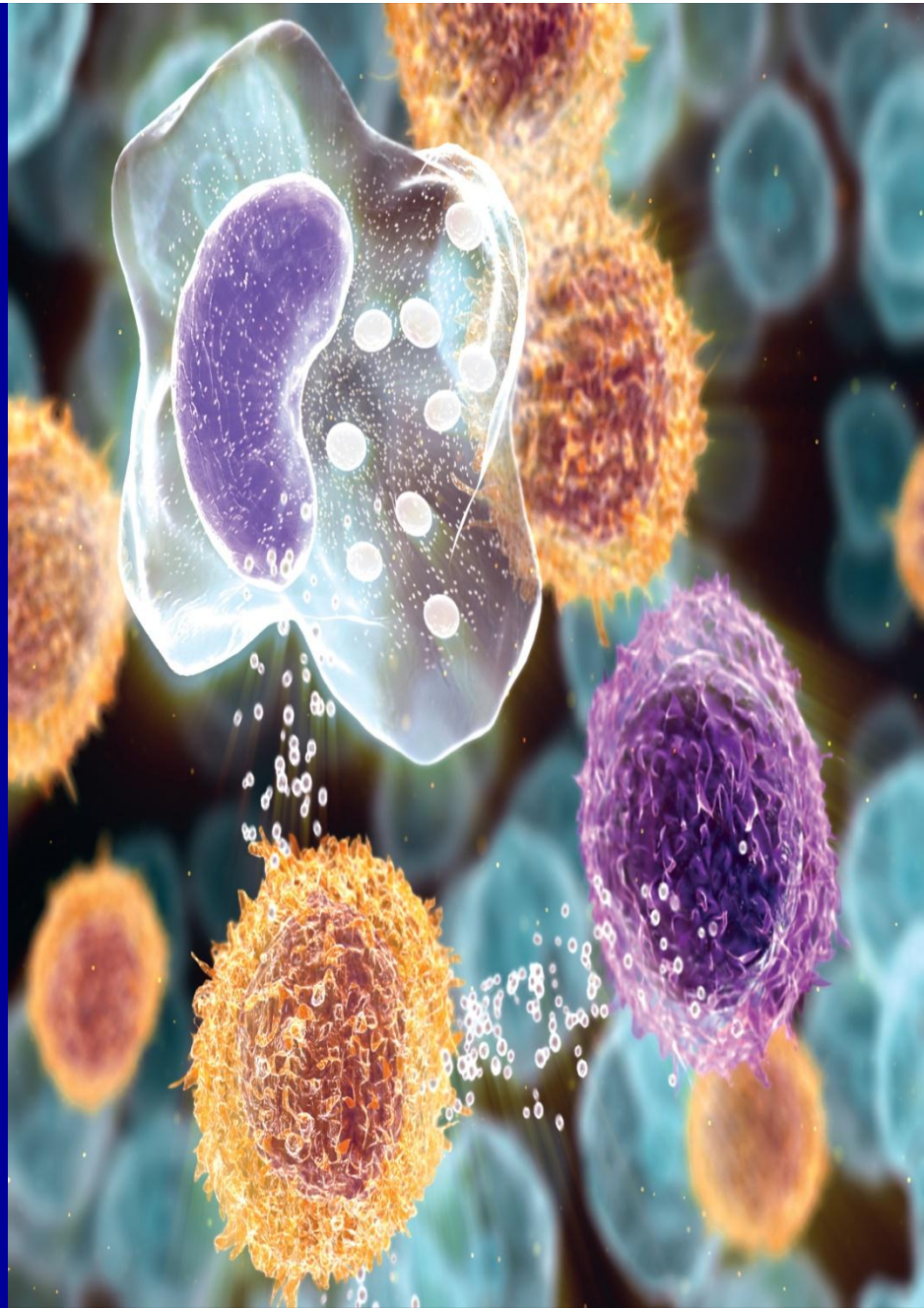
The first factors have been explored and have some efficacy in irradiated preclinical models of **radiation-induced marrow aplasia**. The rationale for using CSFs in irradiated humans is derived from three sources:

- their enhancement of **neutrophil recovery** in oncology patients
- their perceived benefit in a small number of radiation-accident victims
- several prospective trials in animal models exposed to radiation – significant survival and enhanced Ne recovery.

