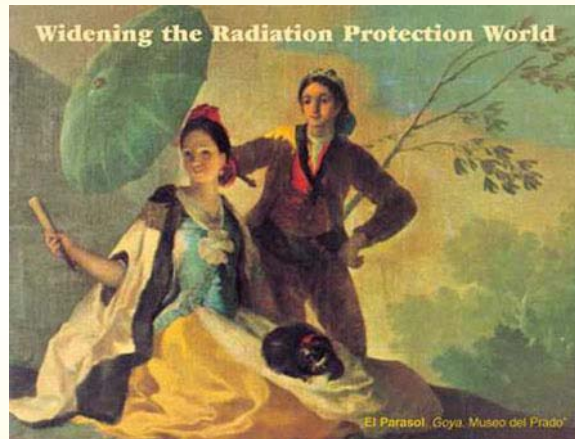




International Radiation Protection Association 11th International Congress Madrid, Spain - May 23-28, 2004



Refresher Course

The Medical Diagnosis and Treatment of Radiation Overexposed People

Jean Marc BERTHO, Nina M. GRIFFITHS and Patrick GOURMELON

Institute for Protection and Nuclear Safety

Radiation Accidents = Rare Events 1950 - 2001

◆	Number of Accidents	~ 500	
◆	Number of Victims:	~ 2,000	
◆	Number of Reported Deaths:		
	● Criticality	30	
	● Reactors		
	Chernobyl + Navy	40	
	Sources		
	Medicine	35	(4 accidents)
	Industry	30	(15 accidents)

Past Doctrine

- ◆ Risk Areas are perfectly identified
 - Accidental exposure to medical, industrial, or military source
 - Breach in nuclear reactor core (Chernobyl)

- ◆ Issue of orphan sealed source

- ◆ Unintended accident scenario

- ◆ Accidents involving a small number of people requiring treatment

Terrorism Threat in the Present Situation

- ◆ **Willingness to inflict mass casualties**
- ◆ **Spread of the suicidal attitude of the terrorists**
- ◆ **Use of sophisticated technologies**
- ◆ **Extension of the nuclear terrorist threat to the chemical and biological fields**

New Doctrine NRBC

- ◆ Situation of « Major » Accident
- ◆ Unpredictable Event Site
- ◆ “All-Hazards” Approach

- ◆ NRBC Doctrine
 - N → Nuclear
 - R → Radiological
 - B → Biological
 - C → Chemical

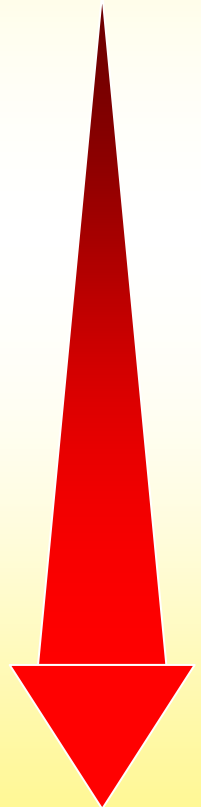
- ➔ Any event must be considered and handled as NRBC a priori until properly classified

- ◆ New strategies, including medical ones, are needed to respond to new specific risks

Potential Intentional Radiation Scenarios

Complexity Design and
Construction of the Scenario

- ◆ Dispersion of radioactivity without explosives
- ◆ Concealment of unshielded Sources
- ◆ Radiation Dispersal Devices (RDD) “Dirty Bombs”
- ◆ Attack of Nuclear Reactors
- ◆ Hijacking of Nuclear Weapons or Improvised Nuclear Devices (IND)



The Scenarios in Terms of Health Consequences

EVENT SCENARIO

Immediate victims
localized in space

Foreseeable Mass Casualties
Immediate Psycho-social impact

Radiation Dispersal Devices
« Dirty Bomb »

Wounds, Burns, Contaminations

Immediate Vital Risk
Long Term Risk : cancer

Unshielded Source Concealment
High activity

Whole Body Irradiation

Immediate Vital Risk
Acute Radiation Syndrome

INSIDIOUS SCENARIO

Victims distributed in time
and scattered in space

Mass Casualties ?
Delayed Psycho-social impact

Radionuclide Dispersion

Strict Contamination

Long Term Risk : cancer

Unshielded Source Concealment
Medium activity

Localized Irradiation

Cutaneous Radiation Injuries
without Vital Risk



- **Scenario 1 : Medical Management Doctrine for**
 - **Radiation Dispersal Device « Dirty Bomb »**

- ◆ **Pyrotechnic Risk + Radiological Risk**
- ◆ **Burns, Blasts, Wounds associated with :**
 - **External Contamination**
 - **Internal Contamination by inhalation and /or by wounds**
- ◆ **Immediate Vital Risk**
- ◆ **Application of the usual principles of the conventional Resuscitation**

Golden Rule

- ➔ **The Medical and Surgical Emergencies prevail over the Radiological Emergency**

- ◆ **Medicochirurgical Triage**
 - ➔ **Absolute Emergency**
 - ➔ **Relative Emergency**

External Decontamination (Undressing, Showering, Washing)

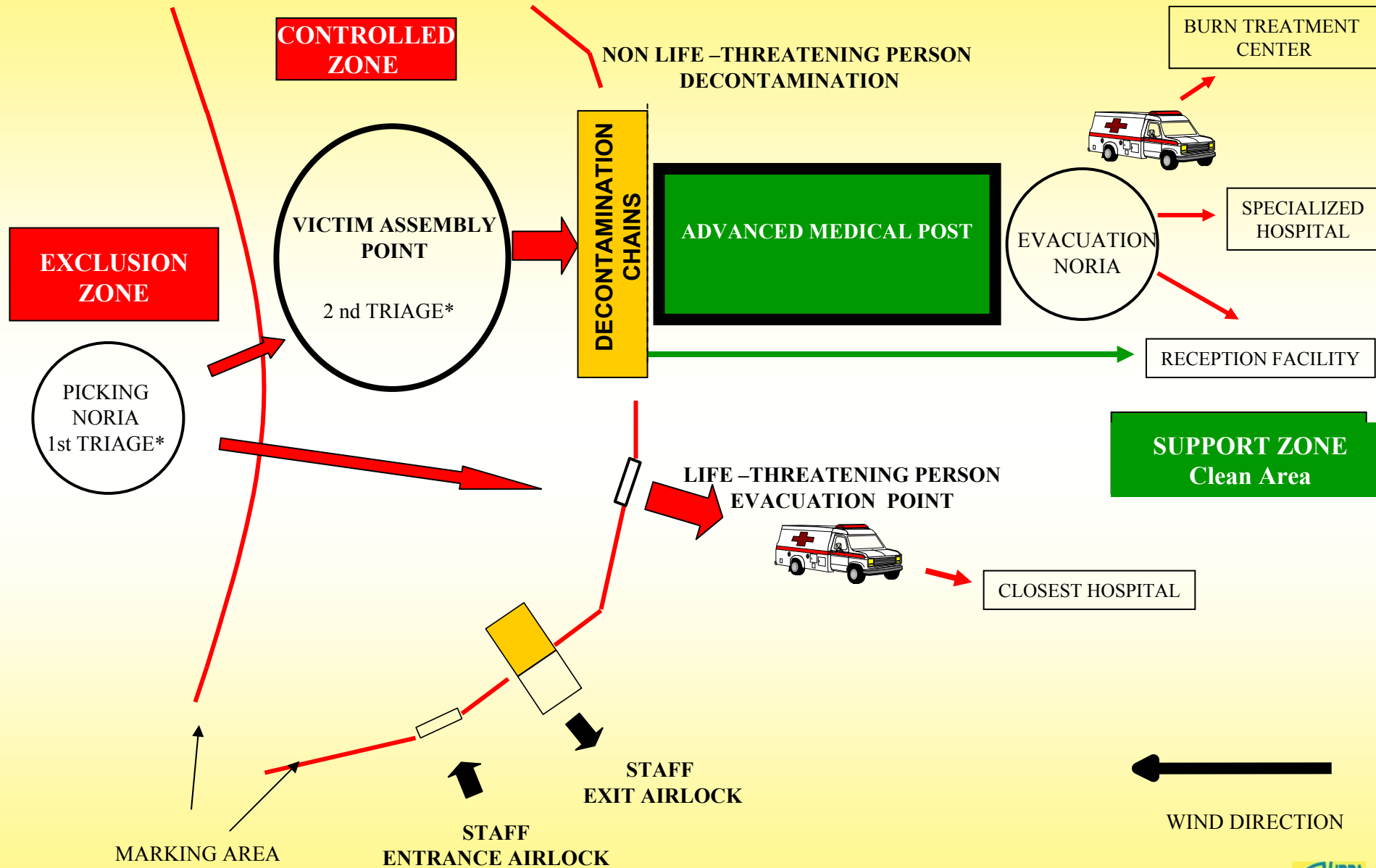
- ◆ **The External Contamination has to be taken into account as soon as Possible**
 - « **Radiological Burn Syndrome** »
 - **Factor of Dispersion of Radionucleides**
 - **Secondary Internal Contamination**

Superficial Beta Radiation Burns

Tchernobyl 30 Days



BASIC SCHEME OF MEDICAL AND RADIOLOGICAL TRIAGE ON SCENE OF THE ACCIDENT OR THE ATTACK



The Scenarios in Terms of Health Consequences

EVENT SCENARIO

Immediate victims
localized in space

Foreseeable Mass Casualties
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Radiation Dispersal Devices
« Dirty Bomb »

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High activity

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Immediate Vital Risk
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Strict Contamination

Long Term Risk : cancer

Unshielded Source Concealment
Medium activity

Localized Irradiation

Cutaneous Radiation Injuries
without Vital Risk



Sealed Source in Subway Acute Radiation Syndrome

Co-60 Source

1000 Ci



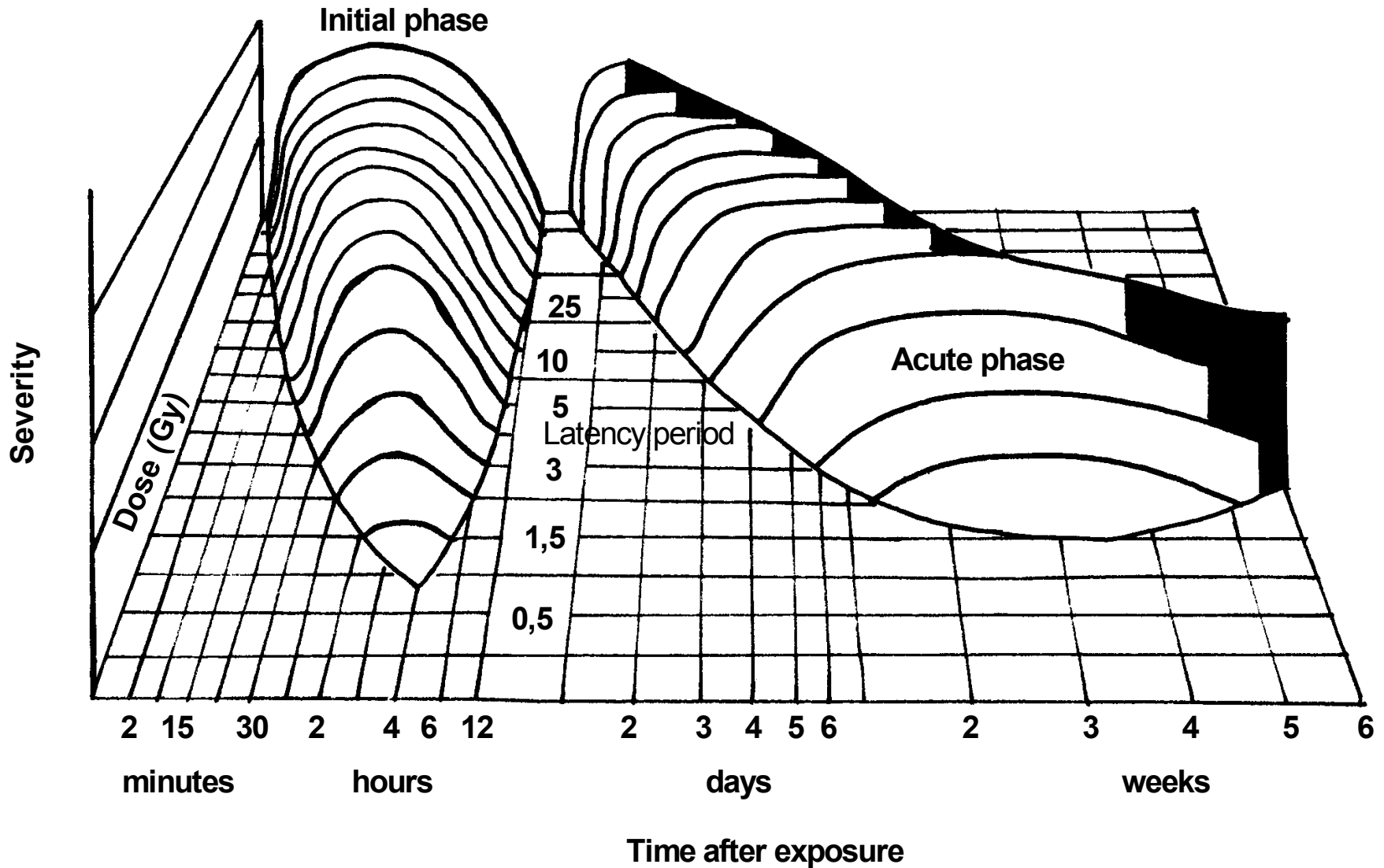
Distance (m)	Dose Rate (Gy/h)	Dose in 30 mn (Gy)	Number of victims Each 30 mn of exposure
0,5	50	25	4
1	12,5	6	8
2	3	1,5	16



