System Responses to Low-Level Radiation Exposure

New Concepts in Radiobiology

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5th Annual International Conference on Hormesis:
Implications for Toxicology,
Medicine and Risk Assessment
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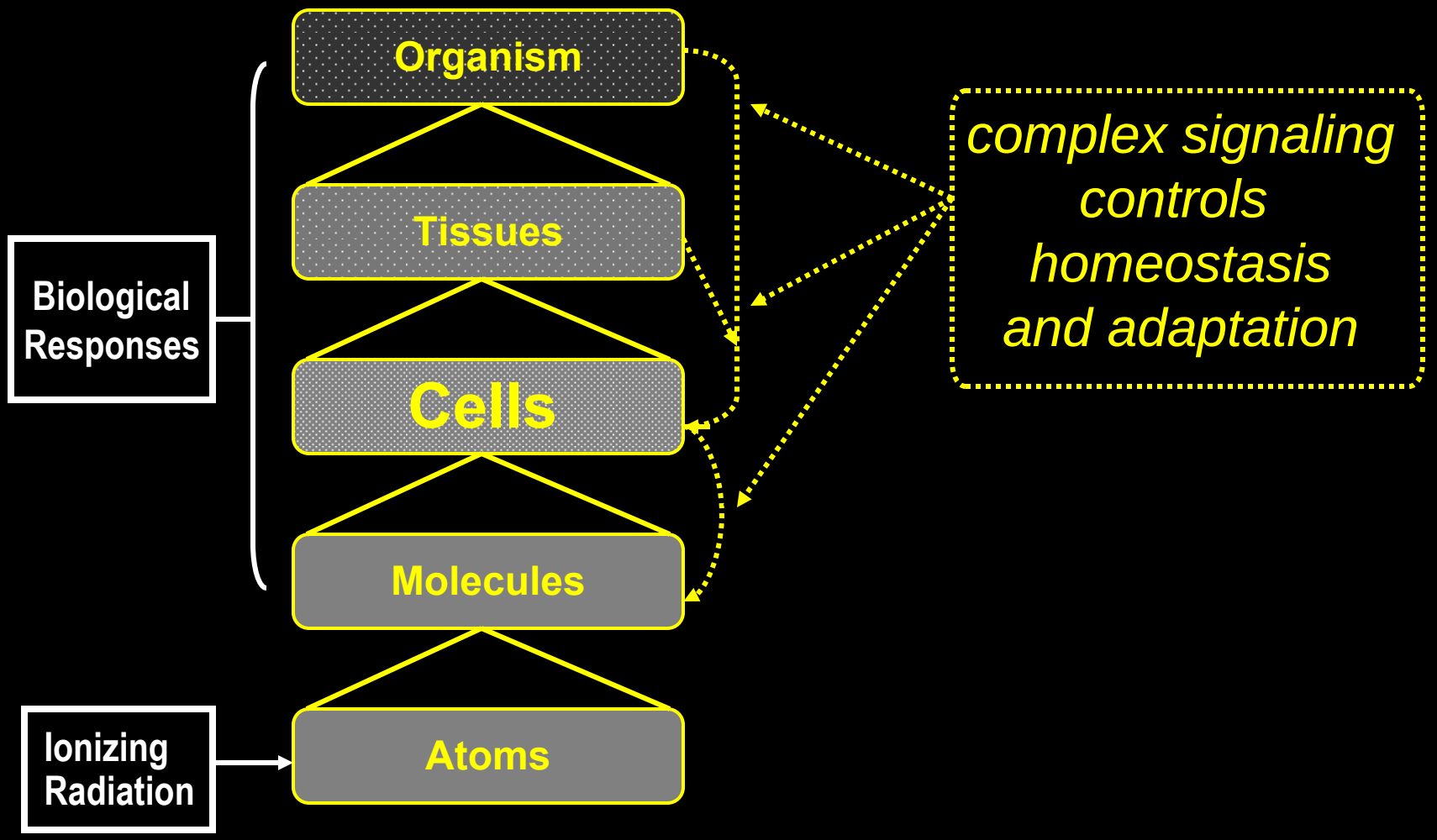
Biological Systems, Levels of Organization and Function



Agenda

Dose	1. Energy deposition in primary target
Effects	2. Primary DNA damage response
	3. Immediate and adaptive protection gene-controlled throughout system
Analysis	4. A model assessing effects from acute exposure, chronic exposure

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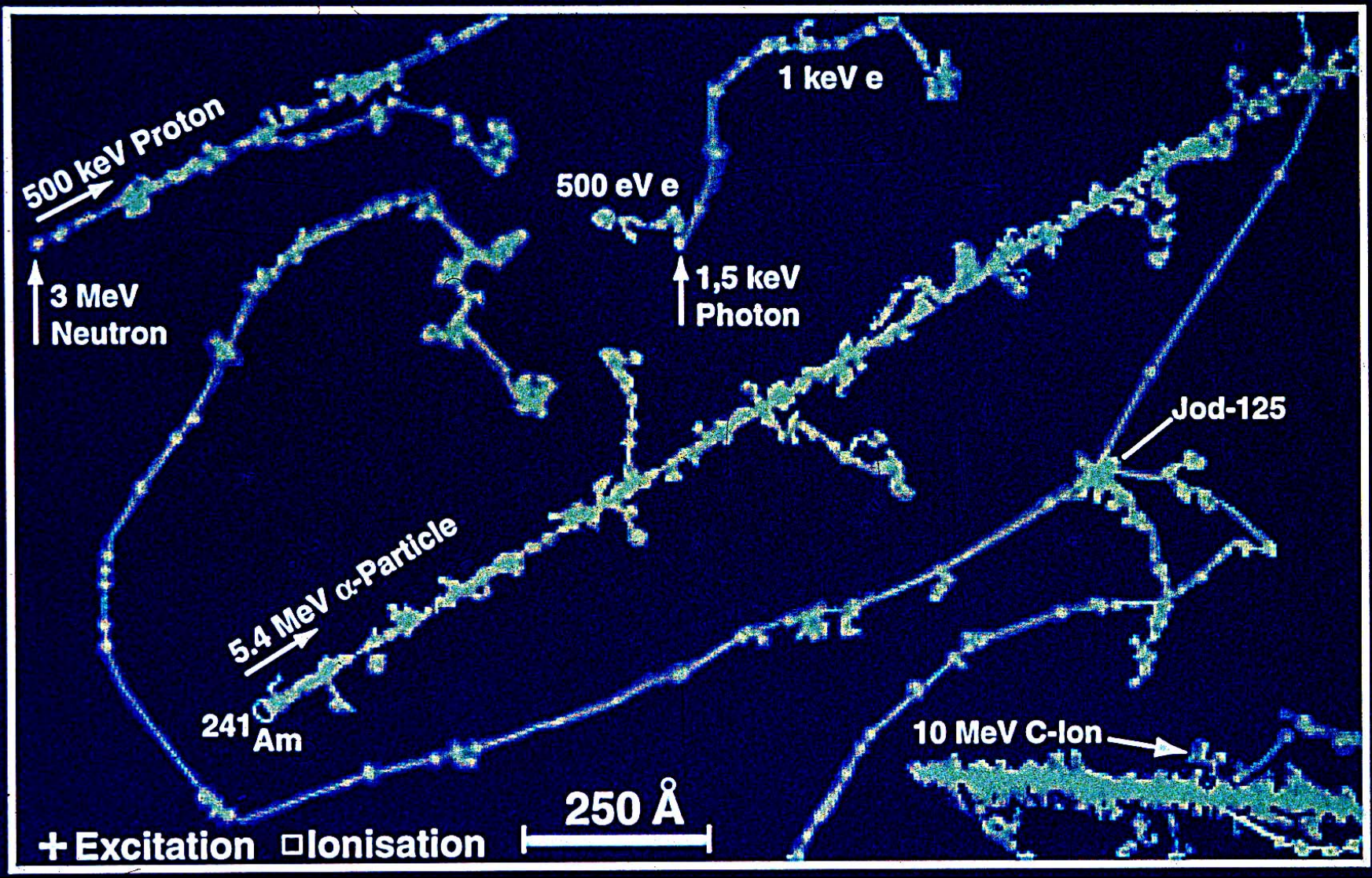
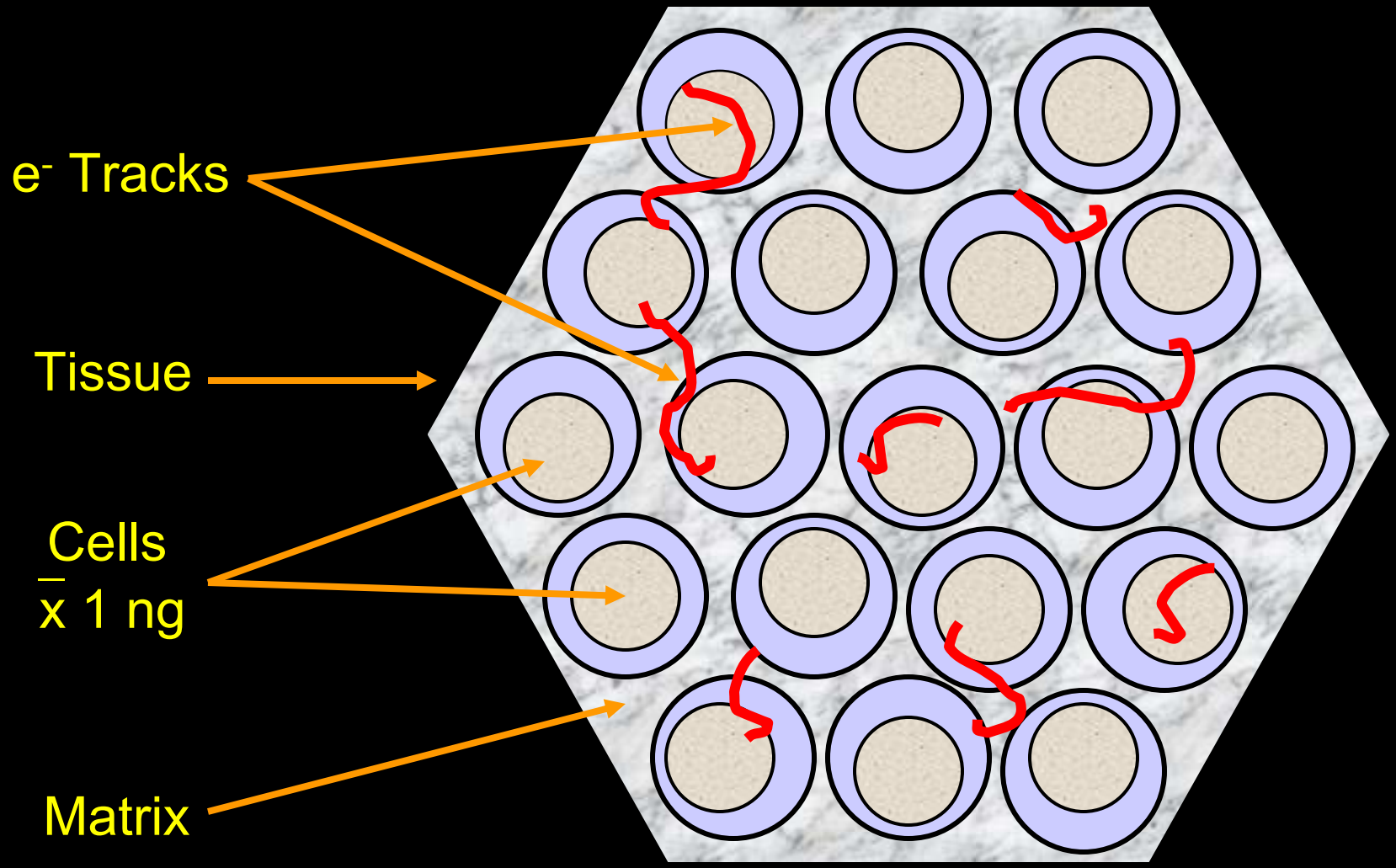
Individual Particle Tracks in Water