CSFs should be initiated **as early as possible** in those exposed to a survivable whole-body dose of radiation and who are at risk of the hematopoietic syndrome **(> 3 Gy**).

Effects of cytokine treatment on the bone marrow:

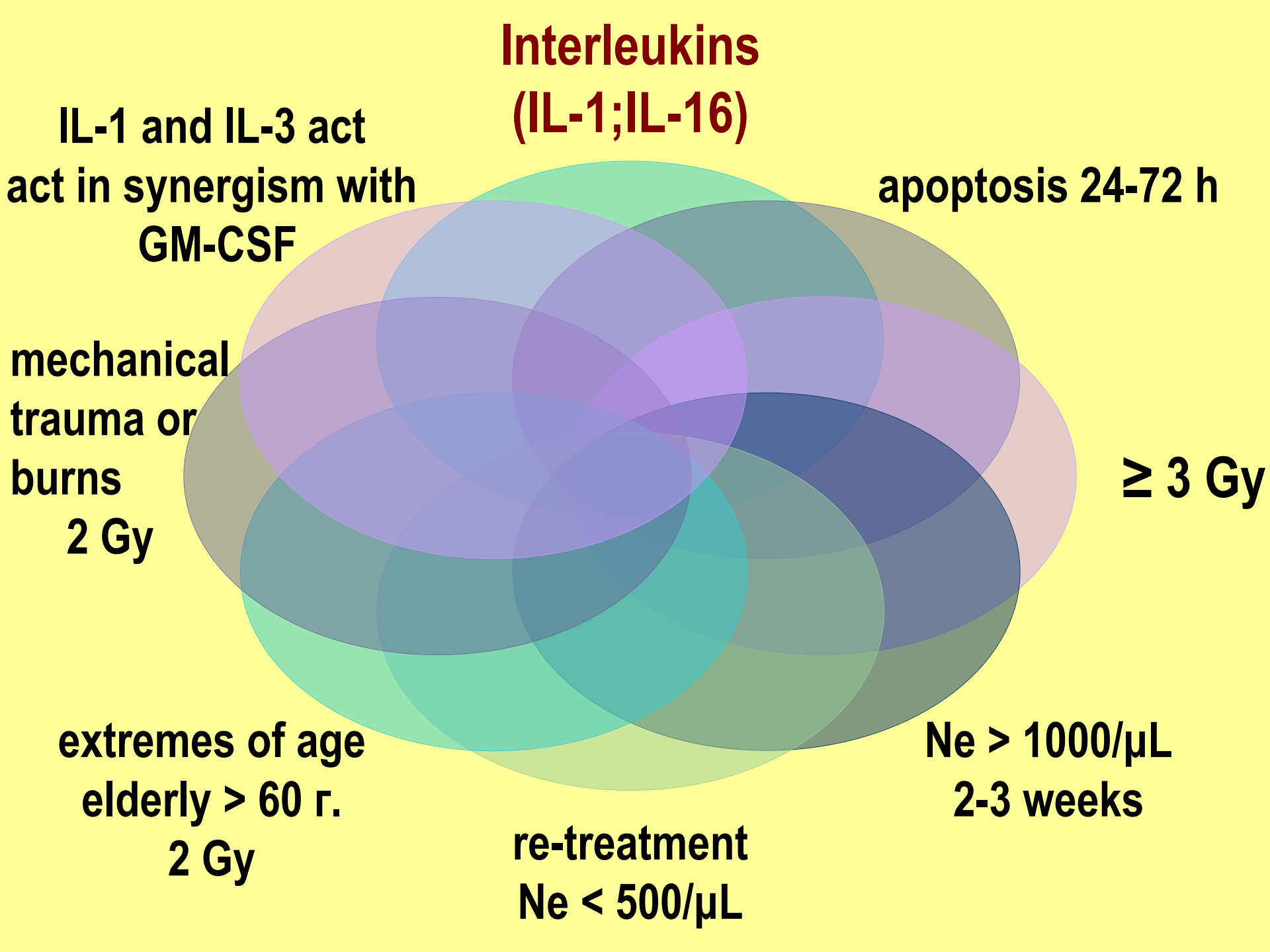
- increase production of granulocytes and activation of their functions (bactericidal);
- stimulate the survival, proliferation, differentiation and function of granulocyte precursors;
- stimulate production of colony forming elements;
- decrease maturation time;
- increase viability of mature cells;
- stimulate additional cytokine release.