**About 30 Acute Radiation Sickness
each 30 mn of exposure and for 1000 Curies**



The Acute Radiation Syndrome (ARS)



The Prodromal Phase of the ARS (24 Hours)

◆ Asthenia, Fatigue syndrome

◆ Anorexia

◆ Nausea

◆ Emesis

◆ Diarrhea

➔ Headache

➔ Hyperthermia

➔ Hypotension

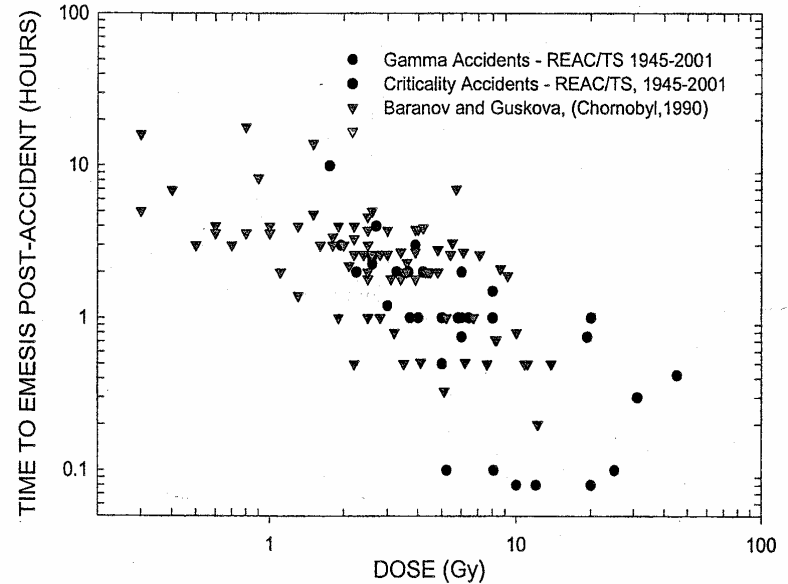
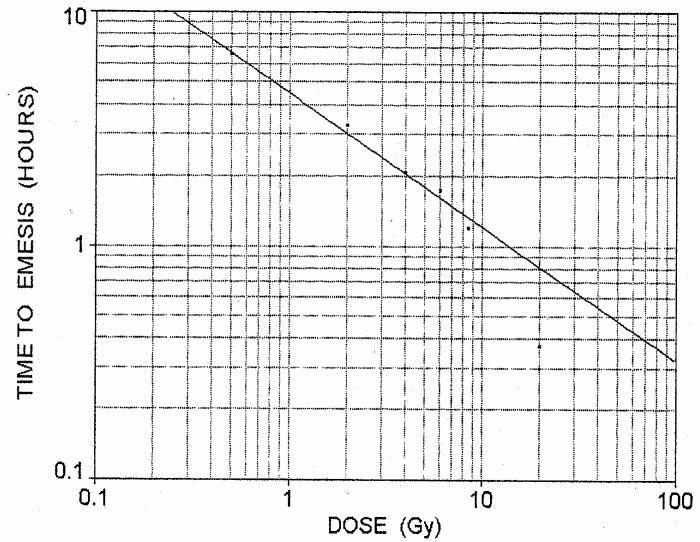
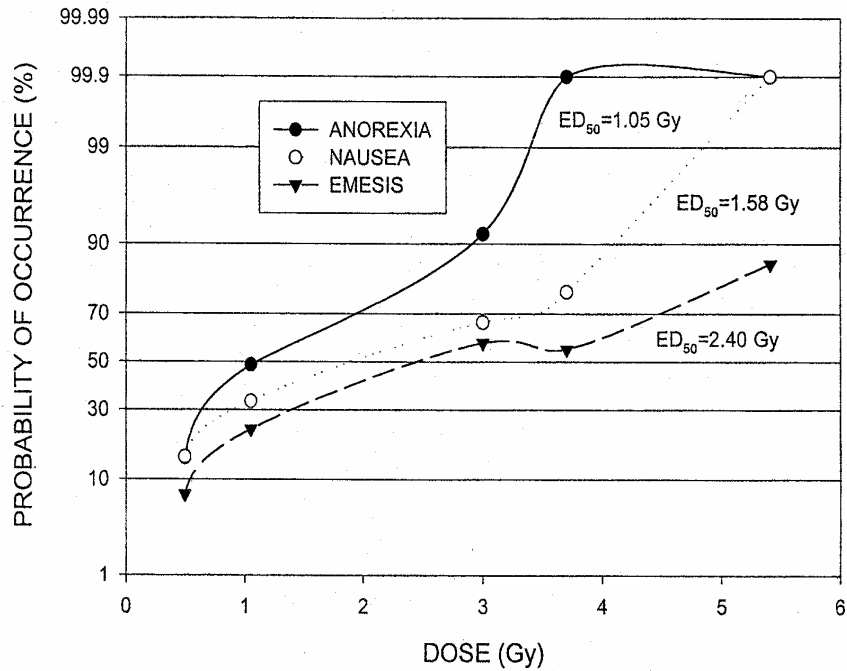
➔ Cognitive deficits « Transient Incapacitation Syndrome »

« Permanant Incapacitation Syndrome »

◆ Erythema

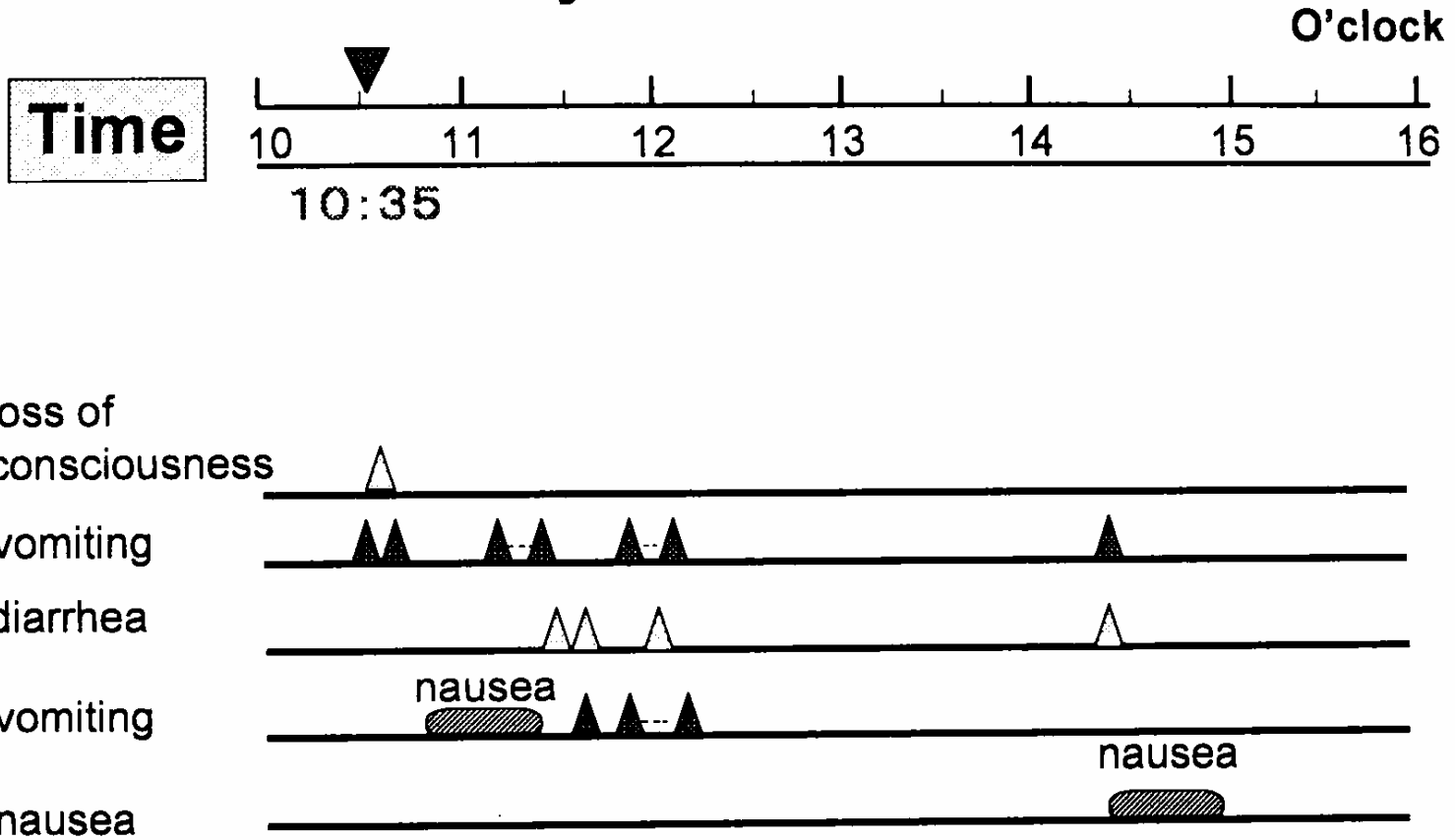
The Prodromal Phase of the ARS

Anorexia, Nausea, Emesis

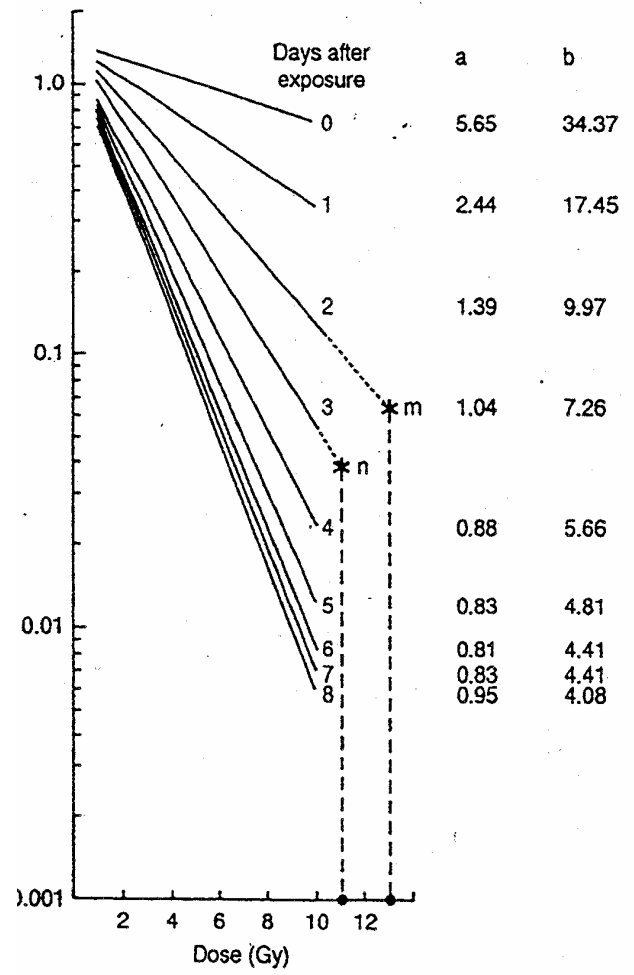
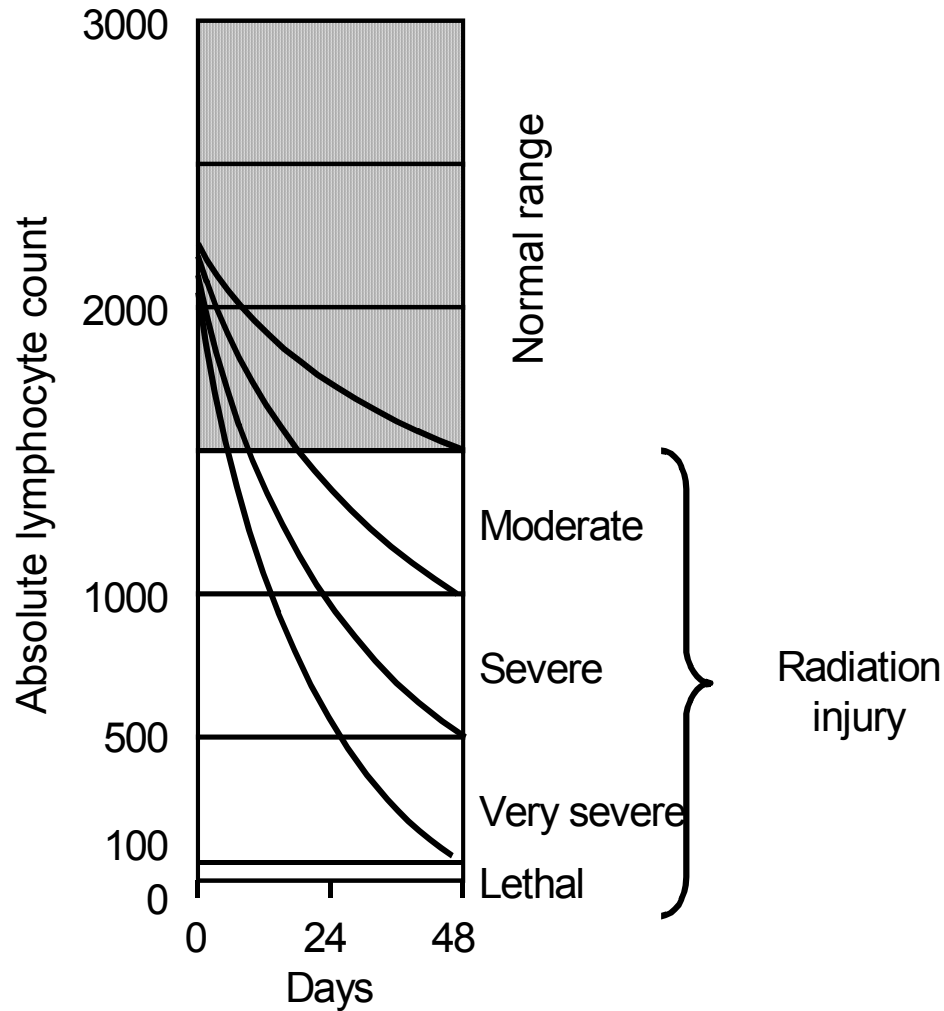