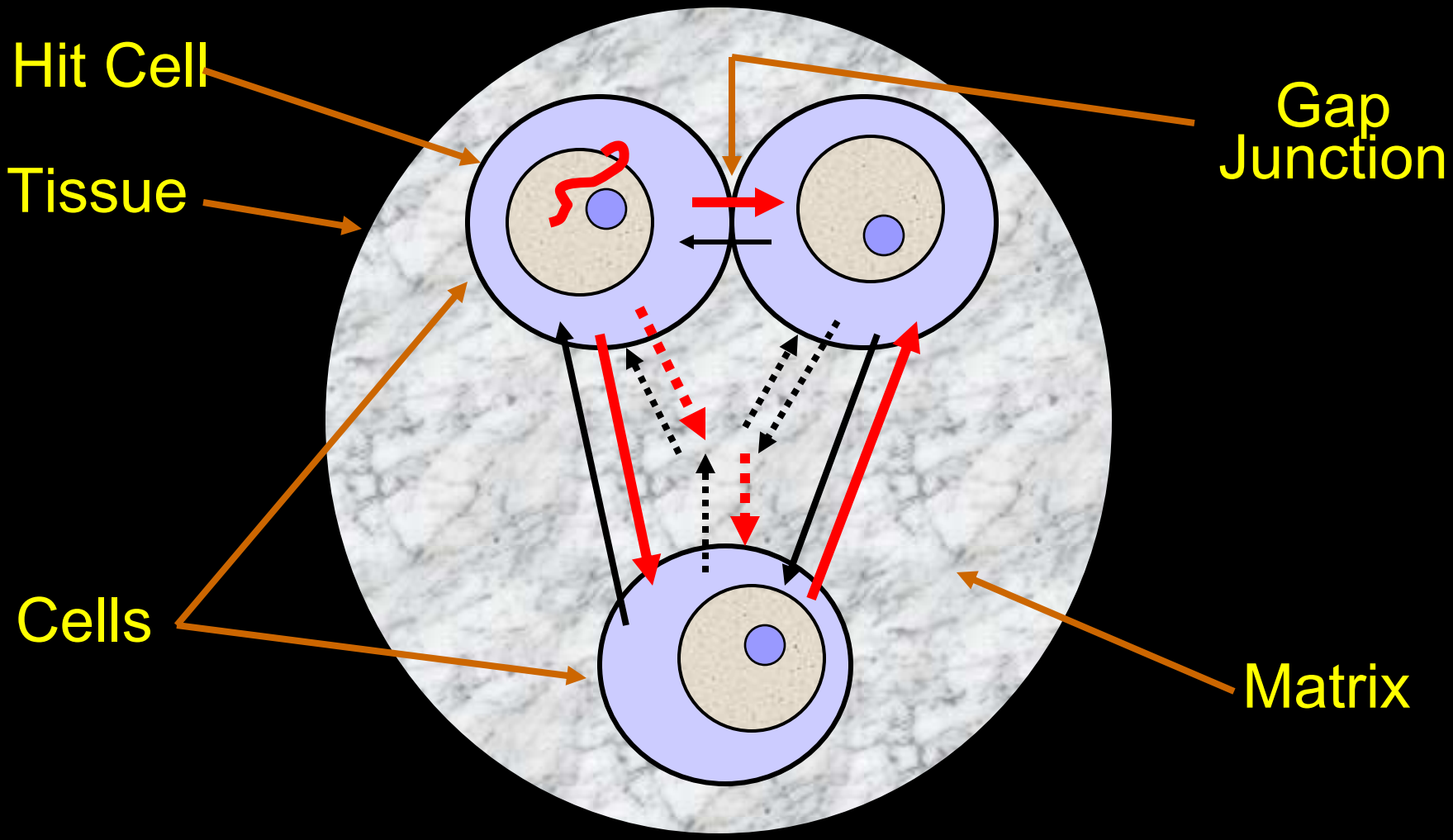
On average, ~ 30 reactive oxygen species (ROS) are produced per absorbed keV

X-Ray Induced Electron Tracks in Tissue



Dose is proportional to number of tracks / exposed mass

Bystander Effects



Signaling between Cells and Matrix in Tissue

For quantifying low-level irradiation
the term dose should be restricted
to
energy imparted to the mass of average cell
(micro- or mini-dose)
and
energy imparted to tissues
should be expressed as multiples
of defined micro- or minidose events.

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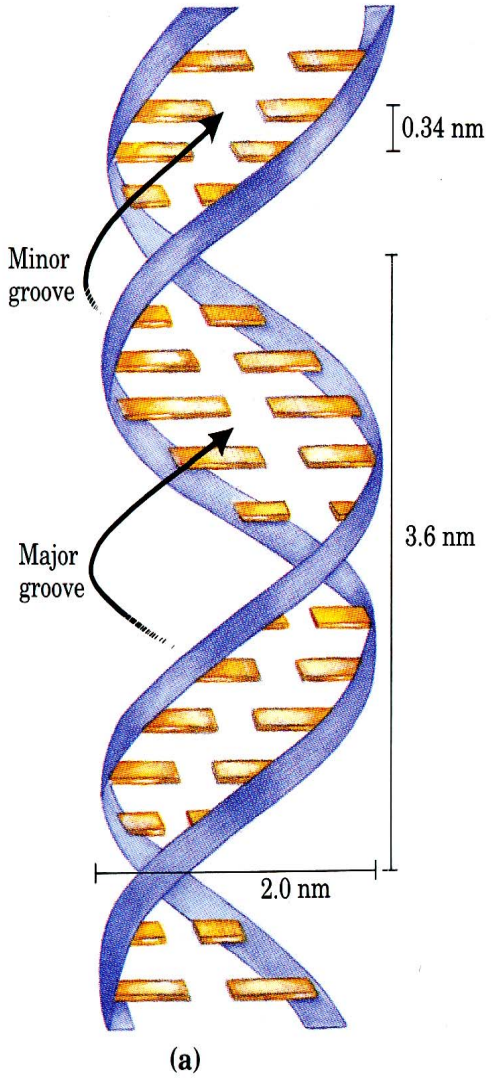
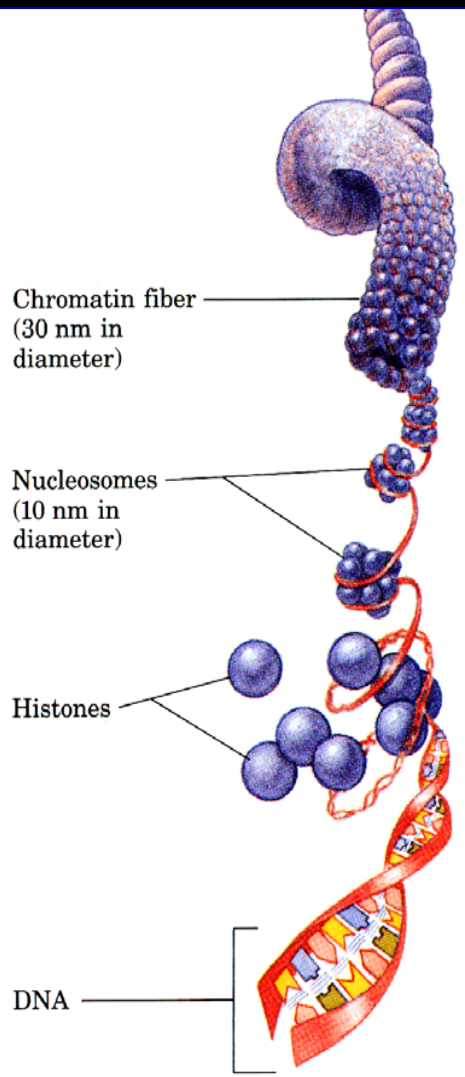
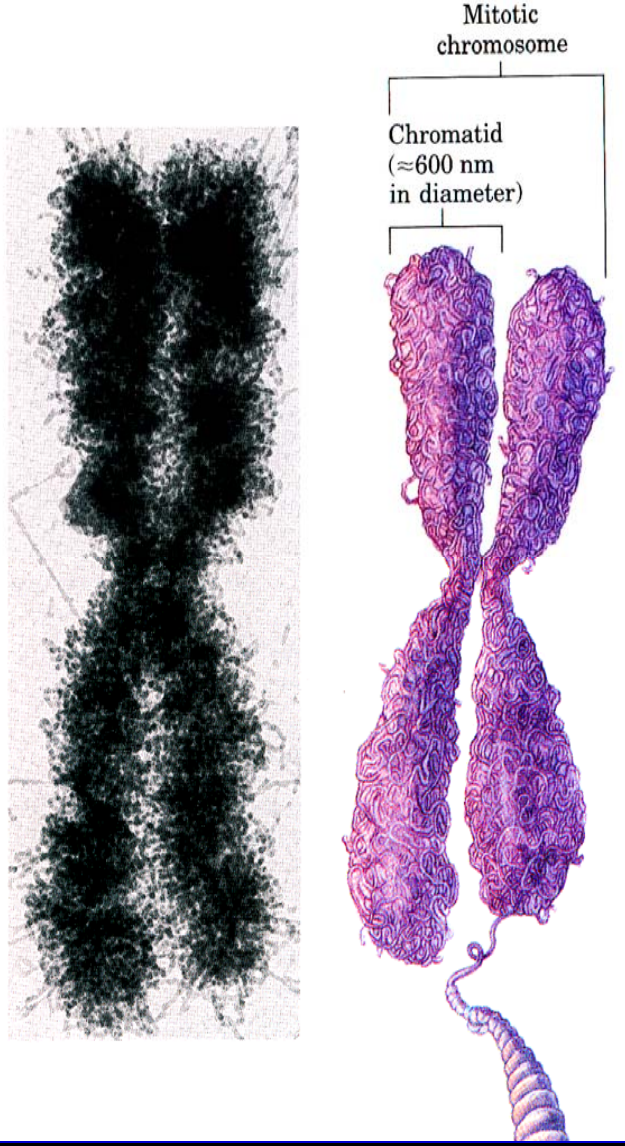
DNA Organization to Chromosomes