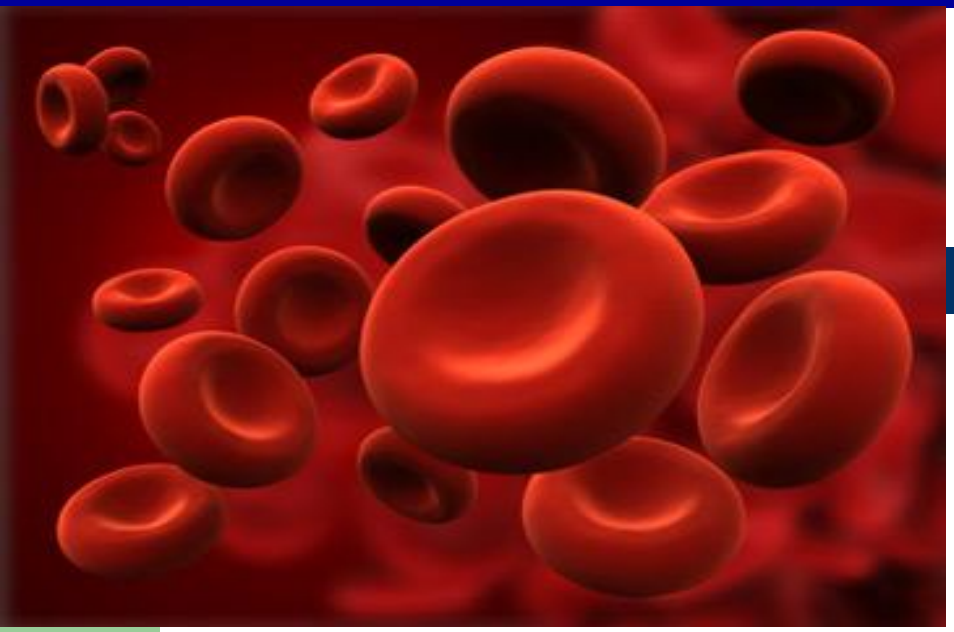
The hematopoietic syndrome may be reduced when cytokines are administered early after exposure (in the first 24 - 72 h when apoptosis occurs). Cytokine therapy should be continued for 2-3 weeks or until the absolute neutrophil count is **> 1000/µL** (**1 x 10^9/L**). **G-CSF** and **GM-CSF** increase rate of hematopoietic recovery in patients after radiation exposure and may obviate need for BMT, when stem cells are still viable. Interleukins (**IL-1 and IL-3**) act in synergism with **GM-CSF**.

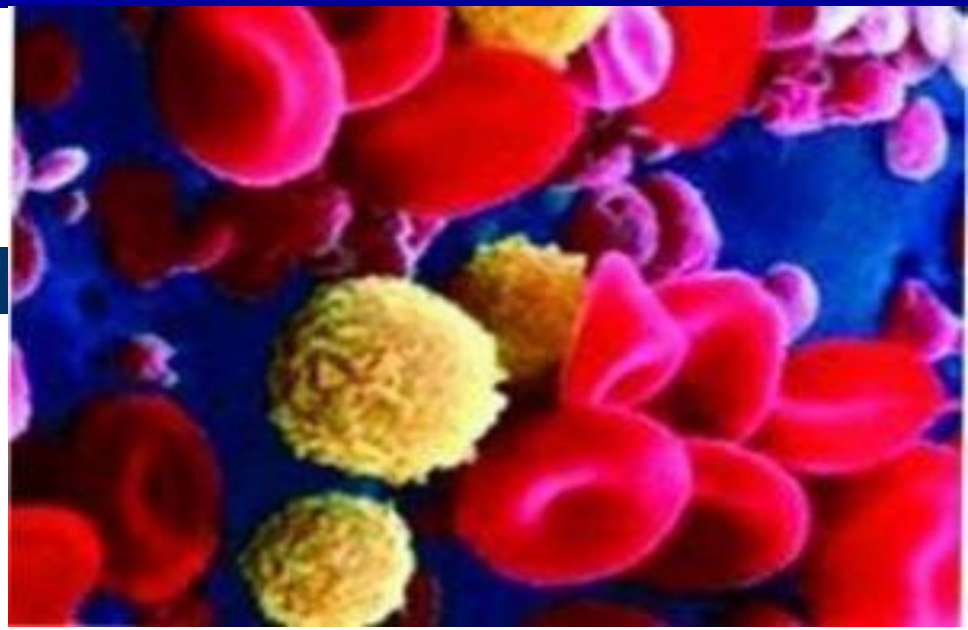
Re-treatment may be initiated if there is a significant drop in the number of neutrophils (**< 0.5x10^{9}/L**). Series of interleukins (**IL1-16**) are used to stimulate hematopoiesis. There is a general agreement that CSFs is an acceptable choice for treatment of individuals receiving a whole-body dose of **3 Gy and more**. Individuals receiving a whole-body dose of **2 Gy with mechanical trauma and/or burns** (i.e., **combined injury**) are candidates for cytokine therapy, as are individuals at extremes of age (i.e., **children < 12 years of age** and **the elderly > 60 years of age**).