Prodromal Phase of Tokai Mura Accident

The Criticality

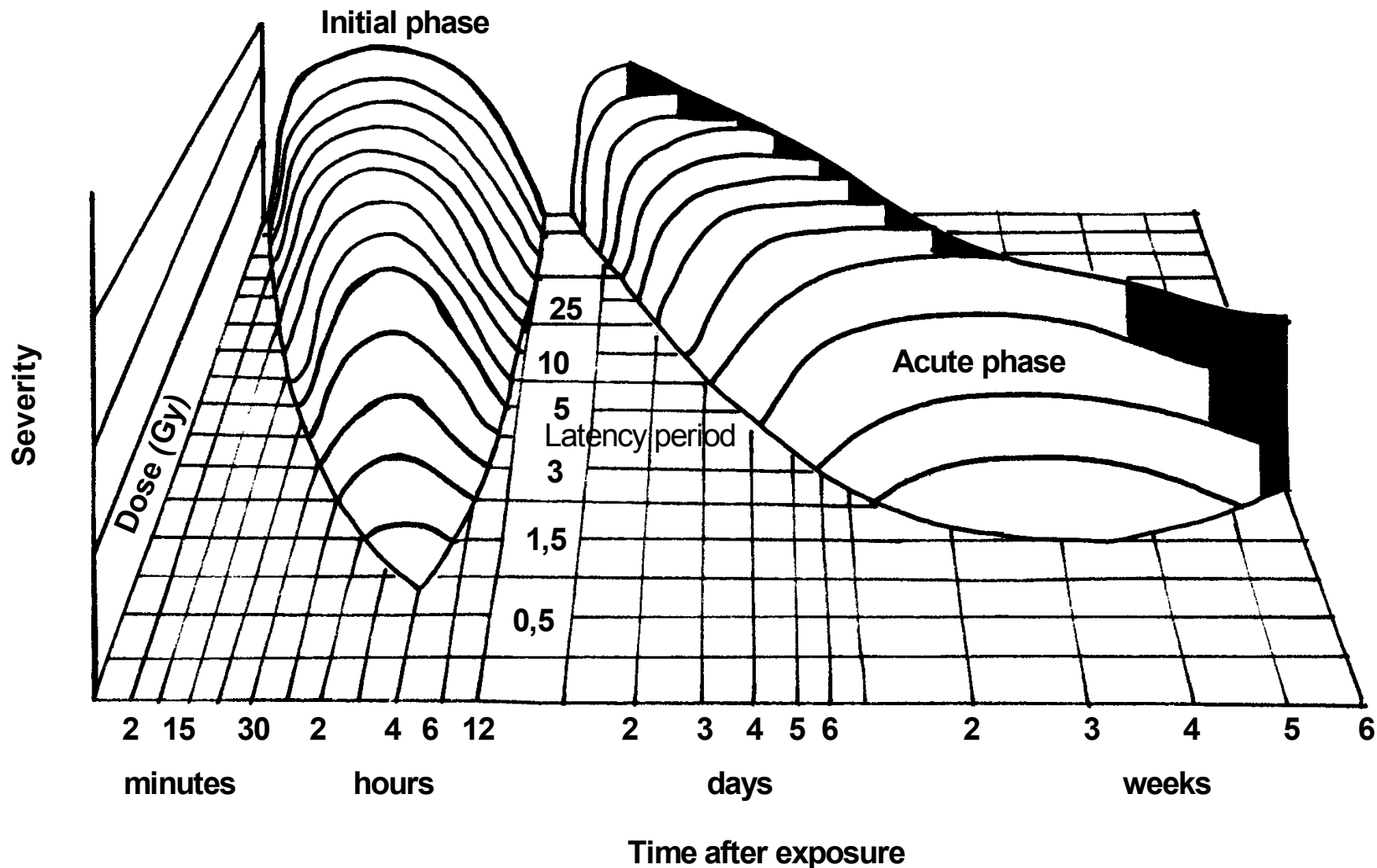


The Prodromal Phase of the ARS Decrease of the Lymphocyte Count

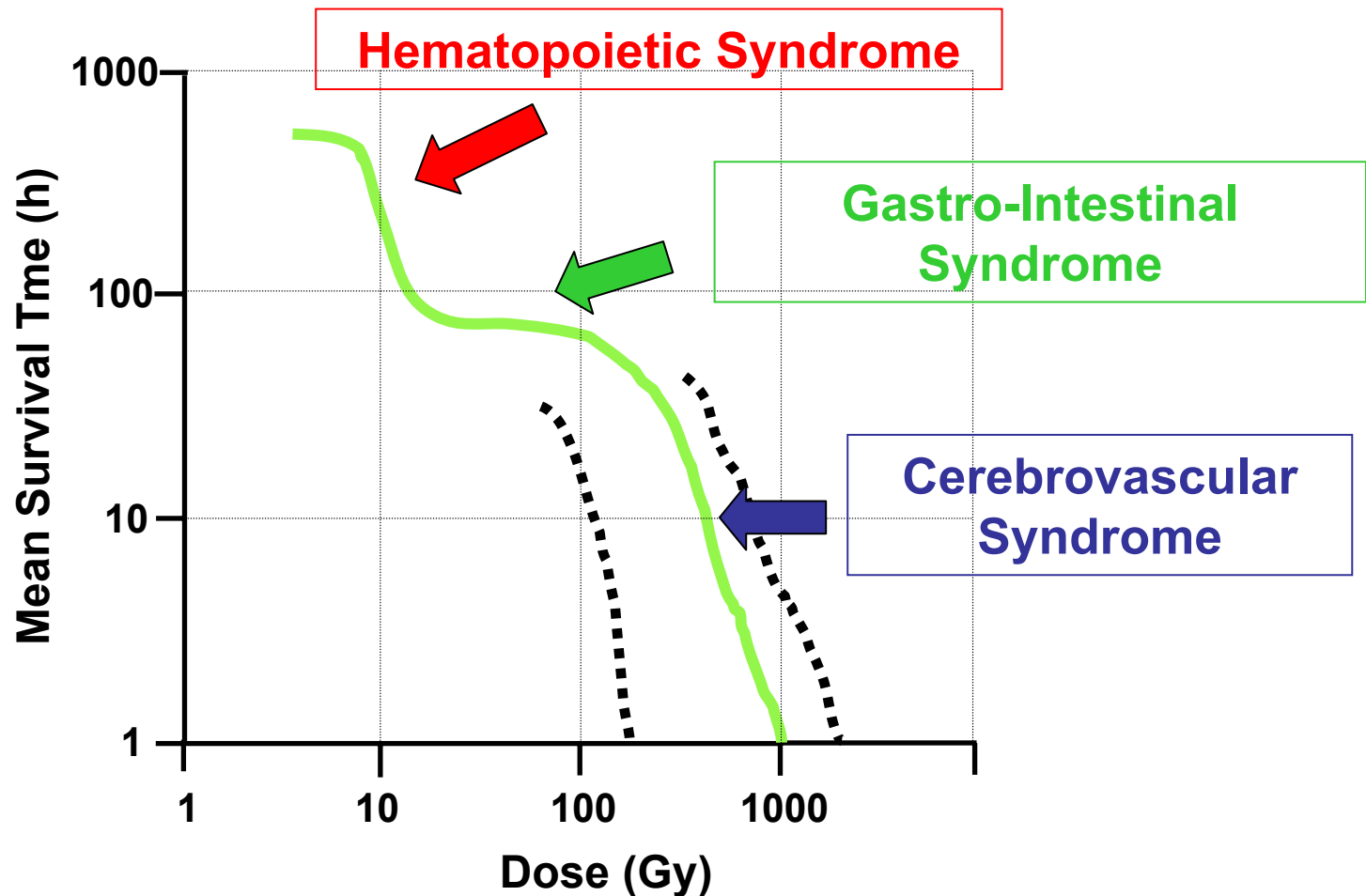


(Adapted from Andrews, 1980)

The Acute Radiation Syndrome (ARS)



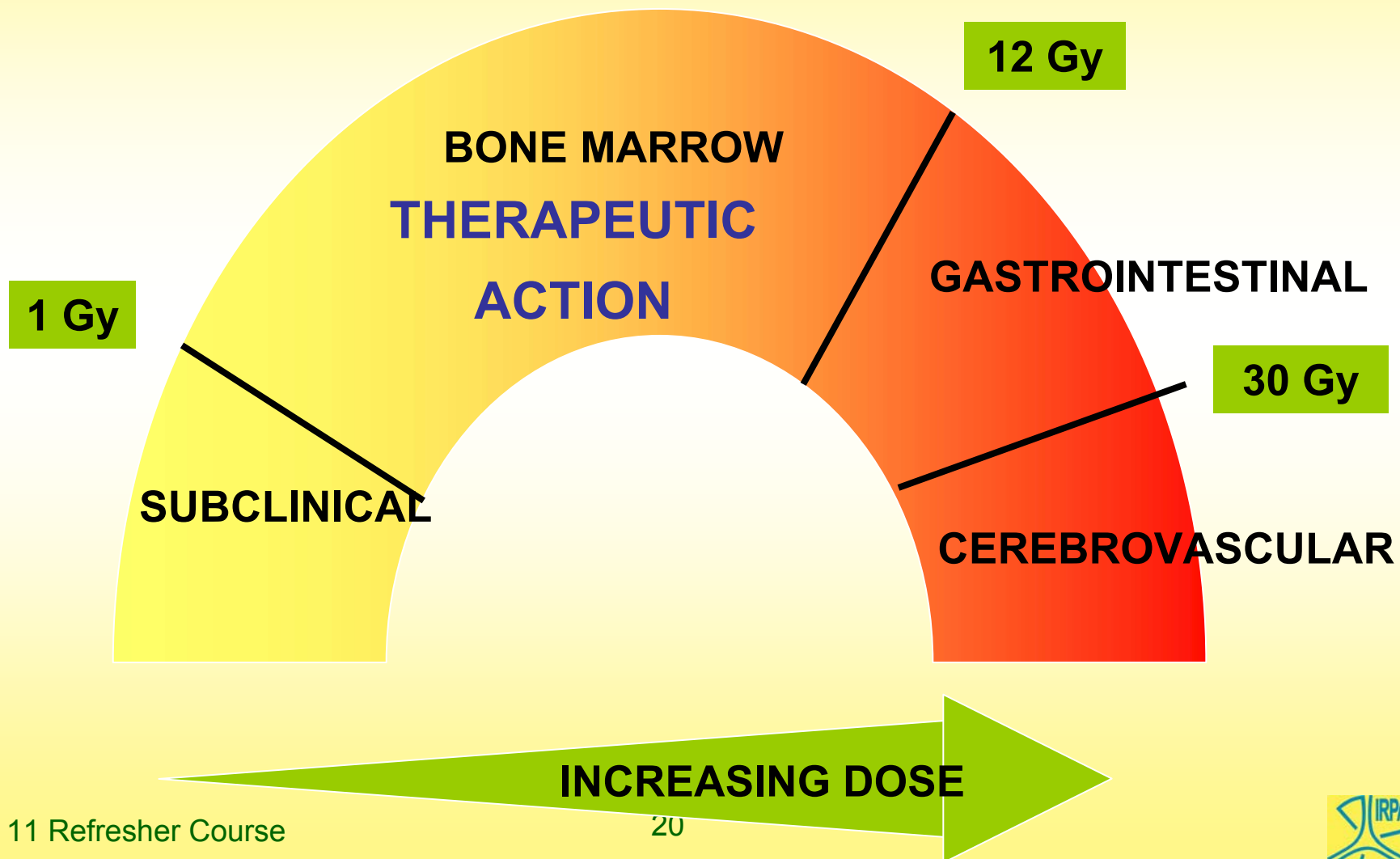
Mean Survival Time without Treatment as a Function of Dose after Homogenous Whole-body Irradiation



(Bond VP et al, 1965, In: Mammalian Radiation Lethality, pp 231-275).