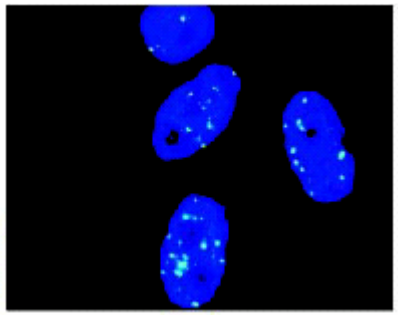




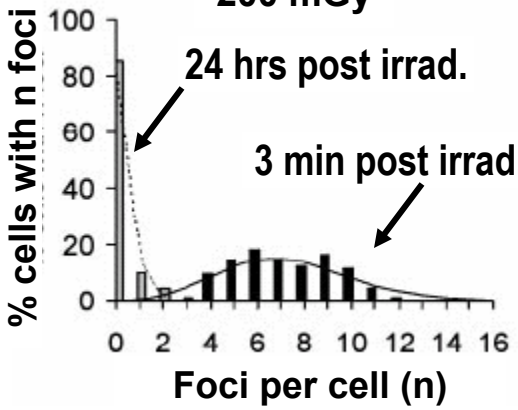


Lehninger et al., Principles of Biochemistry, Worth Publ., 1992

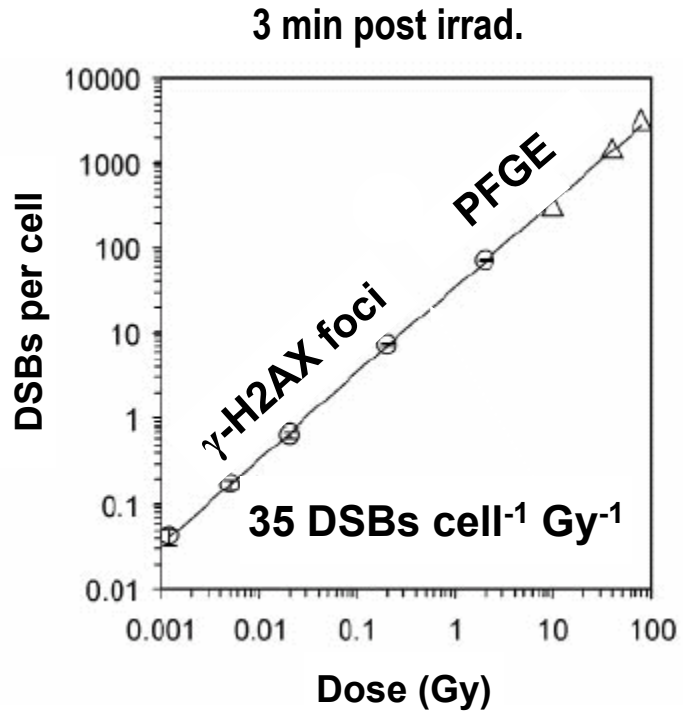
Radiation-Induced DNA-DSB
in γ-irradiated MRC-5 cells in culture



200 mGy



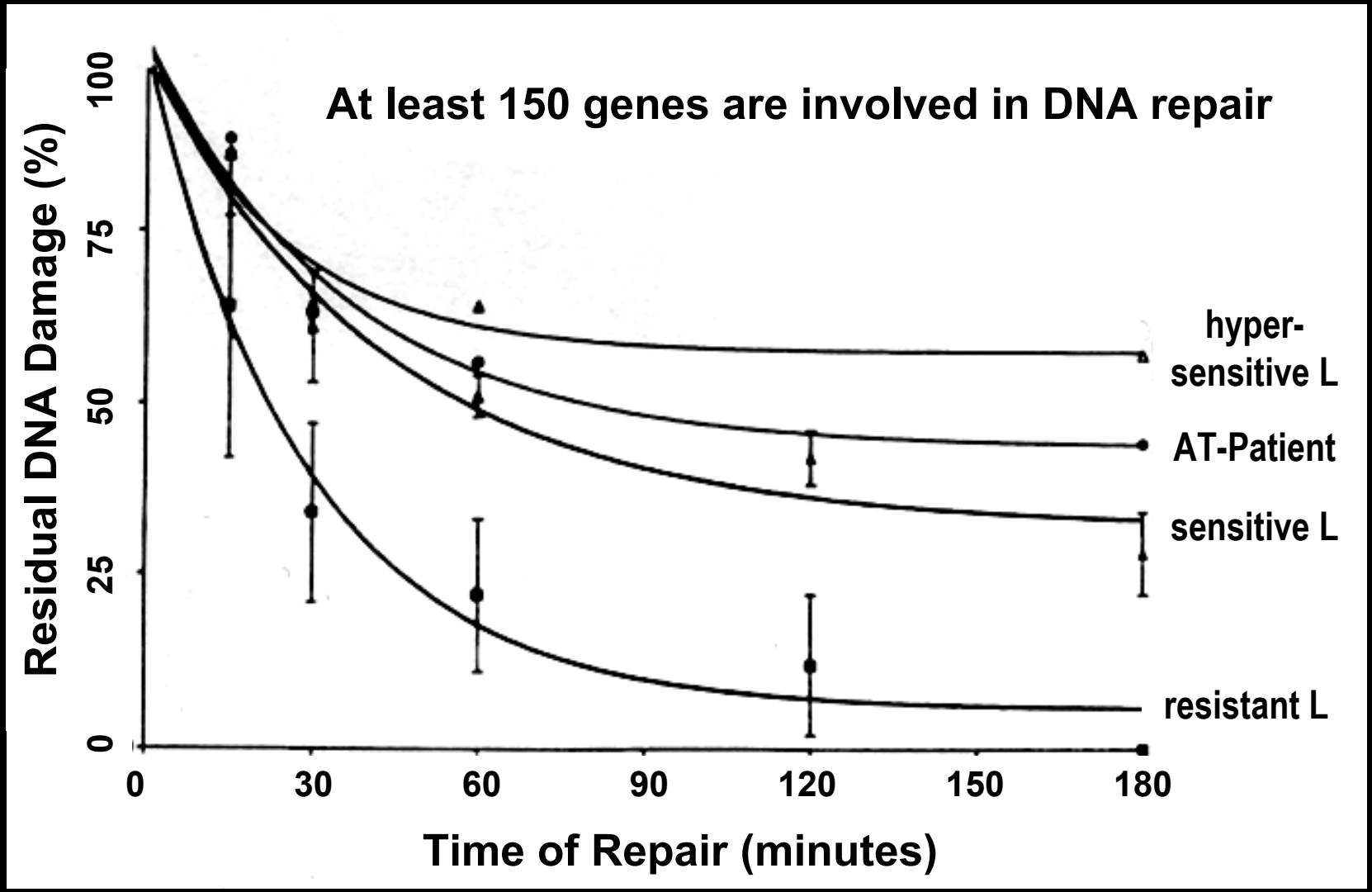
γ-H2AX foci distribution



spont. DSB ≅ $\bar{x}$ 0.04 – 0.06 / cell at steady state

Rothkamm K, Löbrich M, PNAS, 2003

DNA Repair in Lymphocytes (L) in Culture



Müller WU et al., 2001

Ludwig Feinendegen:

nary DNA damage may also cause
genomic instability in the cell's progeny
likely depending on dose.

Genomic instability

may

- enhance malignant cell transformation

but also

- tag damaged cells for removal

by immune response or apoptosis

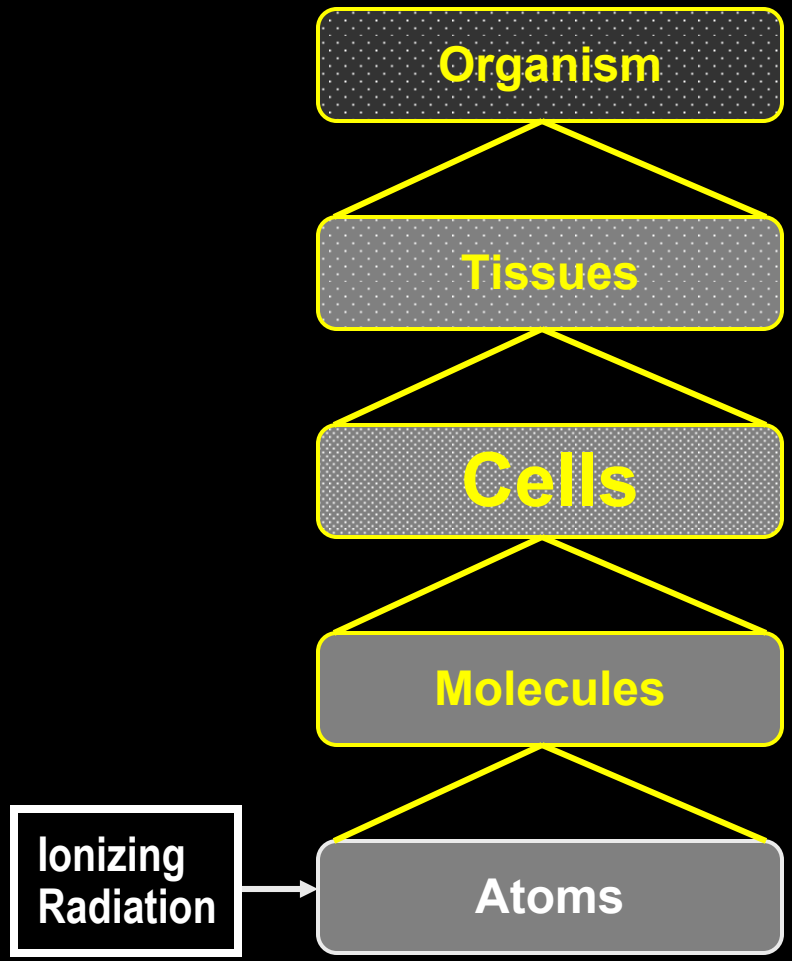
Primary DNA damage rises linearly with dose and may also cause secondary DNA damage.

DNA damage may cause cancer.

This has lead to the assumption that the probability of cancer occurs proportionally with initial DNA damage.

Is this true ?

Complex Adaptive Systems
Levels of Organization



Risk per Human Stem Cell per 1 mGy from 100 kV x-rays projected for blood forming tissue by extrapolation from high to low D

$\sim 10^{-14}$ Malignant transformation with death of individual

?

$\sim 10^{-4}$ Chromosomal aberr.

$\sim 10^{-2}$ DNA - DSB

~ 2 $\sum$ DNA alterations

~ 150 ROS

Feinendegen et al., Stem Cells, 1995

Agenda

Dose	1. Energy deposition in primary target
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Analysis	4. A model assessing effects from acute exposure, chronic exposure