G-CSF causes elevations in certain types of **white blood cells**, it does not stimulate production of platelets.


Interleukins
(IL-1;IL-16)
IL-1 and IL-3 act
act in synergism with
GM-CSF
apoptosis 24-72 h
mechanical
trauma or
burns
2 Gy
≥ 3 Gy
extremes of age
elderly > 60 г.
2 Gy
Ne > 1000/μL
2-3 weeks
re-treatment
Ne < 500/μL

Blood products 2-4 weeks post-exposure





Erythrocytes

to delay anemia

to keep the **hematocrit > 30%**

(to reduce acute bleeding)

to maintain haemoglobin > 8 g/dl

Thrombocytes

Platelets should be maintained at greater than

> 20 x 10^9/L

> 75000/µL

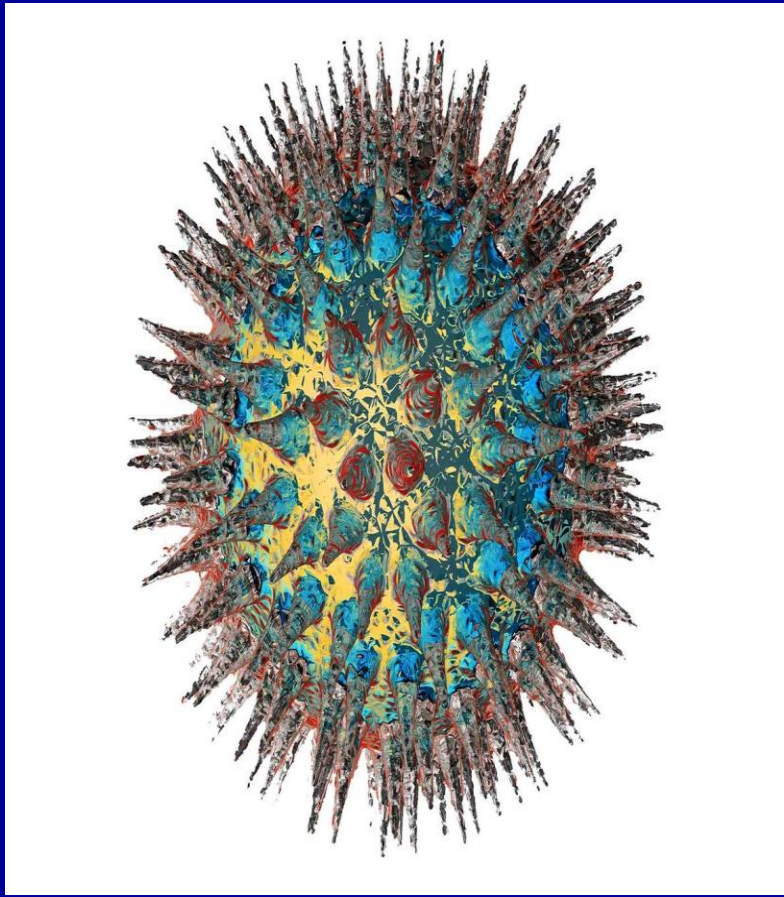
at surgical interventions

Use of thrombopoietic agents immediately after radiation injury is not currently recommended. Consider use of **thrombopoietic agents megakaryocyte growth and development factor/thrombopoietin** (**MGDF/Tpo**) or synthetic IL-3 receptor agonist **Synthokine** in patients with neutrophil recovery but still platelet transfusion dependant after accidental irradiation.