The Acute Radiation Syndrome

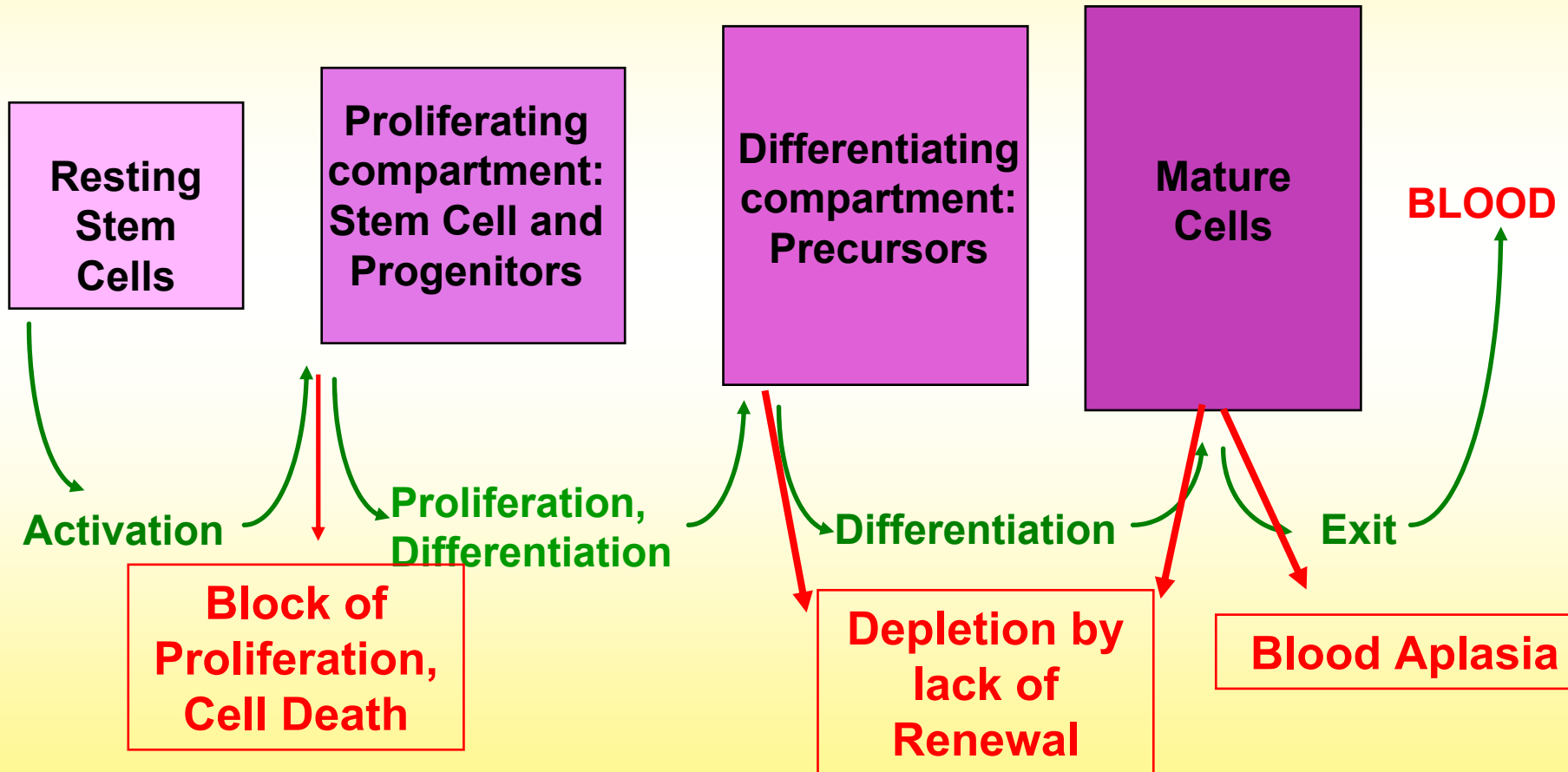
Whole-body Irradiation



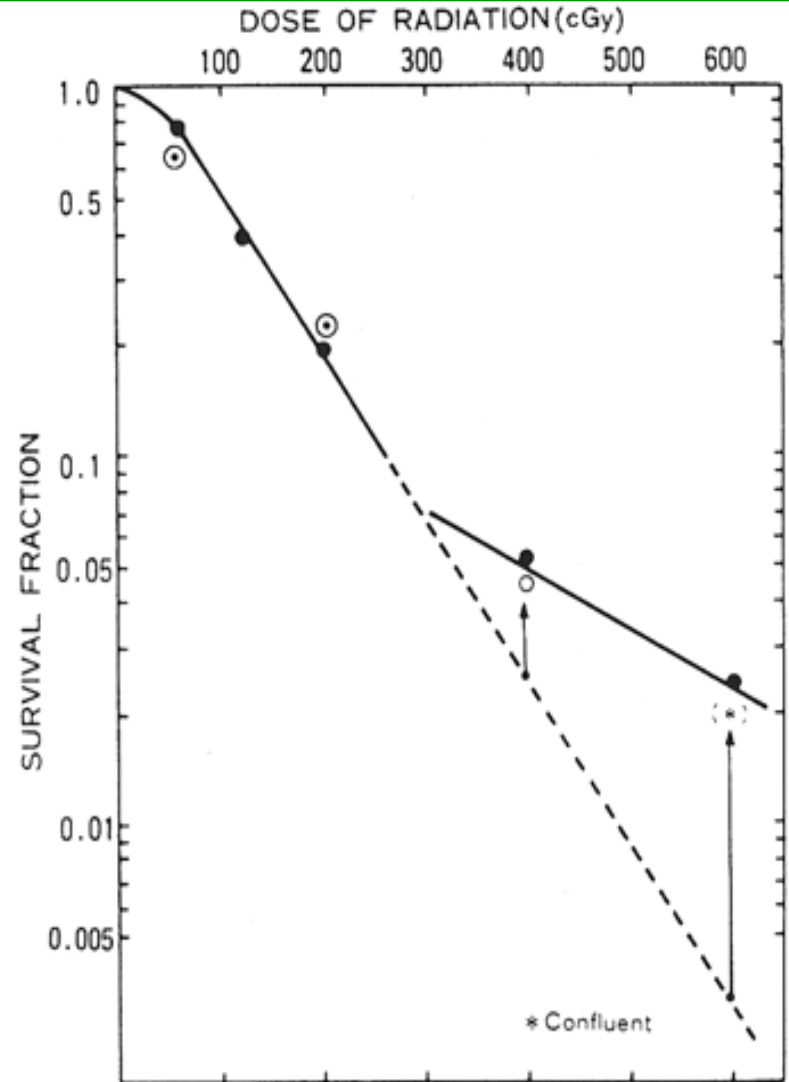
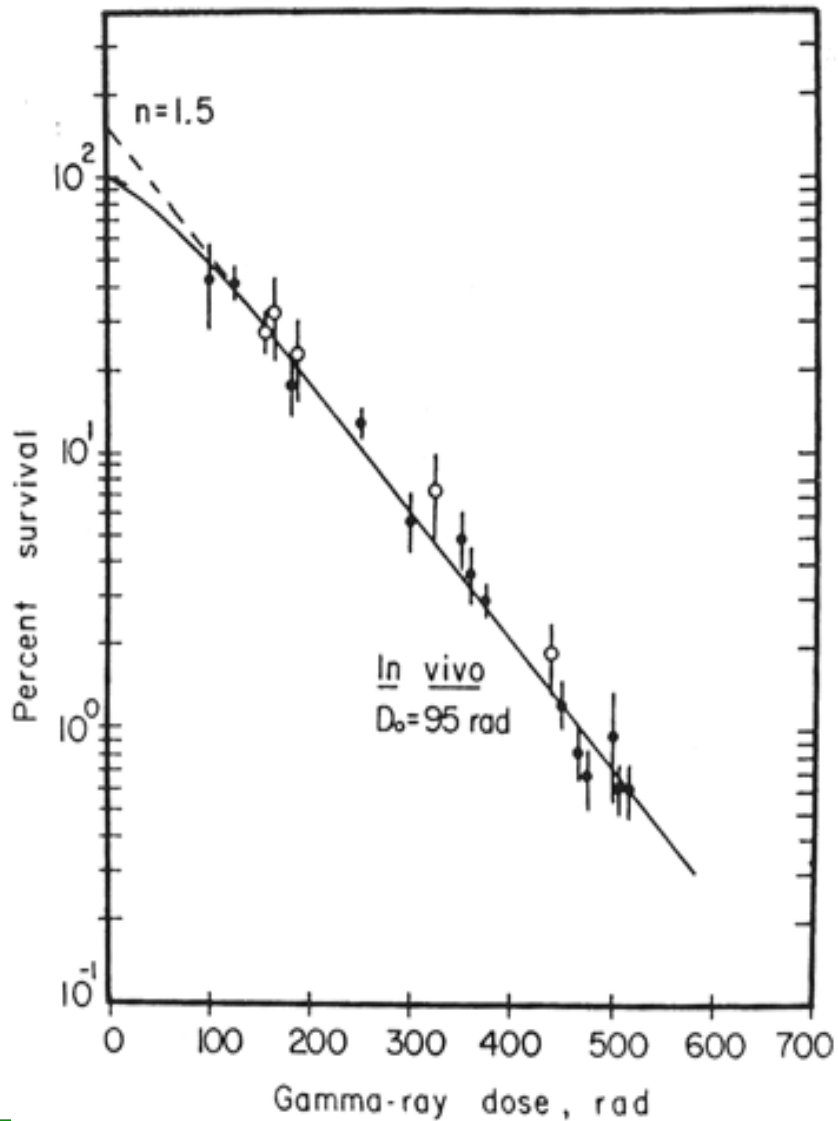
The Hematopoietic Syndrome

The Compartmentalisation of Hematopoiesis

Normal Physiological situation

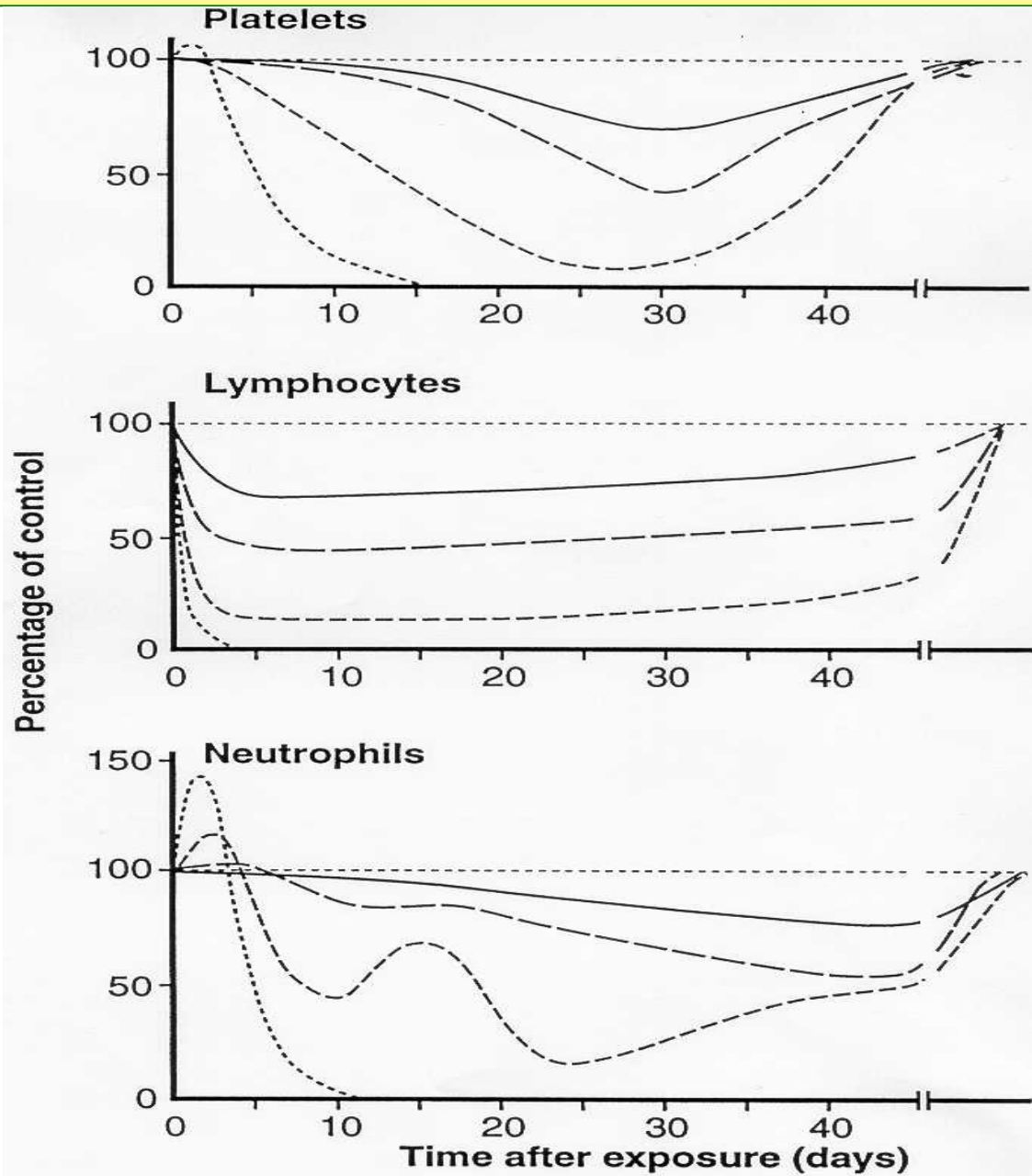


Survival Curve for CFU-S



(Hall E.J. Radiobiology for the Radiologist, 2000)