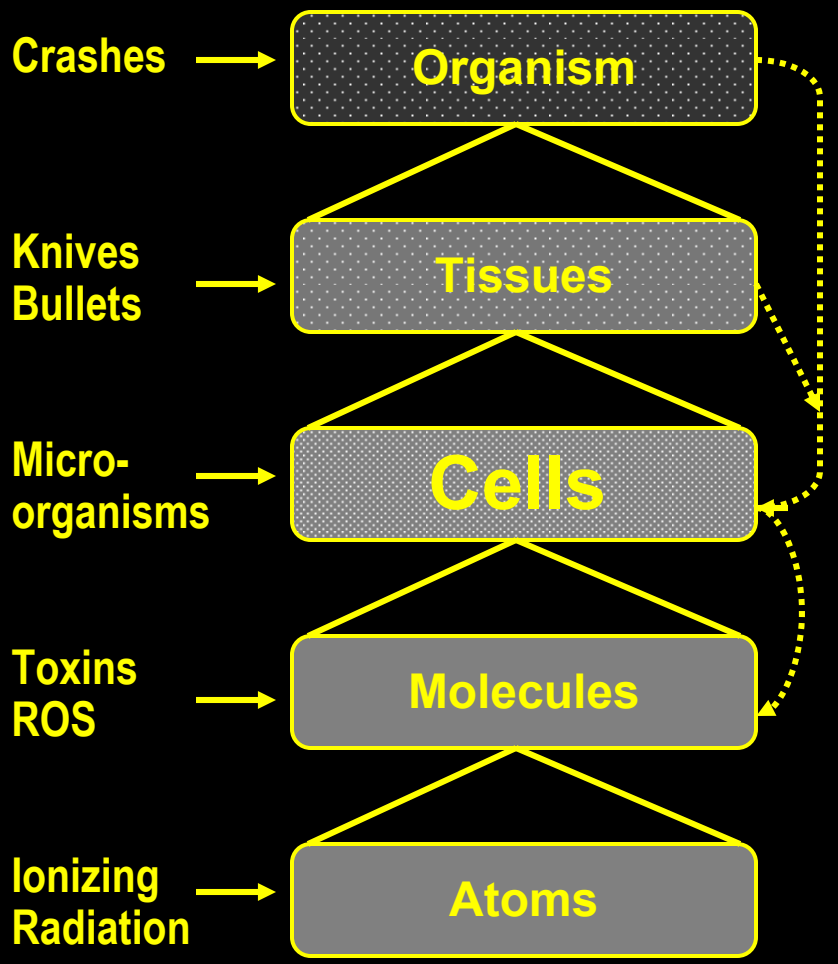
Immediate Protection

direct responses

of existing physiological barriers

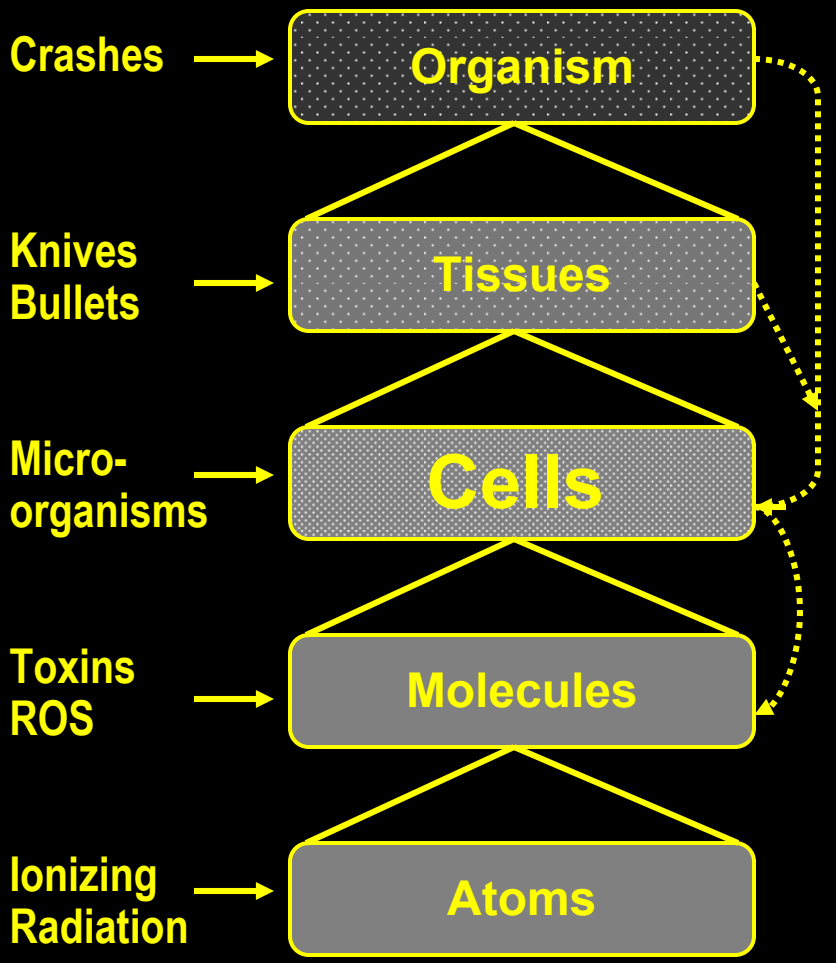
against disease

Complex Adaptive Systems, Threats at Various Levels



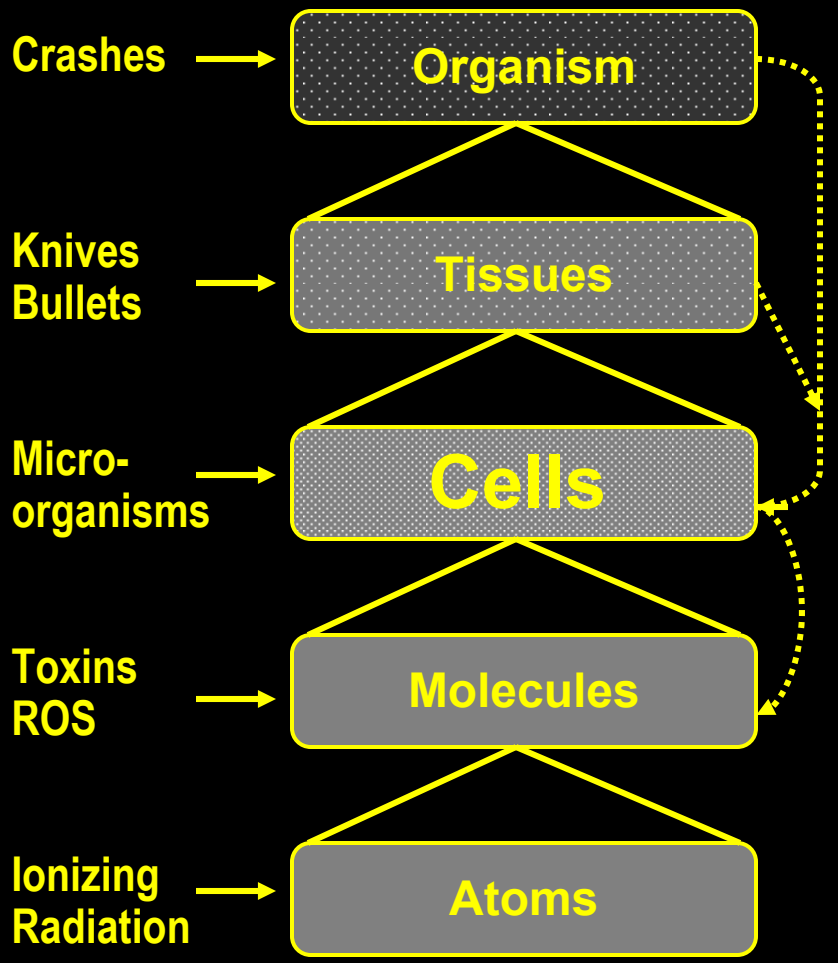
Complex Adaptive Systems, Threats at Various Levels

Immediate Physiological Barrierrs against Disease



Defense, Scavenging

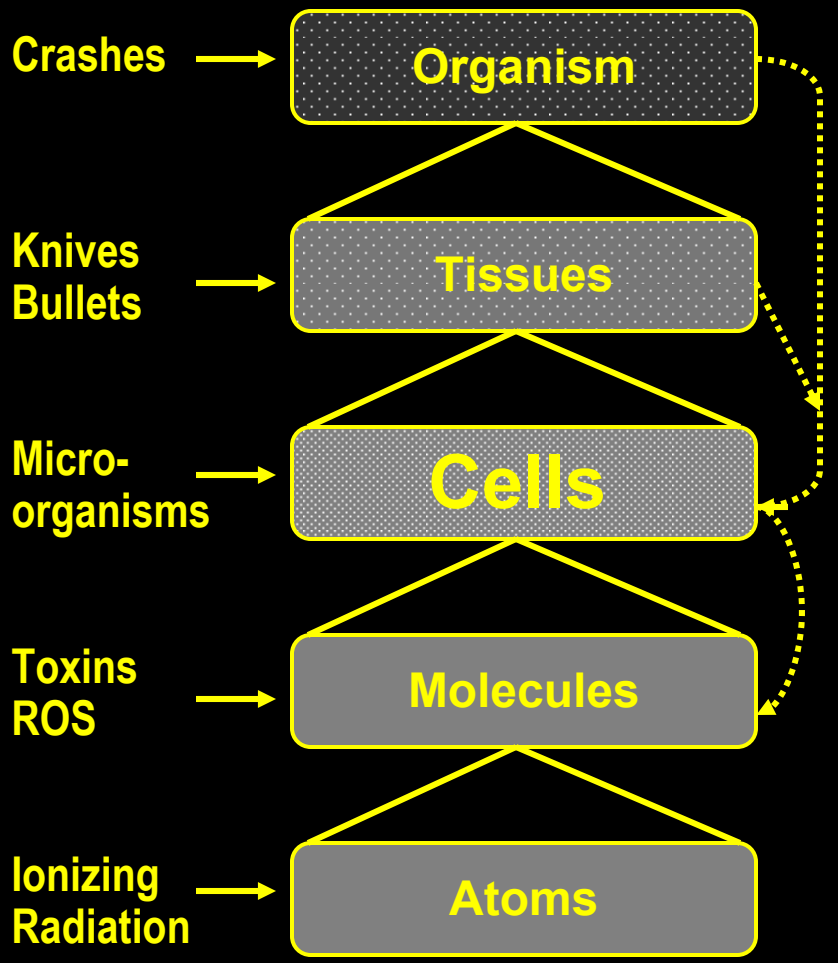
Complex Adaptive Systems, Threats at Various Levels