All cellular products must be:

- irradiated to 25 Gy to prevent transfusion-associated graft-versus-host disease
- leukoreduced (except granulocyte transfusions)

- to diminish the risk of febrile nonhemolytic reactions
- immunosuppressive effects of blood transfusions
- cytomegalovirus infection (CMV)



Use of **erythropoietin** (**Epo**, stimulates erythropoiesis) **anemia therapy** after radiation injury is not recommended even though probably safe as anemia is not generally life-treating in this situation.

Treatment of Infections General Principles

- Direct therapy for infection
- Culture specific antibiotics
- Therapy for leucopenia
- Cytokine administration
- Administer antibiotics for **absolute neutrophil count (ANC) < 500/mm^3**
- Use broad spectrum antibiotic coverage
- Continue antibiotics for duration of **ANC < 1000/mm^3**
- Add **Amphotericin** for prolonged fever lasting 5-7 days after starting standard antibiotics
- If there is evidence of resistant Gram + infection, add **Vancomycin**

Prophylaxis

- barrier/isolation – isolation rooms for ARS patients. Medical personnel should also be aware of the need for rigorous environmental control, incl. strict hand washing, and surgical scrubs and masks for staff;
- decontamination (incl. gastrointestinal decontamination);
- antiviral agents;
- antifungal agents;
- early cytokine therapy;
- prophylaxis of Pneumocystis carinii;

• early surgical wound closure; in the case of coexisting trauma (combined injury), wound closure should be performed within **24 to 36 hours**.

• avoidance of unnecessary invasive procedures;

• **povidone-iodine** (a broad spectrum antiseptic for topical application in the treatment and prevention of infection in wounds (**Betadine**) or **chlorhexidine** for skin disinfection and shampoo, as well as meticulous oral hygiene.

Antimicrobial drugs

- **Fluoroquinolones - Levofloxacin, Avelox 1x 400 mg per os (i.v.), Tavanic i.v. 1x 500 mg i.v.**
- **Antiviral agents (Aciclovir)**
- **Antifungal agents (Fluconazol)**

Antibiotics (AB) treatment

In nonneutropenic patients, AB should be directed toward the foci of infection or not shown

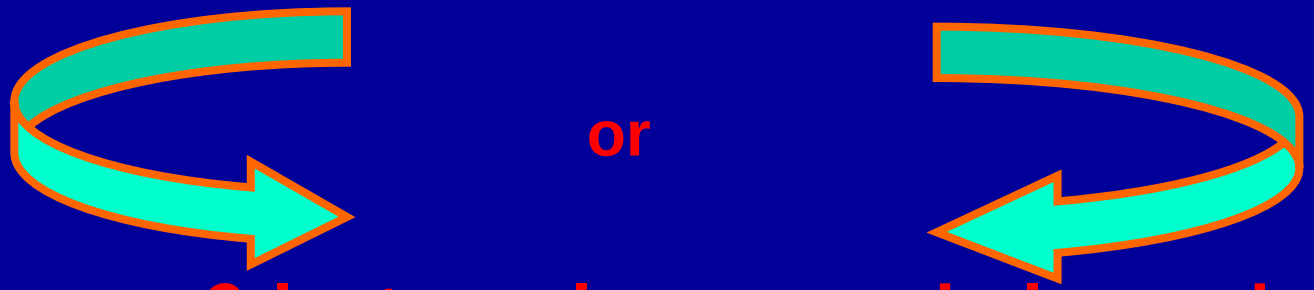
neutropenia ($< 0.5 \times 10^9/L$) should be given during the long duration of neutropenia.

Fever (Fluoroquinolones)

Gram (-) bacteria Pseudomonas aeruginosa

The first approach is

I. antibiotic monotherapy



or

carbapenem β-lactam class

- Imipenem/cilastin
- Meropenem
- Piperacilin/tazobactam

cephalosporin

- Cefepime (IV)
- Ceftazidime (III)
  (Tazicef)

II. The second approach is IV antibiotic combination therapy:

Aminoglycoside + Cephalosporine

(Gentamycin,Tobramycin)