Peripheral Blood Aplasia

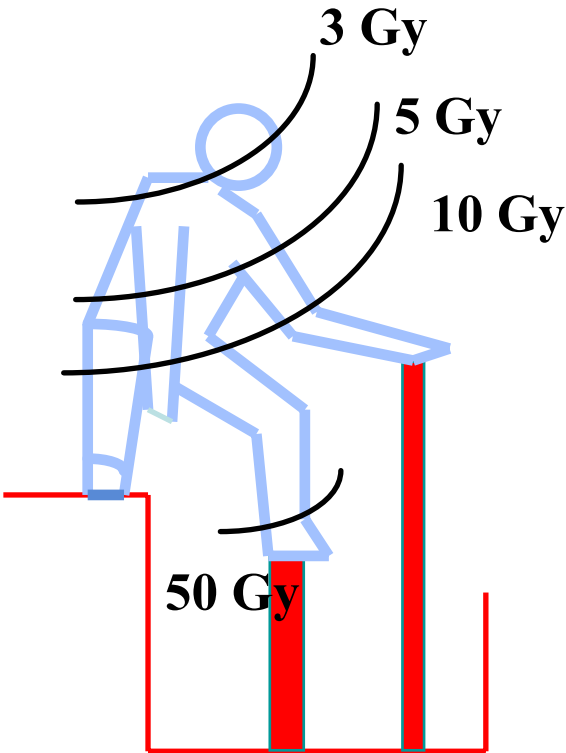


The Concept of Residual Hematopoiesis

- ◆ **Some Hematopoietic Stem Cells can survive to Irradiation :**
 - They are radioresistant due to their resting state
 - Accidental Irradiation are Heterogeneous, leading to the protection of some bone marrow territories
- ◆ **This is the concept of Residual Hematopoiesis.**
- ◆ **Then, an endogeneous reconstitution of the hematopoiesis can be observed, with sub-lethal or lethal doses of irradiation**

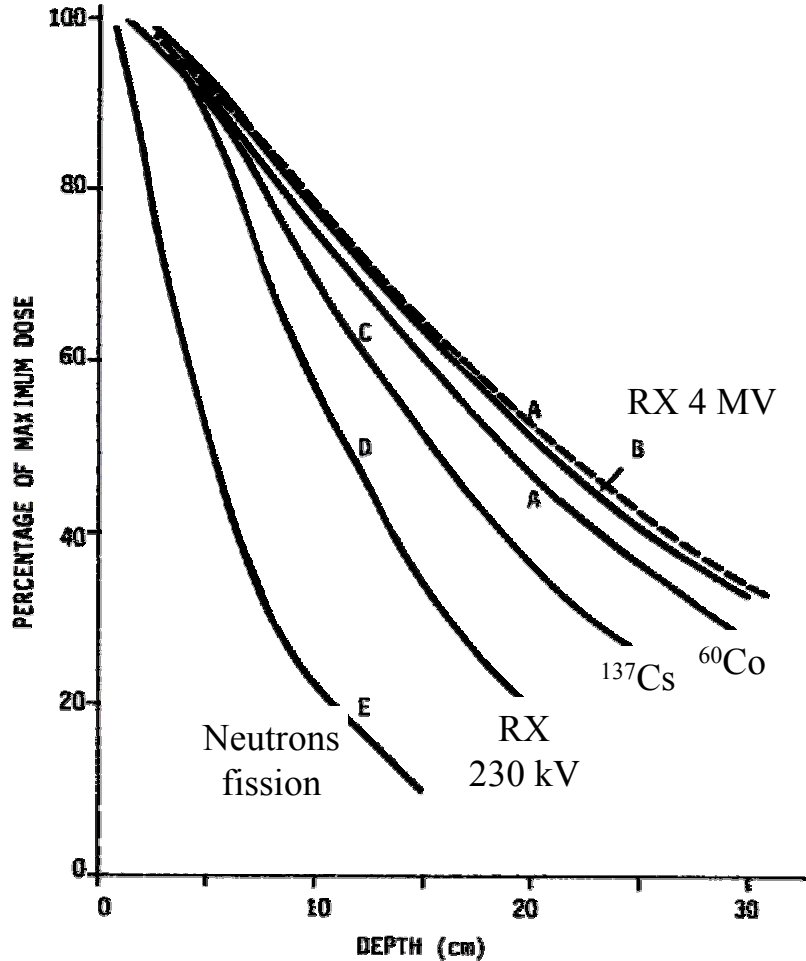
Accidental Heterogenous Irradiation Mol, Belgium, 1965.

Spatial Distribution of the Dose

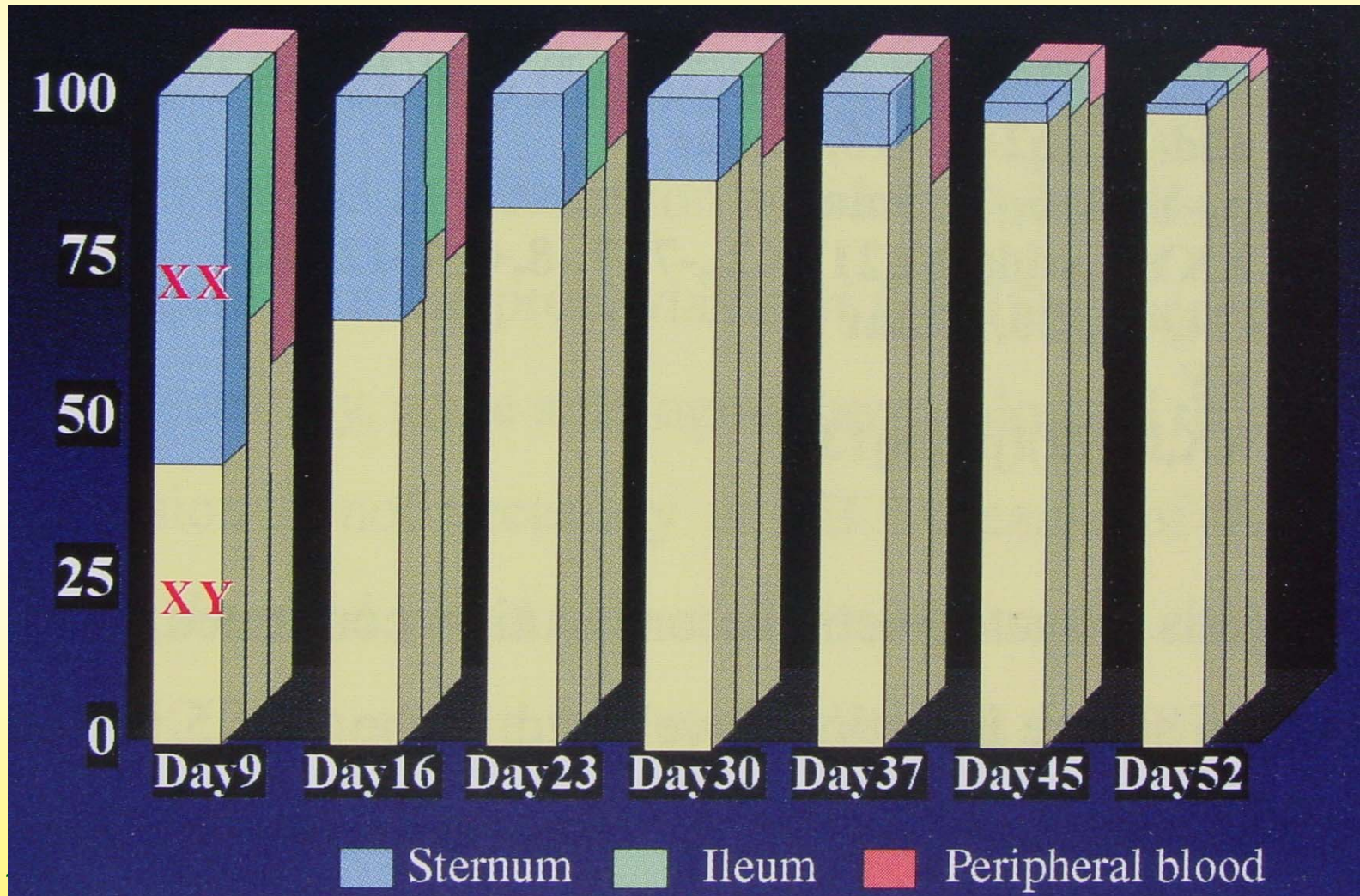


➔ Estimated mean dose to bone marrow: 5 Gy.

➔ But 16% of bone marrow received less than 1 Gy.



Chimerism after Cord Blood Transplantation Tokai Mura Accident



Treatment of the Hematopoietic Syndrome

◆ REVERSIBLE DAMAGE TO THE BONE MARROW

- Substitution And /Or Supportive Therapy
- STIMULATION THERAPY (Cytokine, **G-CSF**, GM –CSF, TPO, EPO)

◆ IRREVERSIBLE DAMAGE TO THE BONE MARROW

- Substitution And Supportive And Stimulation Therapy
- Additionally to Stem Cell Transplantation Therapy

◆ ASSOCIATED WITH IRREVERSIBLE DAMAGE OF OTHERS ORGANS (Gut, CNS)

➔ Palliative Therapy

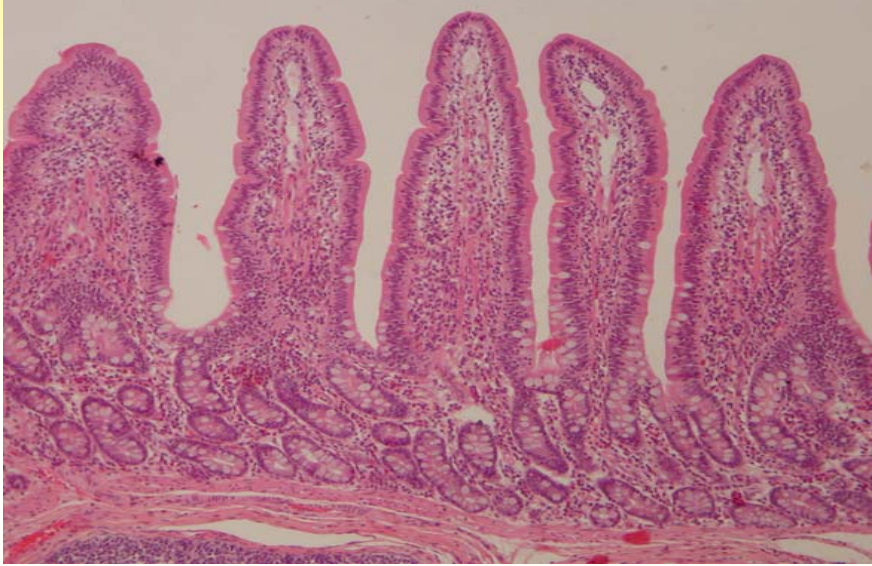
Stem Cell Therapy

- ◆ **Accidental Radiation Overdose**
- ◆ **29 Patients with Hematopoietic Stem Cell Transplantation**
- ◆ **No Permanent Engraftment**
- ◆ **24 % of patients Graft-versus-host Disease (GVHD)**

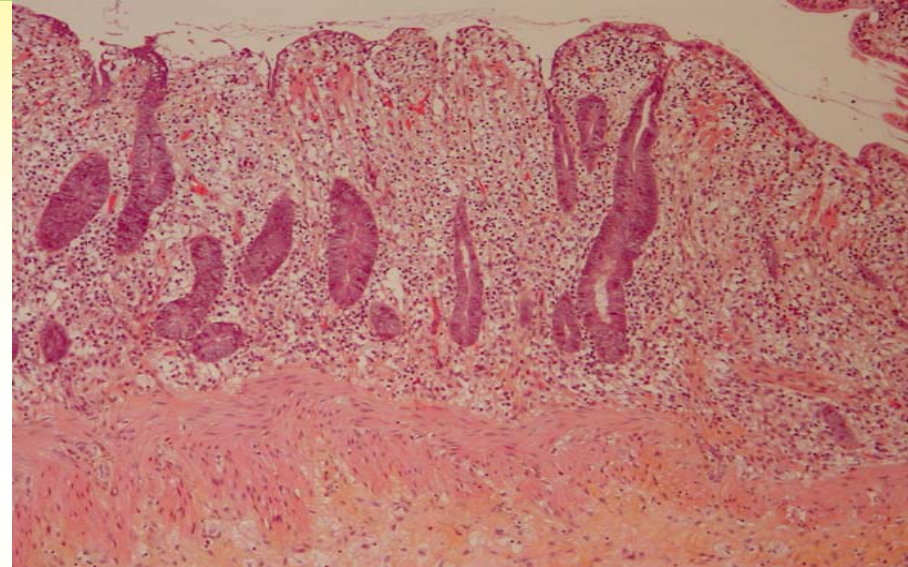
- ◆ **Case Selection :**
 - **Autologous or syngenic Hematopoietic SCT**
 - **Narrow Dose Therapeutic Window :**
Lethal Marrow Injury without Lethal Injury to other organs (<10 Gy)