Immediate Physiological Barrierrs against Disease

DNA Repair
Defense, Scavenging

Complex Adaptive Systems, Threats at Various Levels

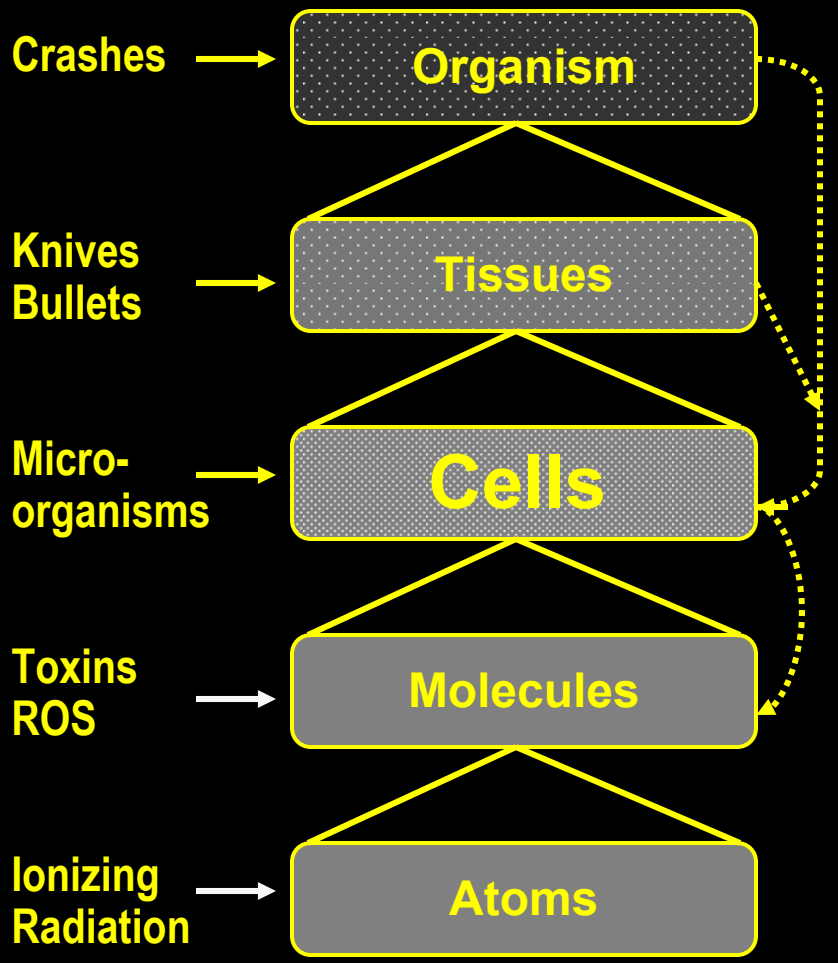


Immediate Physiological Barrierrs against Disease

- Cell Differentiation
  Apoptosis
- DNA Repair
  Defense, Scavenging

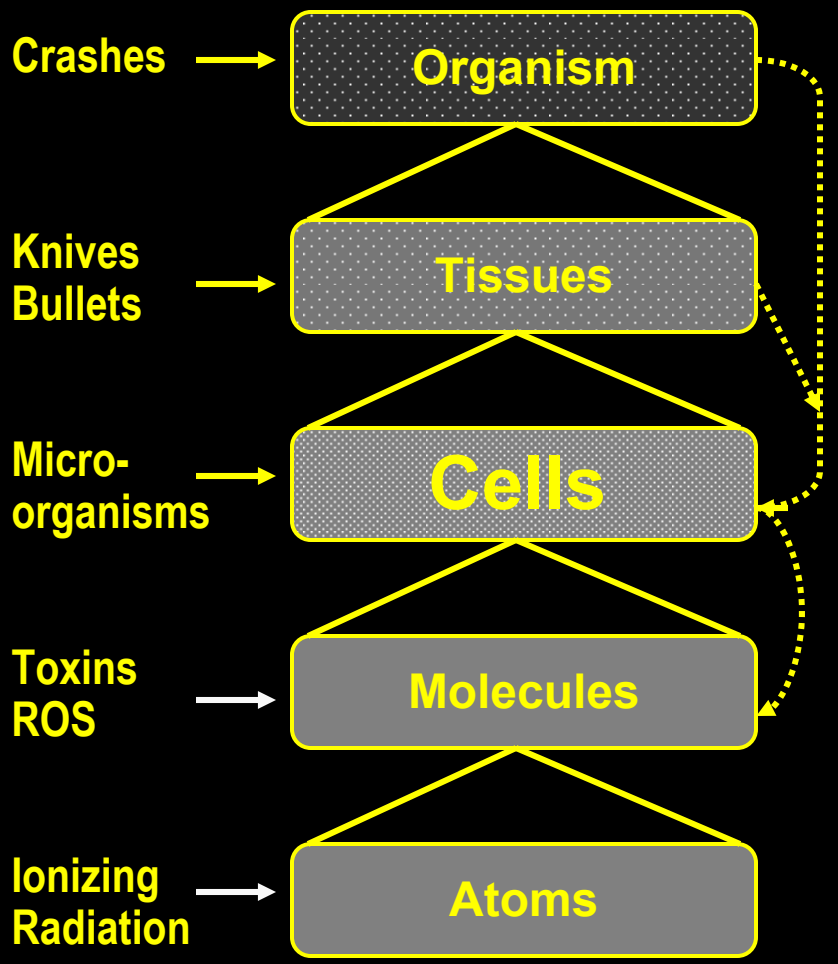
Complex Adaptive Systems, Threats at Various Levels

Immediate Physiological Barrierrs against Disease



- Immune Response
- Cell Differentiation
  Apoptosis
- DNA Repair
  Defense, Scavenging

Complex Adaptive Systems, Threats at Various Levels



Immediate Physiological Barrierrs against Disease

Death

Cancer

Pathology

- Immune Response
- Cell Differentiation
  Apoptosis
- DNA Repair
  Defense, Scavenging

The immediate physiological barrierrs

against disease

are genetically controlled

and known to operate

not proportional to the degree of toxic impact

(deterministic type of responses).

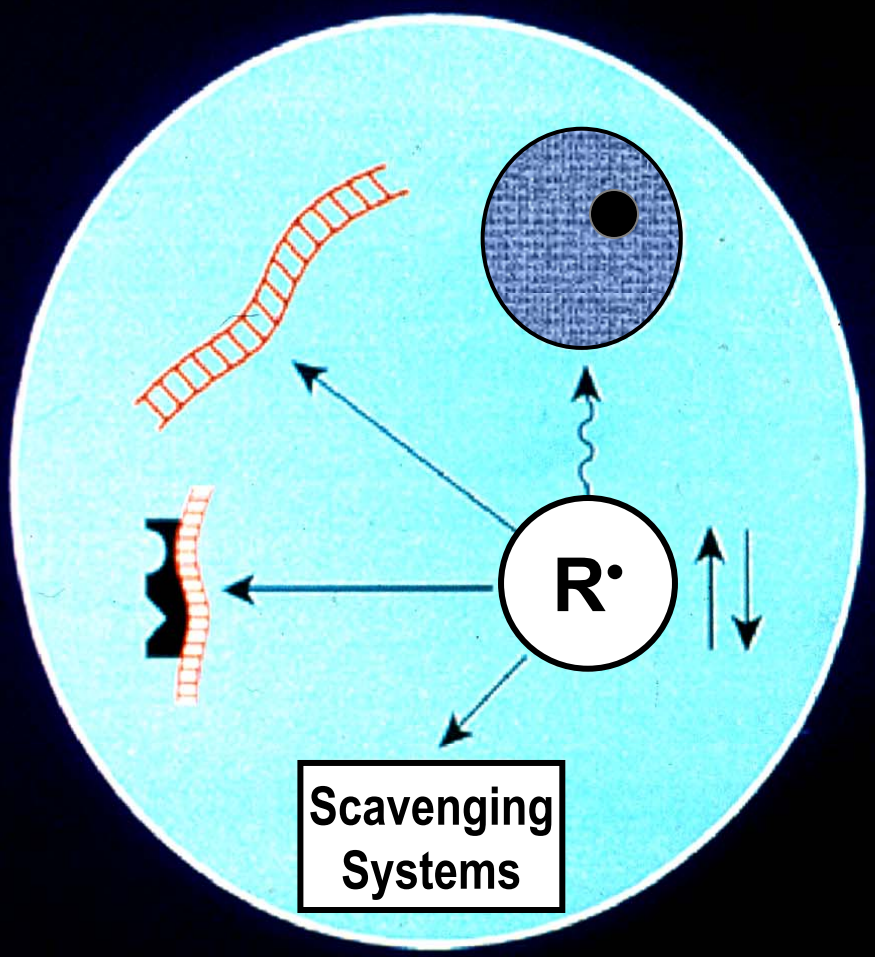
Adaptive Protection

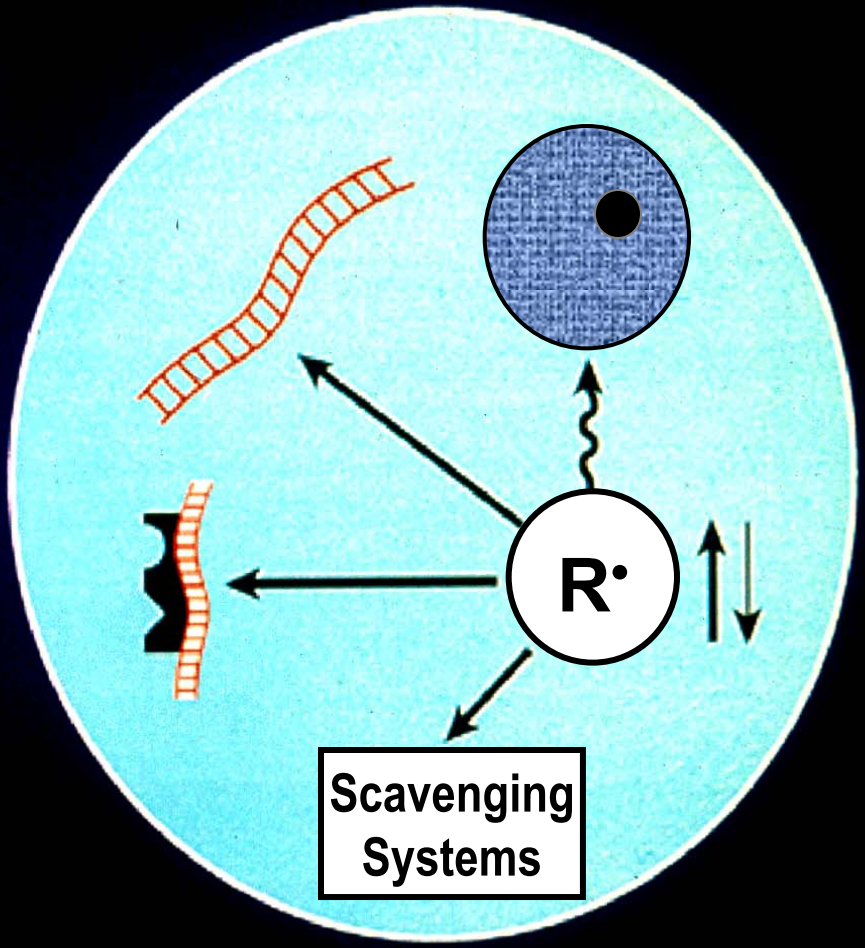
delayed responses

such as stress-responses

to non-destructive amounts of toxins

Reactive Oxygen Species, ROS, in Cells





In normal cytoplasm
~ 10^4 ROS / cell / second

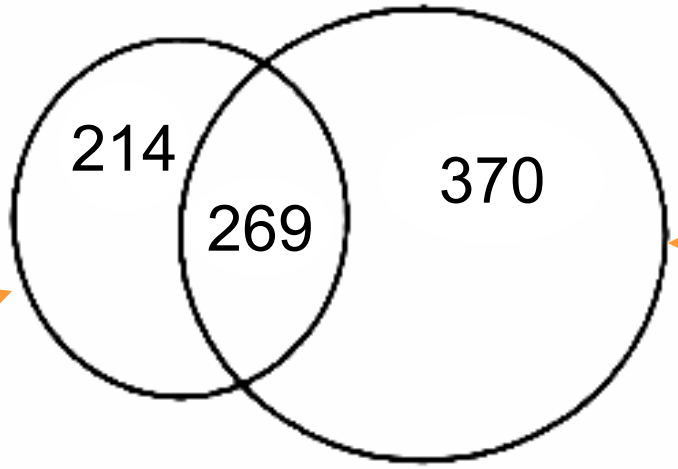
Low-dose x-irradiation
~ 150 ROS / e^- hit (6 keV)

Low-Dose Effect on Gene Expression

cDNA microarray analysis in human keratinocytes after low and high dose γ-irradiation

1 cGy

stress response genes mainly



2 Gy

853 of 10,500 genes modulated between 3 – 72 hr

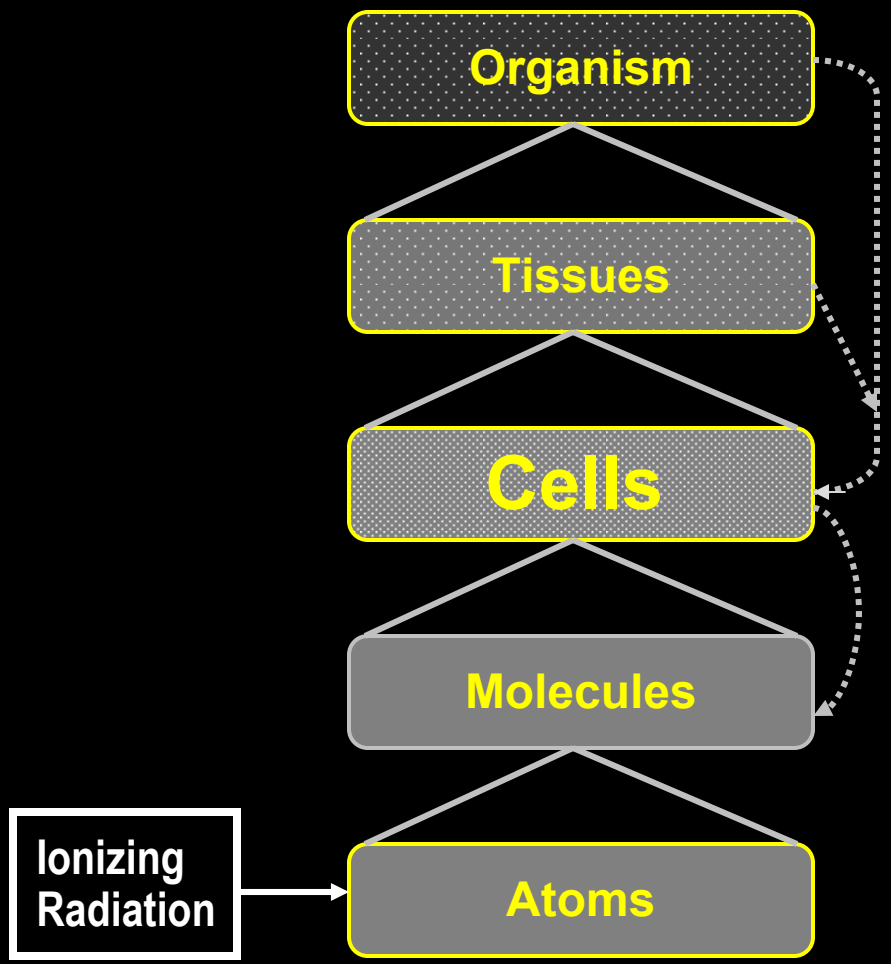
Franco N et al., Radiat. Res. 163: 623 – 635, 2005