III. Vancomycin → **AB monotherapy**

AB combination therapy

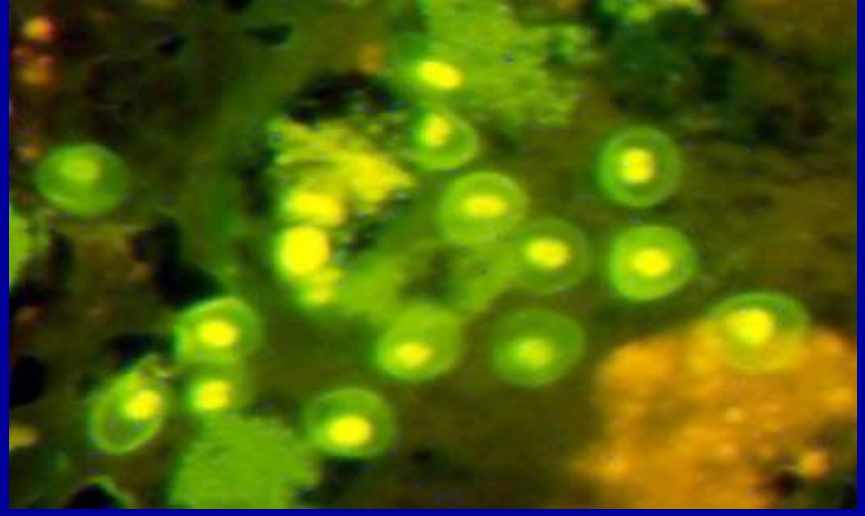
resistant to Gram + infection

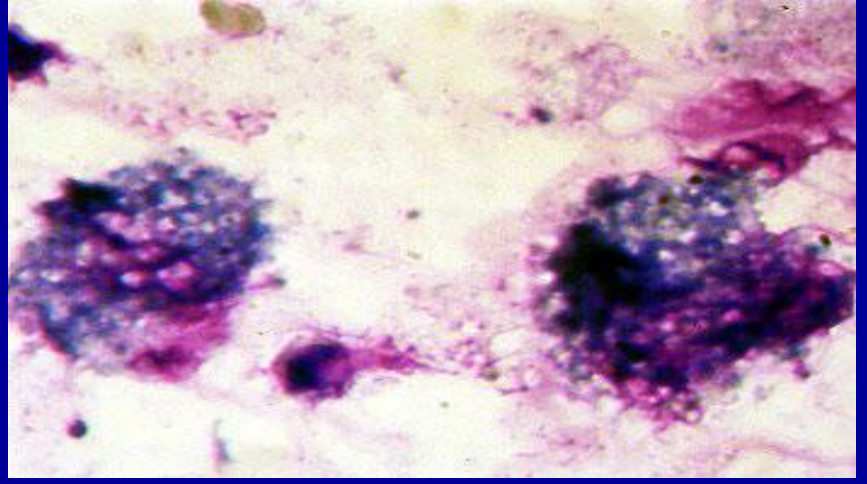
In resistance to cephalosporines:

- **Carboxypenicillin (Carbenicillin, Ticarcillin)**
- **Ureidopenicillin (Azlocillin or Mezlocillin)**
- **Streptococcal** coverage with the addition of **Penicillin or Amoxicillin** should also be considered, if not inherently covered by the **Fluoroquinolone.**

Opportunistic infections

The incidence of reactivation of **cytomegalovirus (CMV)** in irradiated patients (T-cell immunodeficiency) may be increased. Patients with evidence of early viremia should be treated preemptively, prior to the development of CMV disease, with either **Ganciclovir** or **Valganciclovir**.