- ➔ **It is difficult to be optimistic about the contribution of hematopoietic SCT to treat patients of radiation overdose.**

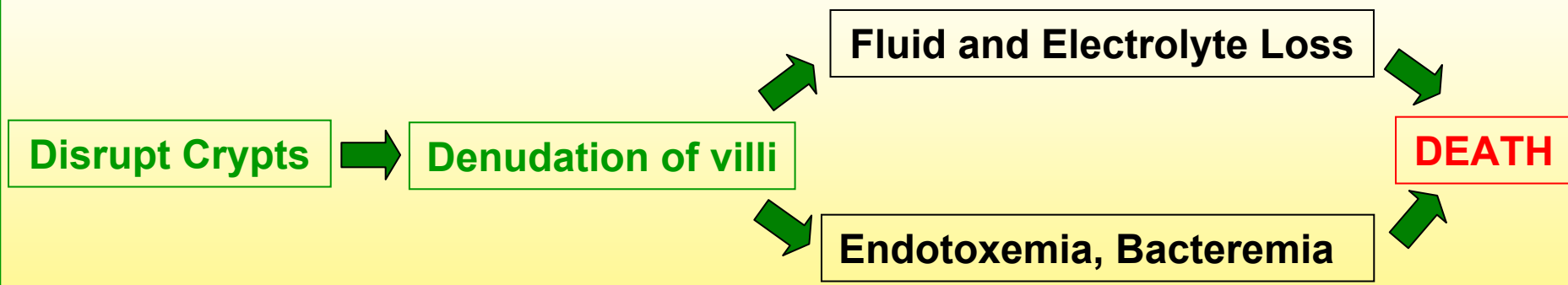
The Gastro-intestinal Syndrome



Control



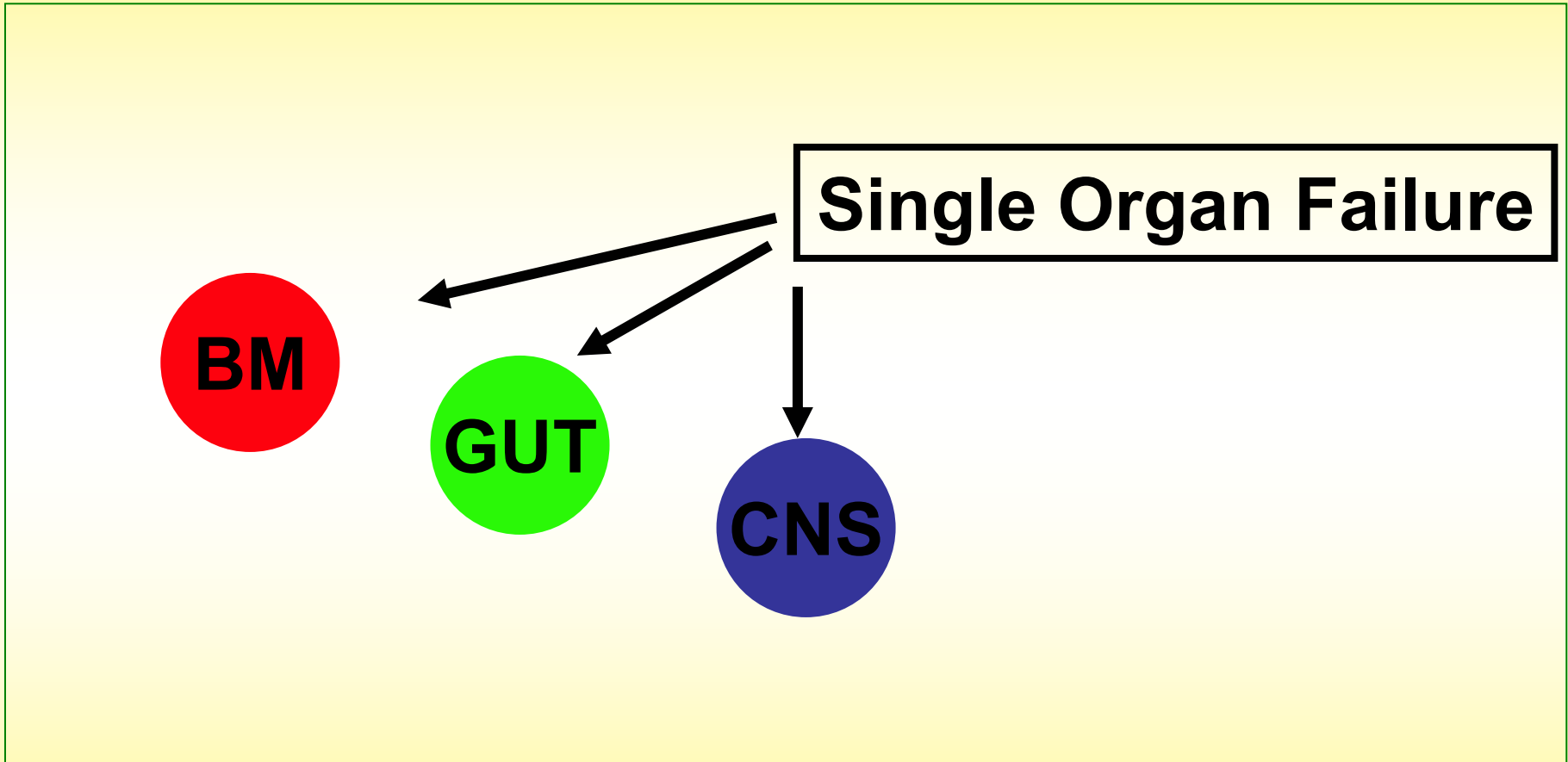
16 Gy Day 5



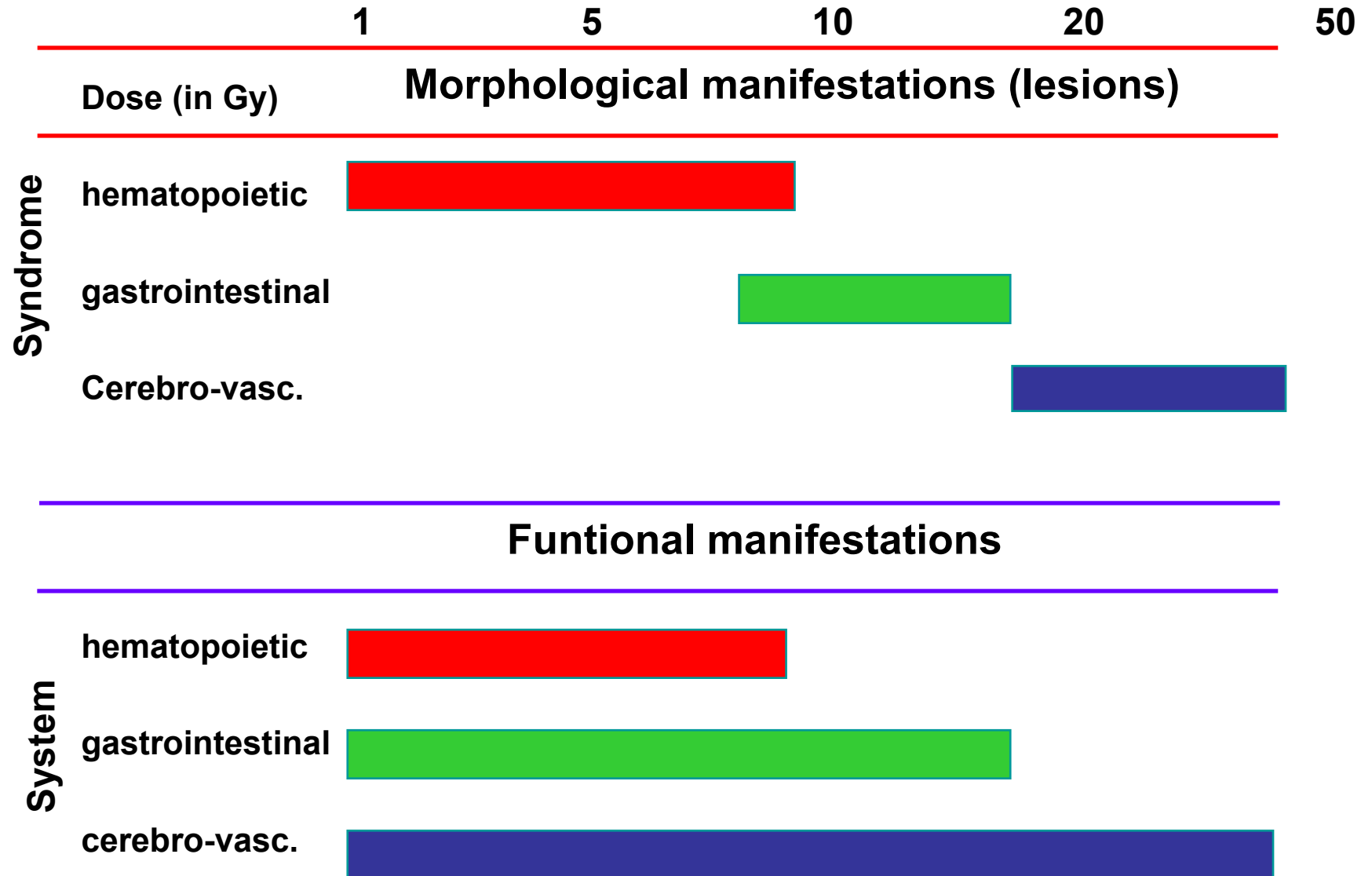
The Cerebrovascular Syndrome

- ◆ **> 50 Gy**
- ◆ **Permament Incapacitation Syndrome**
- ◆ **Disorientation**
- ◆ **Confusion**
- ◆ **Prostration**
- ◆ **Ataxia**
- ◆ **Seizures**
- ◆ **Absence Deep tendon and Corneal Reflexes**
- ◆ **Hyperthermia**
- ◆ **Respiratory Distress**
- ◆ **Cardiovascular Shock**
- ◆ **Death within 2 days**