Cell Responses to Oxidative Stress
(damage and ROS signaling)

↑	Damage to DNA, Lipids, Proteins (Carbonylation)	→	*Cell Damage*
↓	Cystein Function in DNA Binding Proteins	→	*Gene Expression*
↑↓	Transcription Factors	→	*Gene Expression*
↑	Different Growth Factors	→	*Gene Expression*
↑	ERK [Extracell. Signal-Regul. Kinase]	→	*Survical*
↑	PI(3)K/Akt [Phosphoinositide-3-Kinase]	→	*Survival*
↑	NFκB [Nuclear Factor κB]	→	*Survival*
↑	Hsp-70 [Heat Shock Protein 70]	→	*Survival*
↑	Nuclear Translocation of NFκB	→	*Survival*
↑	p53 [Regulatory Protein]	→	*Apoptosis*
↑	$p66^{she}$ Serine Kinase	→	*Apoptosis*
↑	JNK [c-Jun Amino-Terminal Kinase]	→	*Apoptosis*
↑	MAPK [p-38 Mitogen-Activated Protein Kinase]	→	*Apotposis*
↓	G-SH Tranferase Bonds to JNK	→	*Apoptosis*
↓	Thioredoxin Bonds to ASK1	→	*Apoptosis*

Finkel and Holbrook, Nature, 2000

Complex Adaptive Systems
Levels of Organization



Adaptive Protection by
Delayed Upregulation of Barriers

Death

Cancer

Pathology

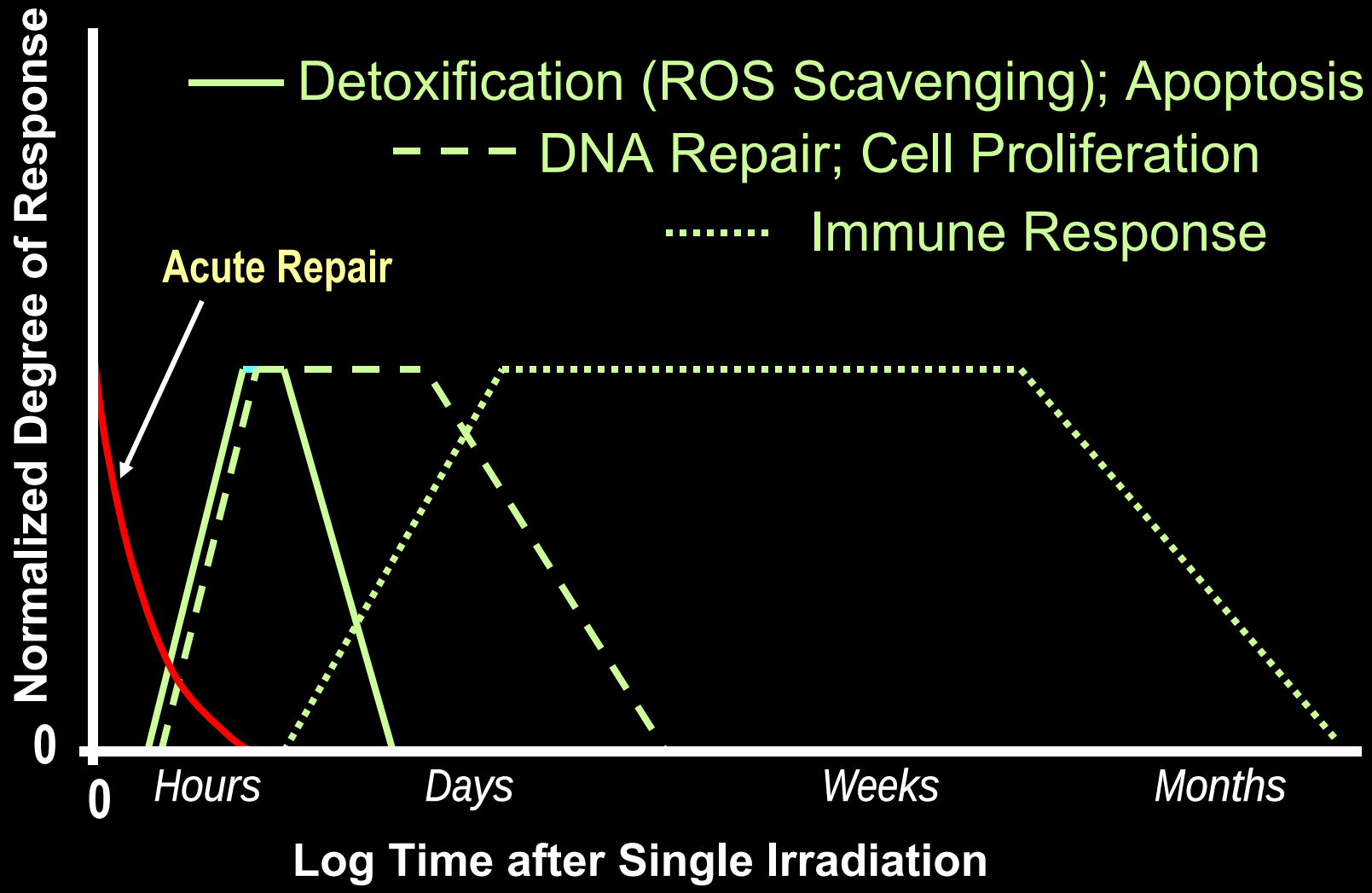
Immune Response

Cell Differentiation
Apoptosis

DNA Repair
Defense, Scavenging

Low-Dose (Low-LET) Induced Adaptive Protection

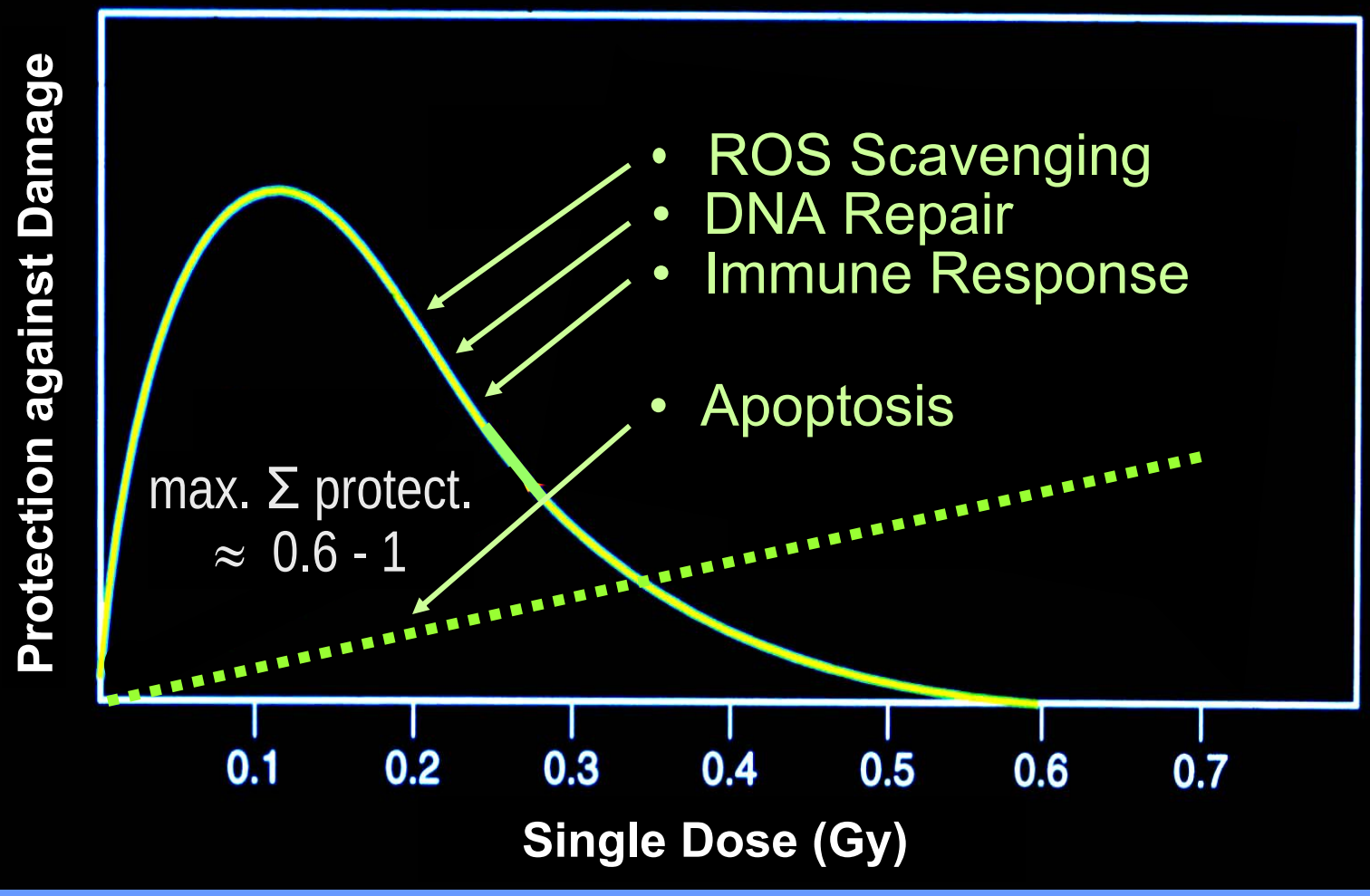
scheme of durations of protection (t_p)