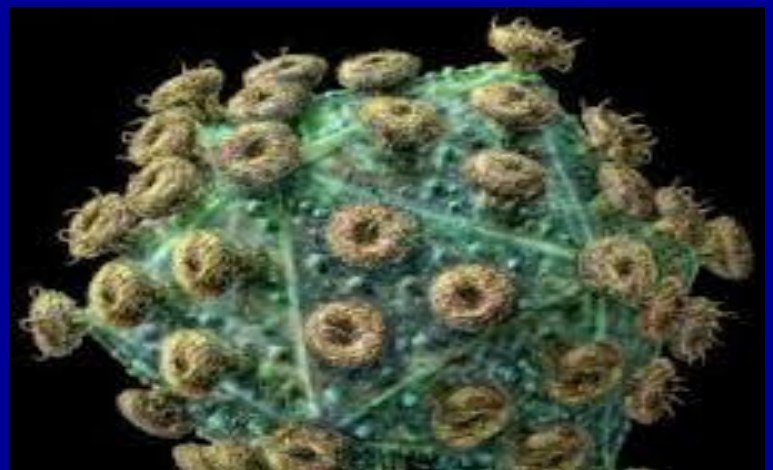


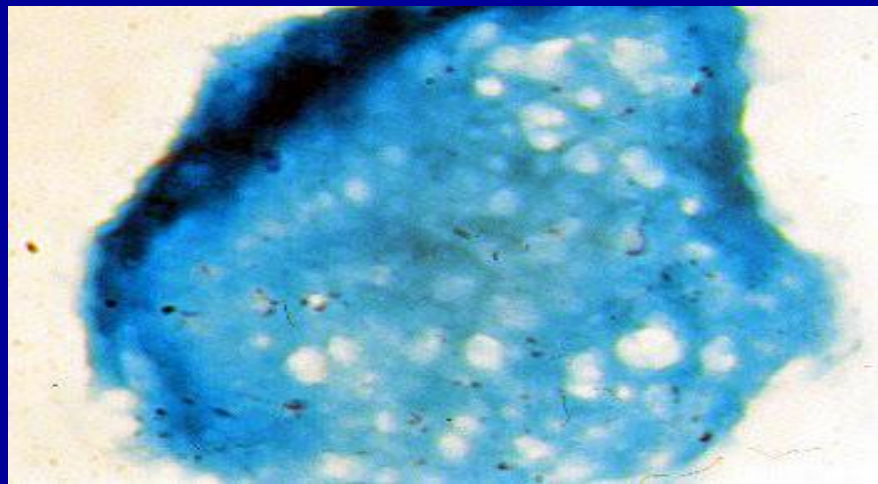
Pneumocystus carinii (unique tropism for the lungs)

Trimetoprim/Sulfamethoxazole;

Co-trimoxazole

myelosupression should be avoided – it may worsen cytopenia





Bone marrow (Hematopoietic cell) transplantation (BMT, HCT)

- Irradiated with doses of 7-10 Gy (for those receiving allogenic HCT)
- Without severe burns and organ damage
- Irradiated (granulocytes >0.5 x 10^9/L and thrombocytes >10 x 10^9/L) not subject to transplantation
- Under suitable donor (autologous or syngenic bone marrow available), BMT can be discussed in irradiated with doses > 4 Gy
- At **Chernobyl**, of the 50 patients who received more than 5 Gy, a lethal dose, 21 (42%) survived after receiving bone marrow transplants.

The most serious **complications of allogenic or xenogenic** bone marrow transplantation **is delayed mortality** due to **secondary decease**.

The symptoms occur during **the 4th or 5th week after transplantation** and include **primarily emaciation (**extreme weight loss and thinness due to a loss of subcutaneous fat)**, diarrhea** and **skin** lesions (**ulcers and local loss of hair**), **colitis, late hepatic necrosis**, extensive **atrophy of lymphatic tissues**.

The use of BMT in patients is complicated by a variety factors:

- radiation exposure is often not homogeneous. Some parts of marrow containing structures might be minimally or unradiated because the patient was partially shielded by a barrier;
- concomitant injuries such as burns or trauma can greatly complicate the care of patients who also have radiation-induced bone marrow failure.

Gastrointestinal syndrome

- gastrointestinal decontamination with **FQs**, **Vancomycin**, **Polymyxin B sulfate**, and **antifungals** (as medically indicated);
- **L-glutamine**
- Parenteral nutrition;
- Elemental diet;
- Fluid and electrolyte repletion
- Use of **growth factors** to protect intestinal stem cells from radiation-induced apoptosis.

Criteria for choice of therapy – I

Therapeutic recommendations:

If **lymphocyte** count during **first** week **200-500 cells/µL**, spontaneous recovery possible.

Therapy: Isolation, antibiotics, supportive therapy including platelet infusion. Growth factors (cytokines) can be used.

Criteria for choice of therapy –II

If **lymphocyte** count in **first** week below **200 cells/µL**, stem cells probably irreversibly damaged.

Therapy: Isolation, antibiotics, supportive therapy including platelet infusion. Additional growth factor therapy method of choice

.