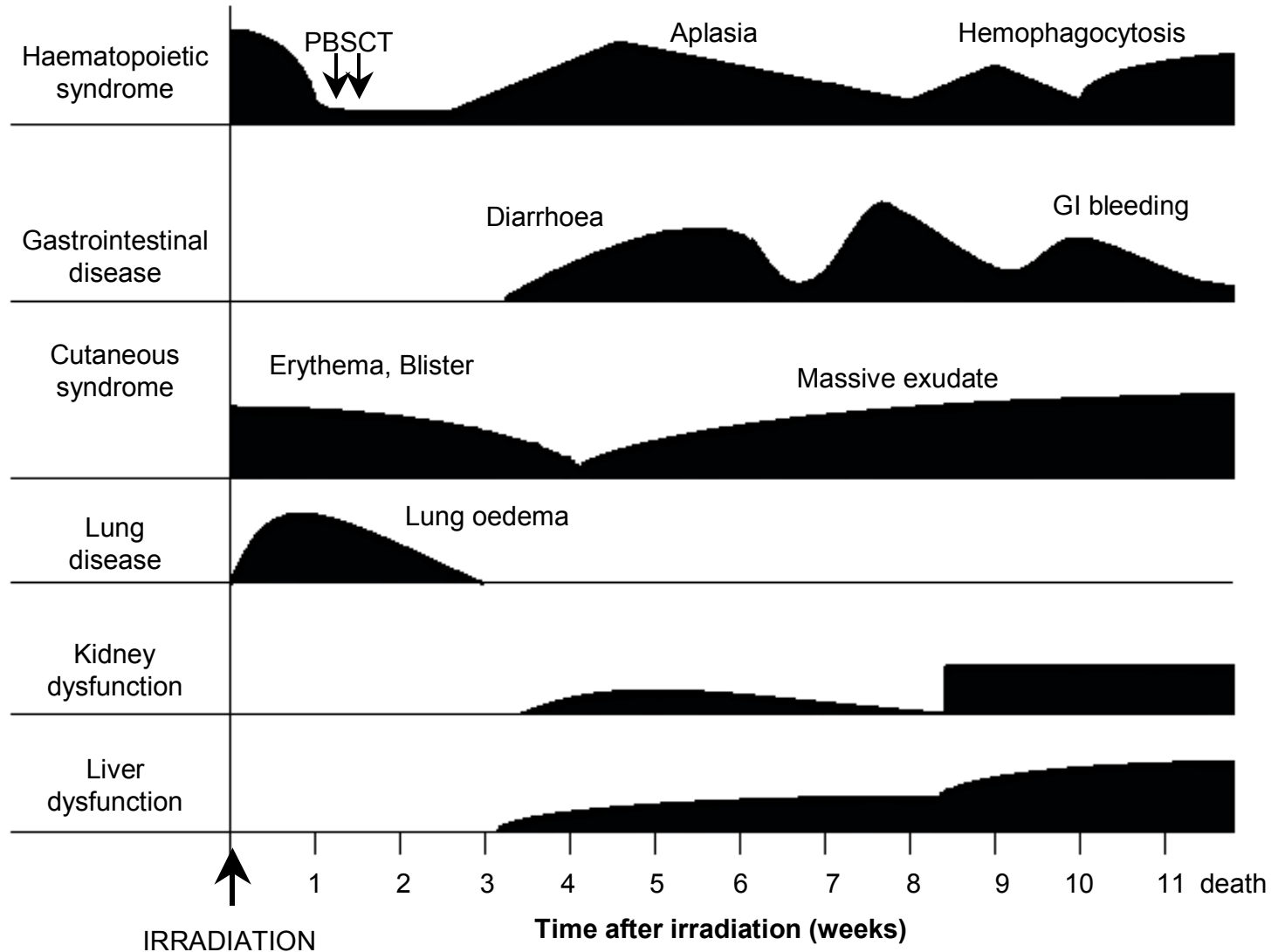
THE DOGMA OF THE ARS



Manifestations of the ARS



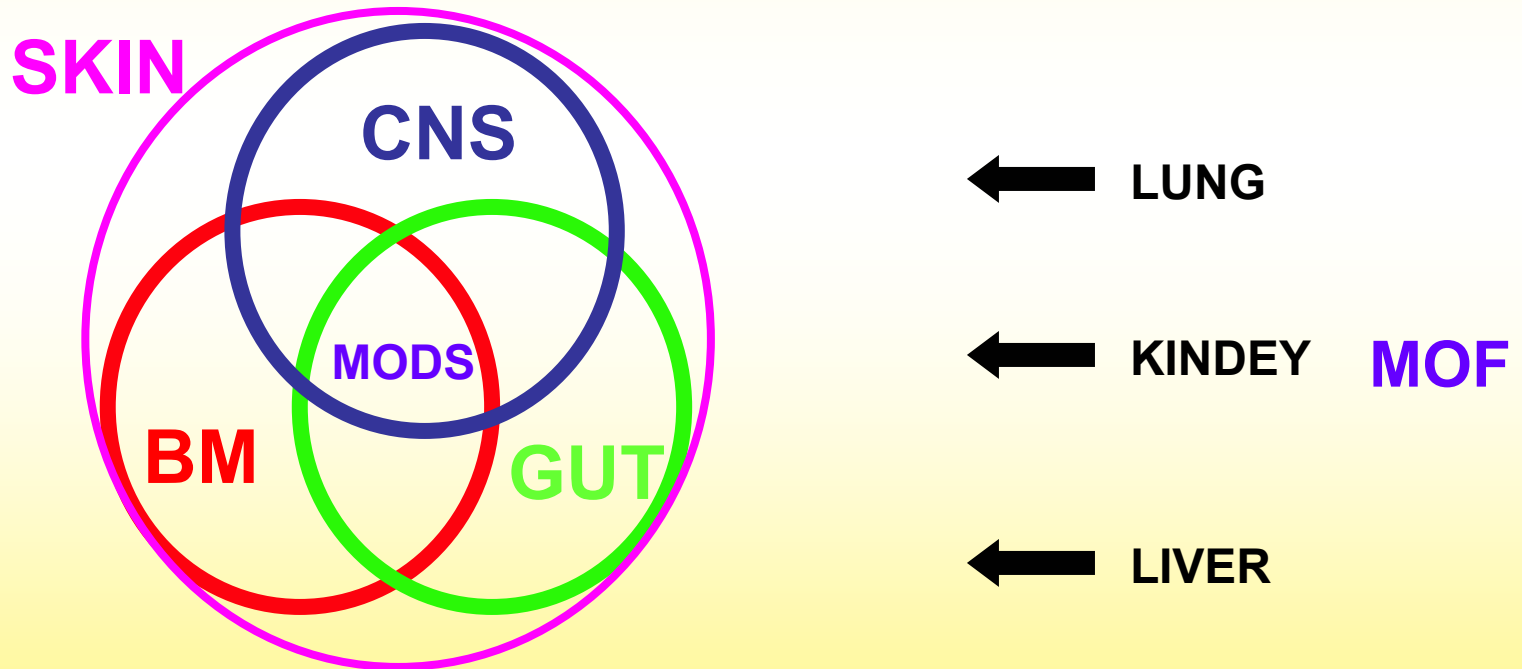
Multiple Organ Dysfunction Syndrome (MODS) Tokai-Mura Accident



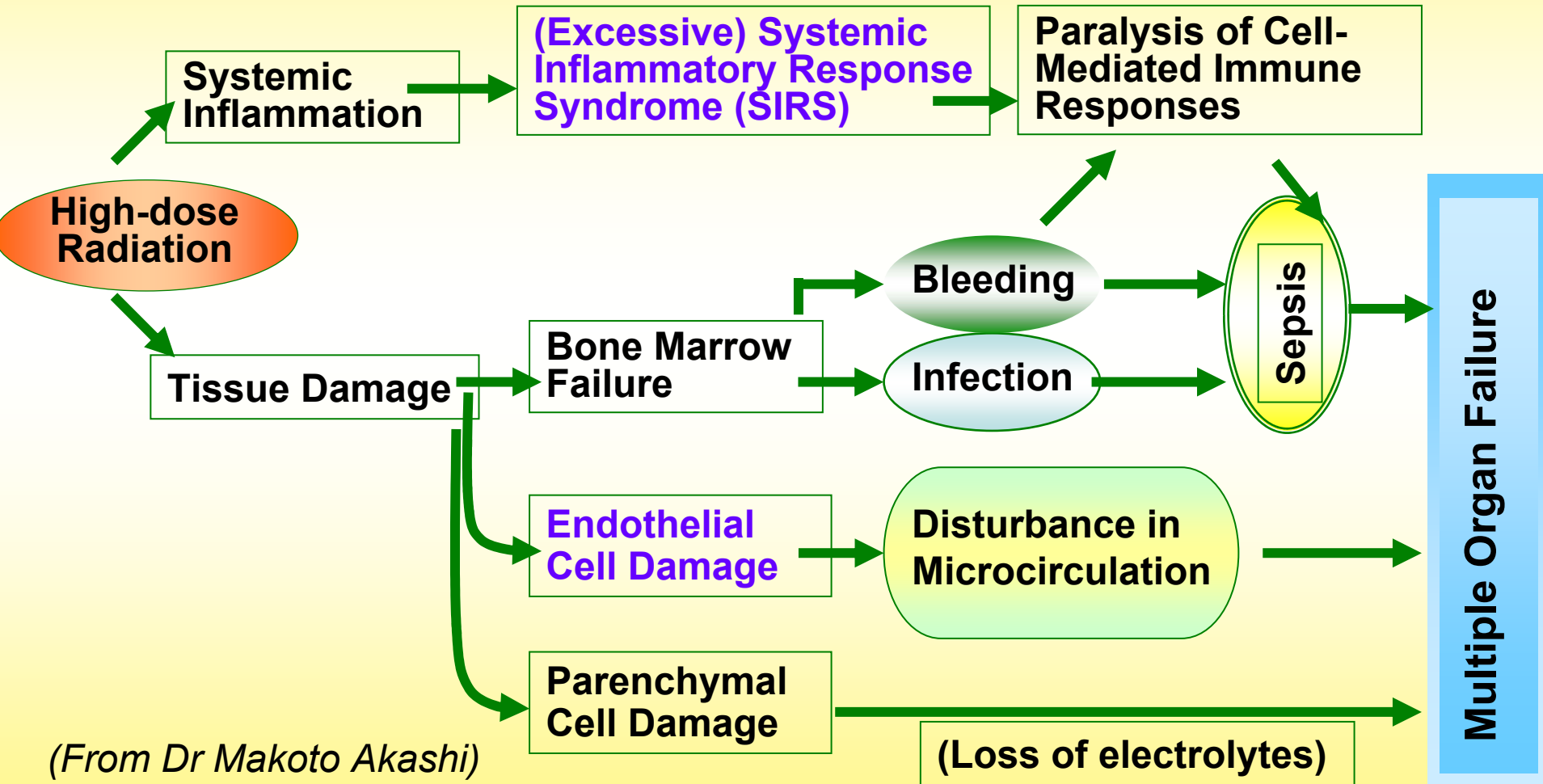
The New Concept :

Multiple Organ Dysfunction Syndrome (MODS)

Multiple Organ Failure (MOF)



Possible Mechanisms for MOF in Radiation



(From Dr Makoto Akashi)

DOSE

TYPE OF PARTICLE

Neutron, Gamma, X

**MULTIPLE ORGAN
DYSFUNCTION SYNDROME (MODS)**

IRRADIATED VOLUME

Heterogeneity of the Dose

**HOST RESPONSE TO THE
INSULT**

Biological Dosimetry Versus Biological Indicators

- ◆ **Dose assessment is not well adapted for the medical management of overexposed victims**
- ◆ **Absolute necessity to identify biological indicators of damages and if possible prognosis indicators**
- ◆ **The assessment of the heterogeneity of the irradiation and the spatial distribution of the dose is a high priority for the diagnosis and the therapeutic strategy (Bone marrow transplantation decision)**

MEDICAL MANAGEMENT OF RADIATION ACCIDENTS

Edited by T M Fliedner, I Friesecke and K Beyrer



MANUAL ON THE ACUTE RADIATION SYNDROME

BIR Published by The British Institute of Radiology

METREPOL

Overall Prognostic Aspects of the ARS on the Basis of the Organ Specific Grading and Manifestations

N = neurovascular system

H = haematopoietic system

C = cutaneous system

G = gastrointestinal system

Manifestations of the Acute Radiation Syndrome				
Organ System	Degree 1 Mild Damage	Degree 2 Moderate Damage	Degree 3 Severe Damage	Degree 4 Serious/fatal Damage

Organ Specific Grading System for the Gastrointestinal System (G)

Symptom Diarrhea	Degree 1 Mild	Degree Moderate	Degree 3 Severe	Degree 4 Serious/fatal
Frequency, stools/day	2-3	4-6	7-9	≥ 10
Consistency	Bulky	Loose	Loose	Watery
Bleeding	Occult	Intermittent	Persistent	Persistent with large amount
Abdominal cramps or pain	Minimal	Moderate	Intense	Excruciating

Organ Specific Grading System for the Hematopoietic System (H)

Symptoms	Degree 1 Mild	Degree 2 Moderate	Degree 3 Severe	Degree 4 Serious fatal	Reference values
Lymphocyte changes	$\geq 1.5 \times 10^9$ cells/L	$1-1.5 \times 10^9$ cells/L	$0.5-1 \times 10^9$ cells/L	$< 0.5 \times 10^9$ cells/L	$1.4-3.5 \times 10^9$ cells/L
Granulocyte changes	$\geq 2 \times 10^9$ cells/L	$1-2 \times 10^9$ cells/L I	$0.5-1 \times 10^9$ cells/L	$< 0.5 \times 10^9$ cells/L	$4-9 \times 10^9$ cells/L ² .
Thrombocyte changes	$\geq 100 \times 10^9$ cells/L I	$50-100 \times 10^9$ cells/L	$20-50 \times 10^9$ cells/L	$< 20 \times 10^9$ cells/L	$140-400 \times 10^9$ cells/L ³
Blood loss	Petechiae, easy bruising, normal hemoglobin level	Mild blood loss with <10% decrease in hemoglobin level	Gross blood loss with 10%- 20% decrease in Hemoglobin level	Spontaneous bleeding or blood loss with >20% decrease in hemoglobin level	

General Approach to Triage and Therapy of the ARS

GRADING CODE : N_i H_i C_i G_i

H_i

1

2

3

4

Hospitalization

Ambulatory
Monitoring

Blood Component
Transfusion

Blood Component
Transfusion

Blood Component
Transfusion

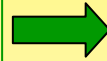
Growth Factor
Therapy

Growth Factor
Therapy

Stem Cell
Transplantation
Therapy

Adapted from N. Dainiak (2003)

GRADING CODE : $N_i H_i C_i G_i$



RESPONSE CATEGORY $RC_{i Max}$

	RC 1	RC 2	RC 3	RC 4
Degree of damage	Mild	Moderate	Severe	Serious/Fatal
Prognosis	Spontaneous recovery certain	Spontaneous recovery likely	Spontaneous recovery possible	Spontaneous recovery most unlikely
Hospitalisation	Not necessary, outpatient care	Observation for 1 week, then outpatient care	Necessary, intense supervision	Emergency, intensive care necessary
Therapy	Not necessary	Bridging therapy	Intensive therapeutic approaches	Invasive therapy necessary



Conclusion of the ARS

- ◆ In accidents, the exposure parameters are generally completely or partially unknown.
- ◆ The accidental situation is **almost always heterogeneous**.
- ◆ There is a residual hematopoiesis.
- ◆ **There is a combined syndrome involving hematopoietic, gastrointestinal and nervous systems and skin leading to MODS and MOF**
- ◆ The pathology is complex, and difficult to treat.
- ◆ The outcome will depend on two factors
 - Physical parameters of irradiation: dose, dose rate
 - Heterogeneity of the irradiation