Low-Dose (Low-LET) Induced Adaptive Protection

scheme of dose-response functions

dose-response functions are mostly not linear



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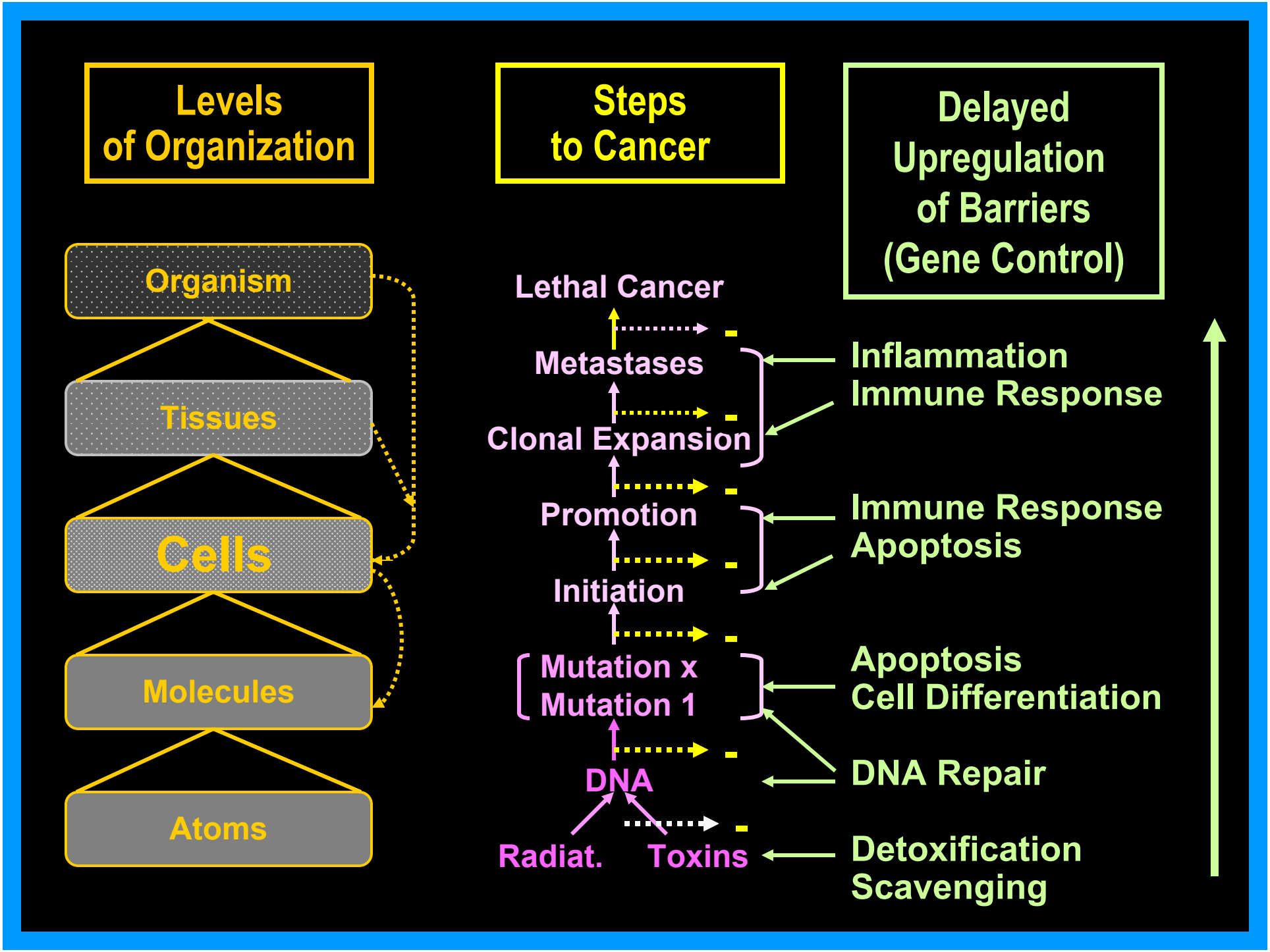
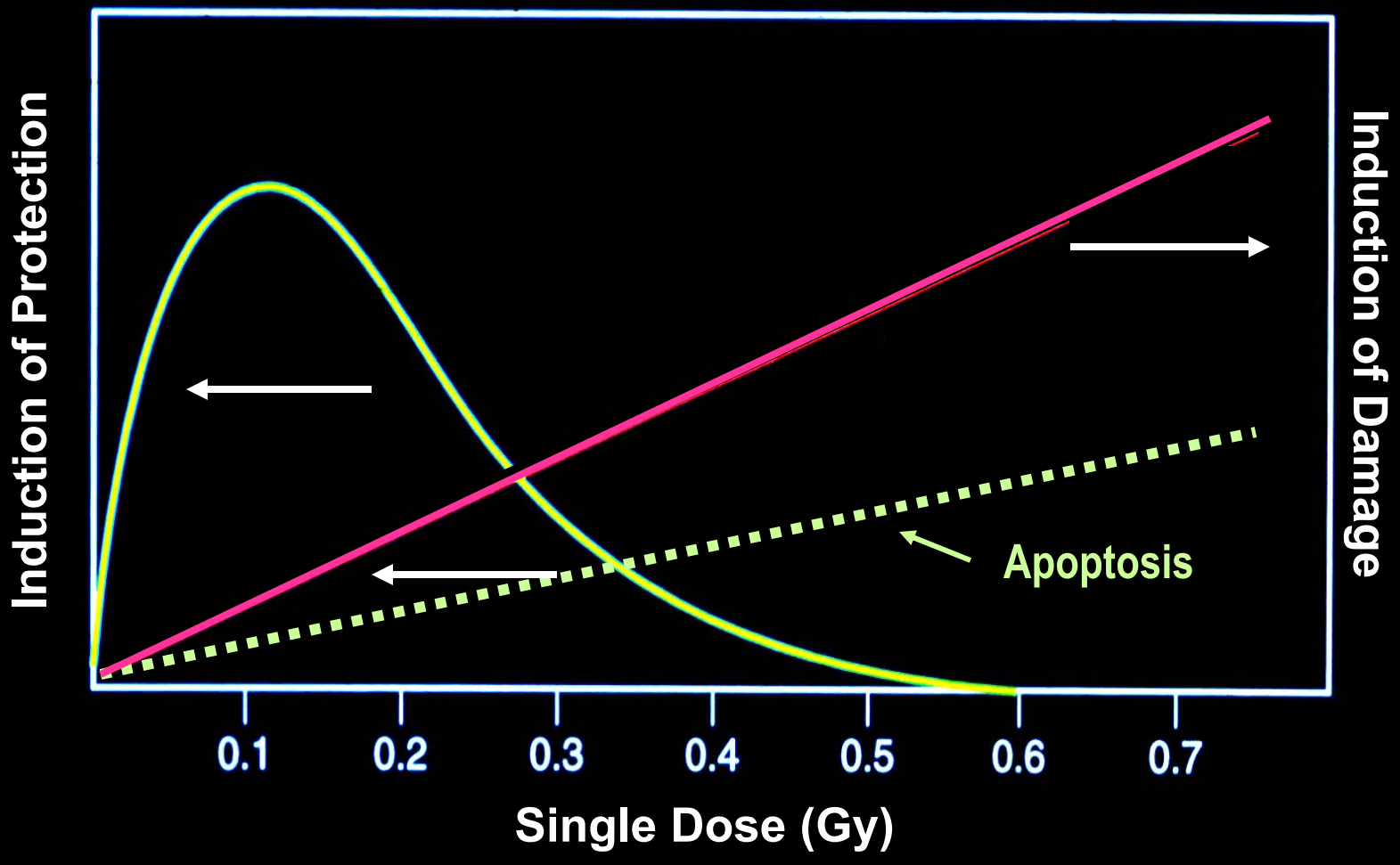
Assessing effects from acute exposure


Levels of Organization
Steps to Cancer
Delayed Upregulation of Barriers (Gene Control)
Organism
Tissues
Cells
Molecules
Atoms
Lethal Cancer
Metastases
Clonal Expansion
Promotion
Initiation
Mutation x
Mutation 1
DNA
Radiat.
Toxins
Inflammation
Immune Response
Immune Response
Apoptosis
Apoptosis
Cell Differentiation
DNA Repair
Detoxification
Scavenging

Dual Effect of Low-Dose (Low-LET) Radiation

Induction of protection ..... induction of damage



Adaptive protection also operates

against

non-radiogenic gene-, cell- and tissue damage

"Metabolic" cancer is at least

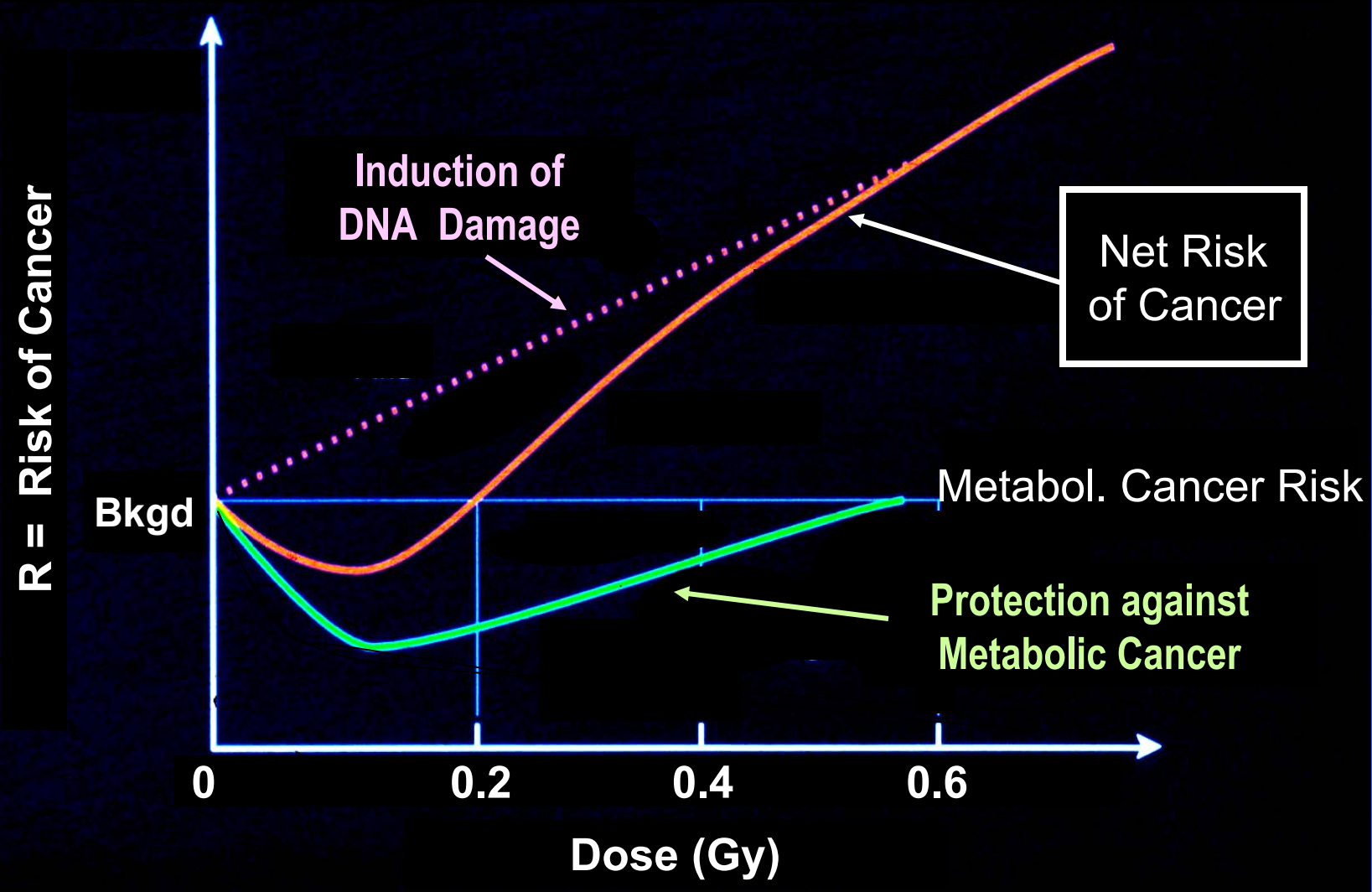
~ 30 to 50 times more frequent

than cancer from background radiation

(per $\bar{x}$ cell: ~ 1000 metab. DSB / 1 backgrd. rad. DSB)

Dual Effect of Low-Dose (Low-LET) Radiation

simplified scheme



Assessing effects from chronic exposure

Tissue low-dose chronic exposure

is expressed conventionally

in terms of absorbed dose per unit time.