Criteria for choice of therapy –III

If **lymphocyte** count in first week below **100 cells/µL**, consider treatment with **growth factors and BMT**. BMT may be recommended for patients exposed to whole-body radiation doses exceeding **9 Gy.**

Therapeutic schemes:

- a) **1 to 2 Gy** (**100 - 200 rads**)
- Survive
- Little or no therapy required
- b) **2 to 5 Gy** (**200 to 500 rads**)
  - Lethal if untreated; many survive with optimal therapy.
  - Maximum supportive therapy, CSFs
  - Treat **bacterial infections, bleeding, electrolyte disturbances, blood loss**.
  - Bone marrow transplant is not recommended - can survive without it.
- c) **5 to 20 Gy (500 to 2000 rads**)

Therapeutic schemes:

- ❑ **Maximum supportive therapy**
  - **Fluids**
  - **Electrolytes**
  - **Antibiotics, CSFs**
  - **Platelet transfusions**
  - **red blood transfusions**
  - **transplantation with matched allogenic bone marrow**
- a) **20 to 50 Gy (2000 to 5000 rads**)
- ❑ **Patients die before** the peripheral blood shows evidence of bone **marrow depression**:
- ❑ fluids
- ❑ analgesics
- ❑ symptomatic therapy
- **d) 50 Gy (5000 rads**) - always fatal in 24 to 48 hours.

Radioprotectors

- Approximately 30 years ago it was discovered that **certain compounds**, when present **at the time of radiation** had **a protective effect** on the organism.
- If administered immediately **following** irradiation, **no protective effect** was noted.
- These compounds, called **radioprotectors**, act by **reducing the effective dose** of radiation to the cells.
- **One group** of radioprotectors consists of chemicals that contain **a sulphhydryl group - cysteine, cysteamine, cystamine**, **glutathione** etc.

- The **cysteine** was one of the **first compounds** found to have **radioprotective properties**. The sulphhydryl compound most widely studied is **WR-2721**.
- When one of these compounds is **given prior to radiation**, a **larger dose** of radiation is necessary to produce the **same response** as when **the compound** is not present.
- The efficacy of radioprotective substances is expressed by the **dose reduction factor (DRF**).
- **The DRF** is defined as the **ratio** of the **radiation dose** necessary to produce a **given effect** in the presence of a protecting compound to the **radiation dose** necessary to produce the **same effect in the absence** of the same compound.
- The **DRF** for the **sulphhydryl-containing** compounds is approximately **1.5 to 2.0**.

- If such compound is present during radiation, almost **twice the dose is required** to produce the **same response** as that produced by one half the dose in the absence of the compound.
- **Many hypotheses** have been advanced concerning the mechanism of action of these dose-modifying agents.
  - The most generally accepted hypothesis today is that these agents protect either **by competing for the radiation-produced free radicals** or by **giving up a hydrogen** atom to ionized molecules in the cell, **neutralizing** the effects of radiation and **restoring the molecule** to its original pre-irradiated state.

- **Other** possible mechanisms are:
  - **producing tissue hypoxia**
  - **formation of mixed disulfide bound** with the tissue proteins, containing SH groups
  - reversibly **inhibition of DNA synthesis**, **which delay DNA replication**.
- The sulphhydryl compounds are **most** efficient **with x- and γ-rays** and have a **negligible effect with high-energetic radiations** such as alpha particles and neutrons.

These agents are not in widespread use due to a number of factors.

- First, the concentration of these compounds necessary to protect an organism is **toxic**, therefore prohibiting their use.
- In addition, these agents **must be present** in the cell **at the time of irradiation, not after** irradiation, making them **useless** for treatment in cases of **accidental overexposure**.

Some **other sulfur containing compounds** also produce any **radioprotective effects**.

- These chemicals **are thiurea, thiouracil, dithiocarbamates** etc.
- There are **pharmacological agents** showing any protective action against radiation (in experiments) by above-mentioned mechanisms:
  - **analgesics (morphine, heroin)**
  - **tranquilizers**
  - **cholinergic drugs**
  - **epinephrine, dopamine, some hormones,** etc.

Modern concepts of Radioprotectors

- Radioprotectors are designed **to be used before or shortly after exposure.** These include antioxidants such as **gamma Tocotrienol** (a vitamin E moiety), or **Genistein** (a soy bioproduct) to increase survivability. Effects of **Genistein** on hematopoietic cell recovery in irradiated mice have documented that **Genistein** operates on **radiation-responsive gene expression. Genistein also protects against** delayed radiation effects in **the lungs** and **induces cytokine production**.
- **Tocopherol succinate** has been found to be a promising radiation countermeasure. **Alpha-Tocopherol succinate** has been shown to protect mice from gamma-radiation by **induction of G-CSF** and by **preventing DNA damage**.