The Scenarios in Terms of Health Consequences

EVENT SCENARIO

Immediate victims
localized in space

Foreseeable Mass Casualties
Immediate Psycho-social impact

Radiation Dispersal Devices
« Dirty Bomb »

Wounds, Burns, Contaminations

Immediate Vital Risk
Long Term Risk : cancer

Unshielded Source Concealment
High activity

Whole Body Irradiation

Immediate Vital Risk
Acute Radiation Syndrome

IR

INSIDIOUS SCENARIO

Victims distributed in time
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Long Term Risk : cancer

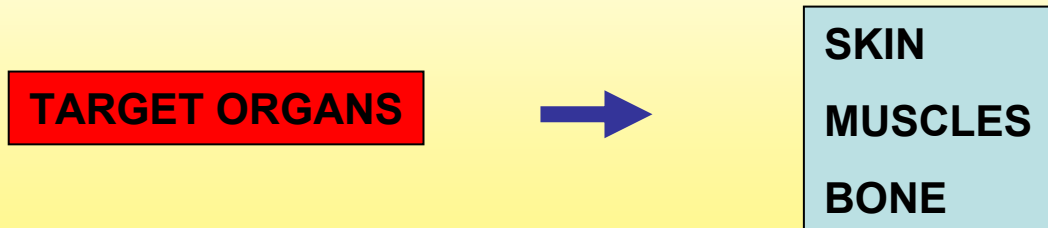
Unshielded Source Concealment
Medium activity

Localized Irradiation

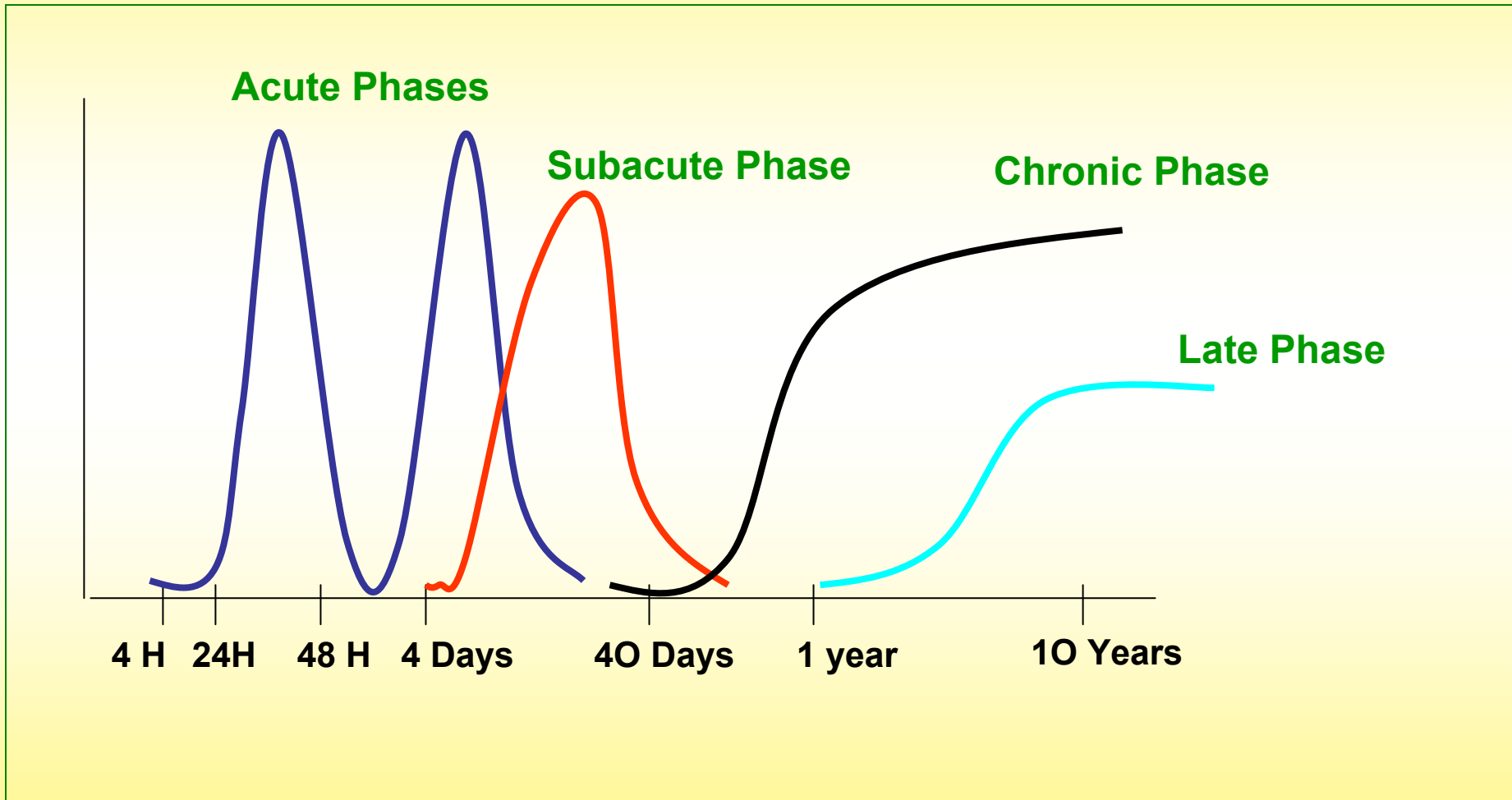
Cutaneous Radiation Injuries
without Vital Risk

The Cutaneous Radiation Syndrome

- ◆ **Three Layers :**
 - **Epidermis (Hierarchical Tissue)**
 - **Dermis (Flexible)**
 - **Hypodermis (Flexible)**
- ◆ **The Skin Can Present Early And Late Post-radiation Reactions**
- ◆ **Early reactions essentially involve epidermis while late reactions involve the 3 skin layers.**



The Cutaneous Radiation Syndrome



The Cutaneous Radiation Syndrome

Early Effects

Erythema	6 - 12 Gy	Hours - 30 days- 10 weeks
Dry Desquamation	12 - 15 Gy	
Moist Desquamation	15 - 20 Gy	5 days –8 weeks
Ulcer/ Necrosis	25 - 30 Gy	5 days - >12 weeks
Hair Loss	4 - 5 Gy	2 - 8 weeks

Late Effects

Hyperpigmentation or Depigmentation	> 12 Weeks
Keratosis	> 12 Week
Atrophy	> 12 Weeks
Telangiectasia	> 12 Weeks
Fibrosis	> 12 weeks

Classical Surgical Treatment of the Cutaneous Radiation Syndrome

- ◆ **Conservative treatment for superficial lesions of distal extremities**
- ◆ **Surgery for painful deep ulcerations and necrosis**
 - **Ulcerectomy**
 - **Necrectomy**
 - **Wound closure by rotation flap**
 - **Amputation**
- ◆ **In cases of profound and large necrosis, the lesion should be excised and the wound bed should be covered with a good quality, full-thickness skin graft**

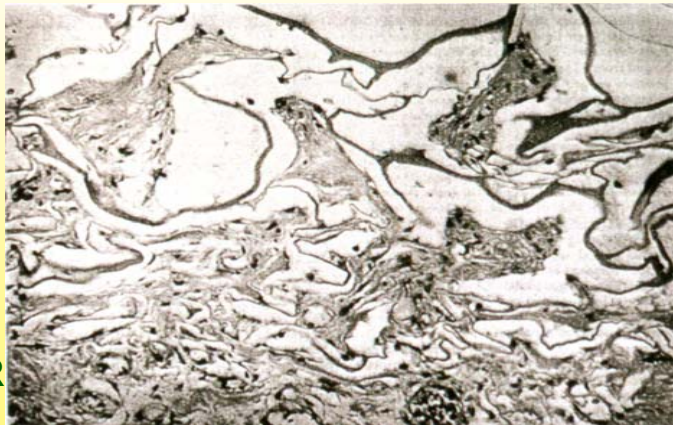
Artificial Skin Description INTEGRA®

Bilayer Membrane Skin Replacement System

Dermal Replacement Layer + silicone layer

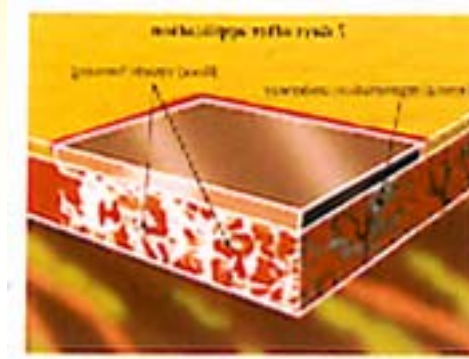


**2 Weeks
Neoderma Formation**



IR

Integra



Neoderma Formation



**Meshed
50 Skin Autograft**

**Silicone Layer
Removal**



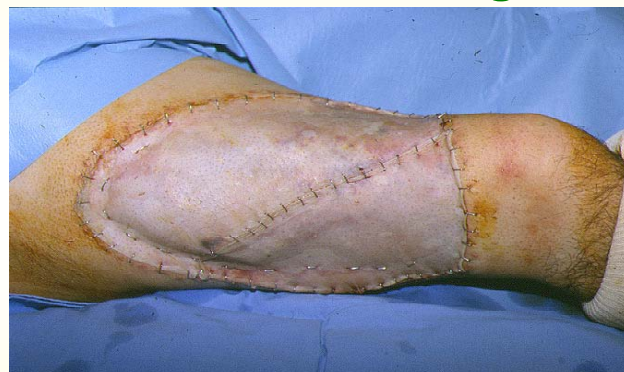
First Georgian Source Accident Lilo 1997



Artificial Skin Graft



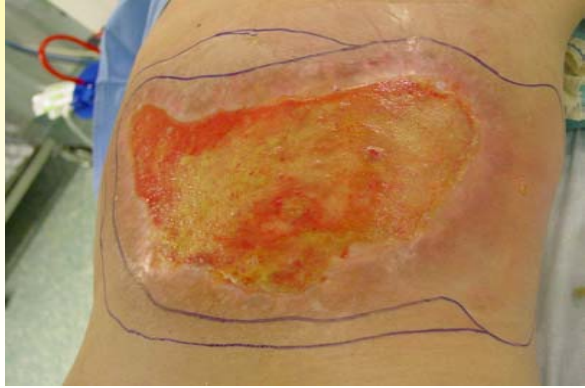
Unmeshed Autograft



Final Aspect



**Second Georgian Accident
Lia 2002
Day 88 P.I.**



Day 140

Intergra Day 110

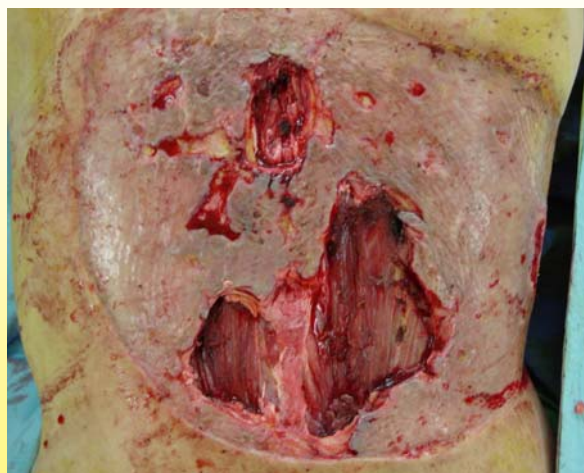


2nd Autograft Day 40

1st Autograft Day 110



Exeresis Day 180



4th Autograft Day 341



Evolution Day 440



OMENTUM



Omentum flap D 440



5th Autograft D 440



Final Aspect D 500 P.I.



Conclusion of the Cutaneous Radiation Syndrome

- ◆ The lesion is dynamic versus time : occurrence of sequence of waves
- ◆ The lesions can occur very late
- ◆ The radiological lesions lasting for more than one month have to be grafted.
- ◆ In any case the wound must left open.
- ◆ Wide and deep excision must be performed beyond of the necrotic tissues
- ◆ The necrosis is deep and can grow after each exeresis
- ◆ Final covering of the lesion by autograft of the lesion must be performed when the lack of the evolution of the wound bed is evident
- ◆ Pain is a prognosis indicator of recurrence
- ◆ The cicatrization is long, fragile and unpredictable

Psychosocial Issues : Major Health Impact

◆ Acute Stress Reactions

- Exposed and Unexposed Persons
- Some of these reactions could mimic radiation overexposure (Nausea, Vomiting, Rashes)
- Anxiety attack, Hysterical attack, Headlong Flight, Stupor

◆ Chronic Reactions

- Social withdrawal, Impaired Concentration, Insomnia, Chronic Anxiety
- Deterioration in Quality of Life
- Post Traumatic Stress Disorder

◆ Social Stigma Social Discrimination (Goiania Accident)

➔ Early Psychological Care of Victims

➔ Post-accidental Epidemiology
Issue of the census of exposed and implicated population



Cytokine-based treatment for radiation-induced myelo- and/or immune suppression

Available now:

Granulocyte colony-stimulating factor (G-CSF)

Granulocyte-macrophage colony-stimulating factor (GM-CSF)

Pegylated G-CSF (Peg-G-CSF)

Future?

Single cytokine treatment

Interleukin- 7 (IL-7)

Keratinocyte growth factor (KGF)

flt-3 (FL)

Thrombopoietin (TPO)