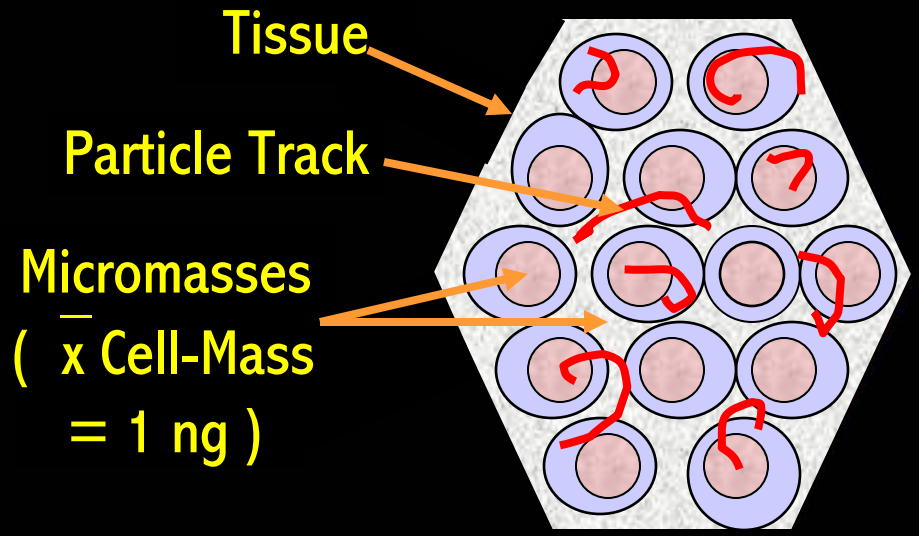
For whole system low-dose chronic exposure

it is more meanigful to scale effects to

numbers of microdose events

per unit time

From Absorbed Dose to Number of Microdose Events in Exposed System



M = Mass of exposed tissue

N_E = No of exposed micromasses

N_H = No of particle hits in N_E

z_1 = Energy abs. per micromass per hit (Microdose)

$$D = E/M = \sum z_1/N_E = [\sum z_1/N_H] \cdot [N_H/N_E]$$

$$\bar{D} = \bar{z}_1 \cdot [N_H/N_E]$$

Bond et al., Int. J. Radiat. Biol., 1988

Some $\bar{z}_{F1}$ Values (mGy) Commonly Used

^{60}Co γ-rays	~ 0.3 mGy
^{137}Cs γ-rays	~ 0.4 mGy
250 kVp x-rays	~ 0.9 mGy
100 kVp x-rays	~ 1.0 mGy
^{3}H β-rays	~ 1.0 mGy
10 MeV protons	~ 6.0 mGy
4 MeV α-particles	~ 350.0 mGy

Modified from: ICRU Report 36, 1983, 1993

Dose Rate in Microdosimetry Terms

$$\bar{D}/t = \bar{z}_1 \cdot [N_H/N_E] \cdot 1/t = \bar{z}_1/t_X$$

$$t_X = t\,[N_E/N_H]$$

$t_X = \bar{x}$ time interval
between two consecutive microdose events
per exposed micromass

The effect of chronic exposure depends on the mean time interval (t_x) between two consecutive microdose events per exposed micromass.

t_x determines effectiveness of direct protection and adaptive protection.

Dose Rate Effects
chronic exposure to tritiated water in mice

Thymic Lymphoma Induction

and

Life Shortening

only appears when dose rate is above 1 mGy / day

($\bar{x}$ ~ 1 mGy-hits; t_x < 1 day)

$\bar{z}_1$ = ~ 5.7 keV / ng ~ 1 mGy

Yamamoto O. et al., Int. J. Rad. Biol. 1998

Dose Rate Effects
chronic whole body ^{60}Co γ-irradiation mice

Life Shortening

only begins when dose rate is above 7 mGy / day

($\bar{x}$ ~ 0.3 mGy-hits: t_x < 1 hr)

Lorenz E. Am. J. Roentg. Rad. Ther, 1950)

Failla and Clement, Am. J., Roentg., 1957)

Grahn et al., ANL Rep. 7635, 1969

Yamamoto O., et al., Int. J. Rad. Biol. 1998)

$\bar{z}_1$ = ~ 2 keV / ng ~ 0.3 mGy

Zablotska LB et al. in 2004 published the mortality among 45,468 Canadian nuclear power industry workers after chronic low-dose exposure to ionizing radiation:

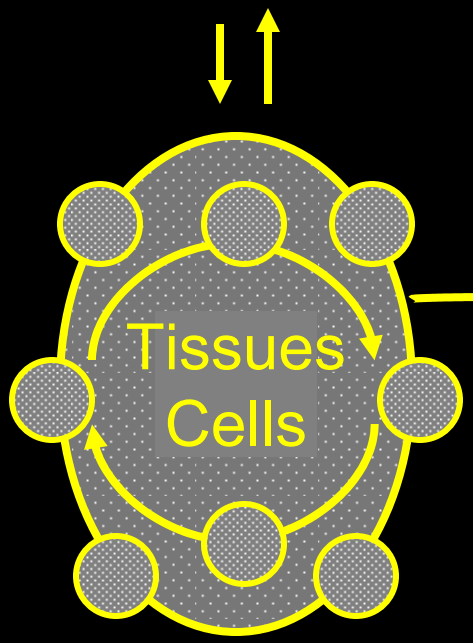
For all solid cancers combined, the categorial analysis shows a significant reduction in risk in the 1- 49 mSv category compared to the lowest category (<1 mSv) with a relative risk of 0.699 (95% CI: 0.548, 0.892).

Above 100 mSv, risk appeared to increase.

Zablotska LB et al., Radiat. Res., 2004

Summary
Biological systems exposed to ionizing radiation

Organism



Direct protection,
and low-dose induced
adaptive protection
block damage propagation
not linearly with dose

Primary DNA damage
rises linearly with dose;
secondary DNA damage
does not rise linearly
with dose.

Conclusion 1

System responses to low-level exposures depend on

- quality and number of energy depositions in tissue micromasses (microdoses),
- time interval between two microdose events per exposed micromass,
- pattern of responses to microdose events.

Conclusion 2

2. System responses to acute or chronic low-level exposures are not linear, in agreement with experimental and epidemiological data. Single tissue doses below $\cong$ 0.1 Gy tend to bring benefit rather than detriment.

Conclusion 3

3. Quality and extent of system responses are under genetic control. Thus, biological responses are expected to vary among individuals.

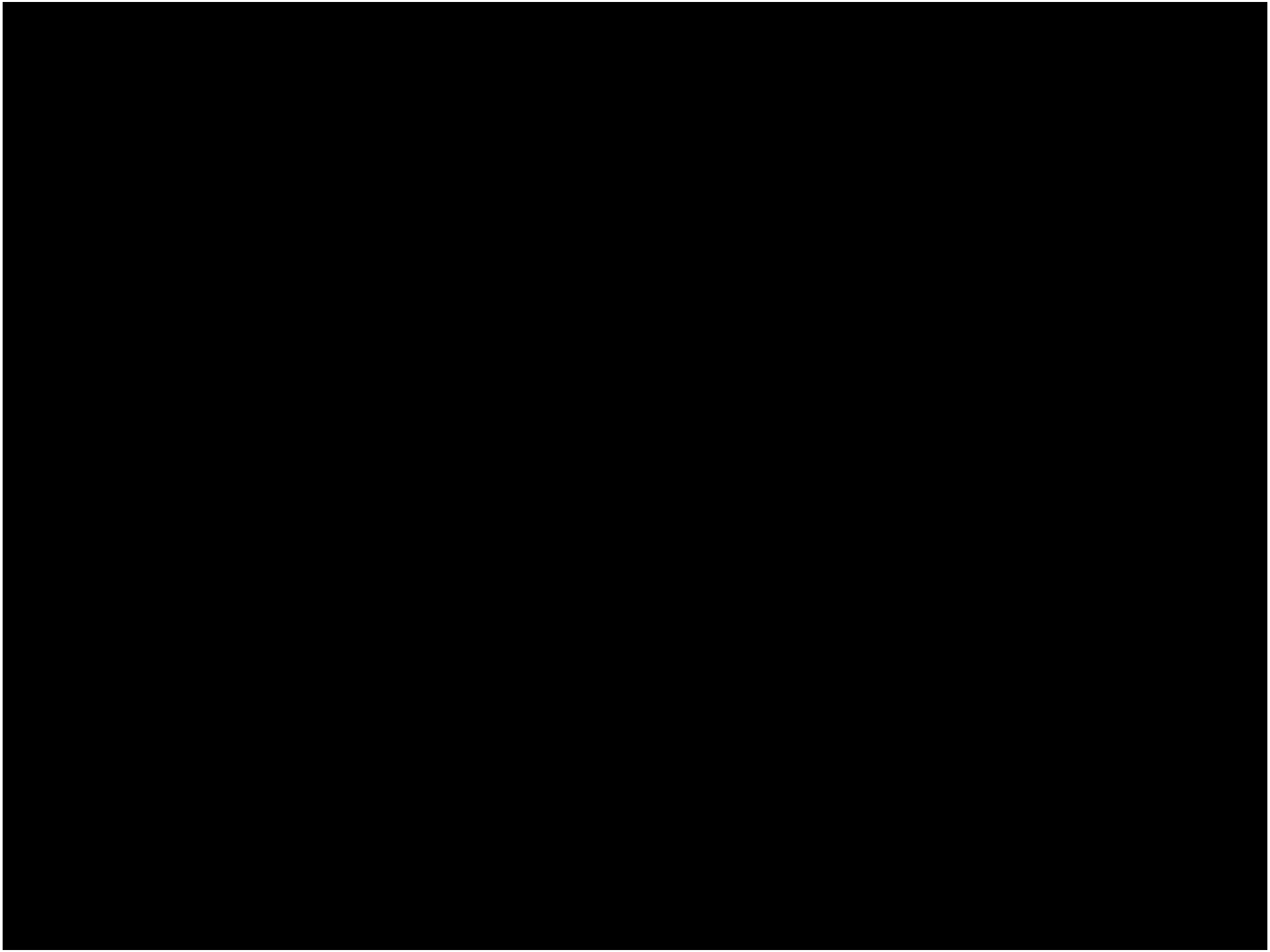
Conclusion 4

4. The balance between health risk and benefit of low-level exposure for a given individual may become predictable by gene-expression profiles in control and irradiated cells of this individual.

Conclusion 5

5. Clinical trials applying low-level irradiation are justified.

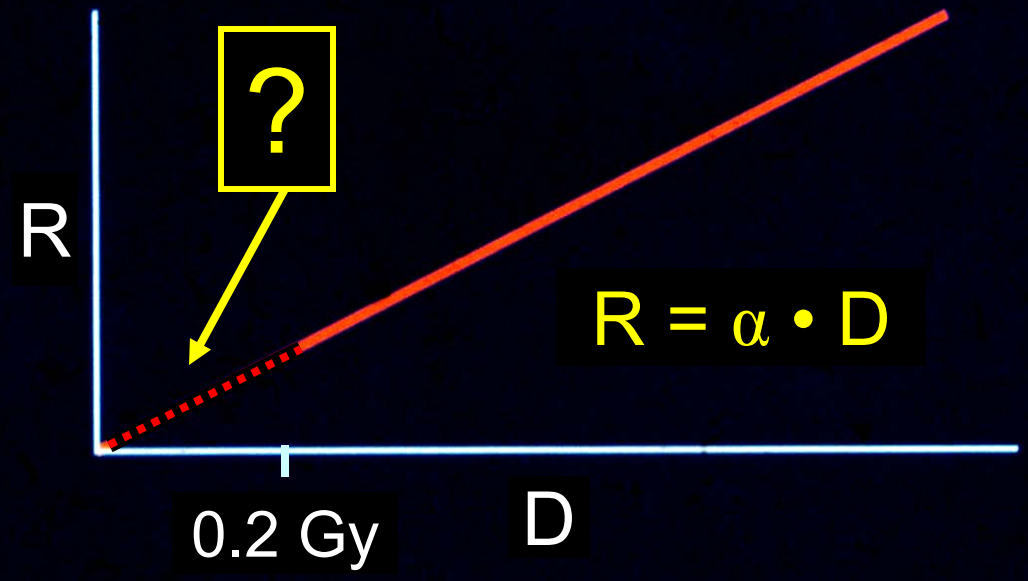
Thank you



Hiroshima after the Atom Bomb (6. 8. 1945)

The Linear-no-Threshold (LNT) Dose-Risk Function

was proposed for radiation protection to minimize radiation-induced cancer



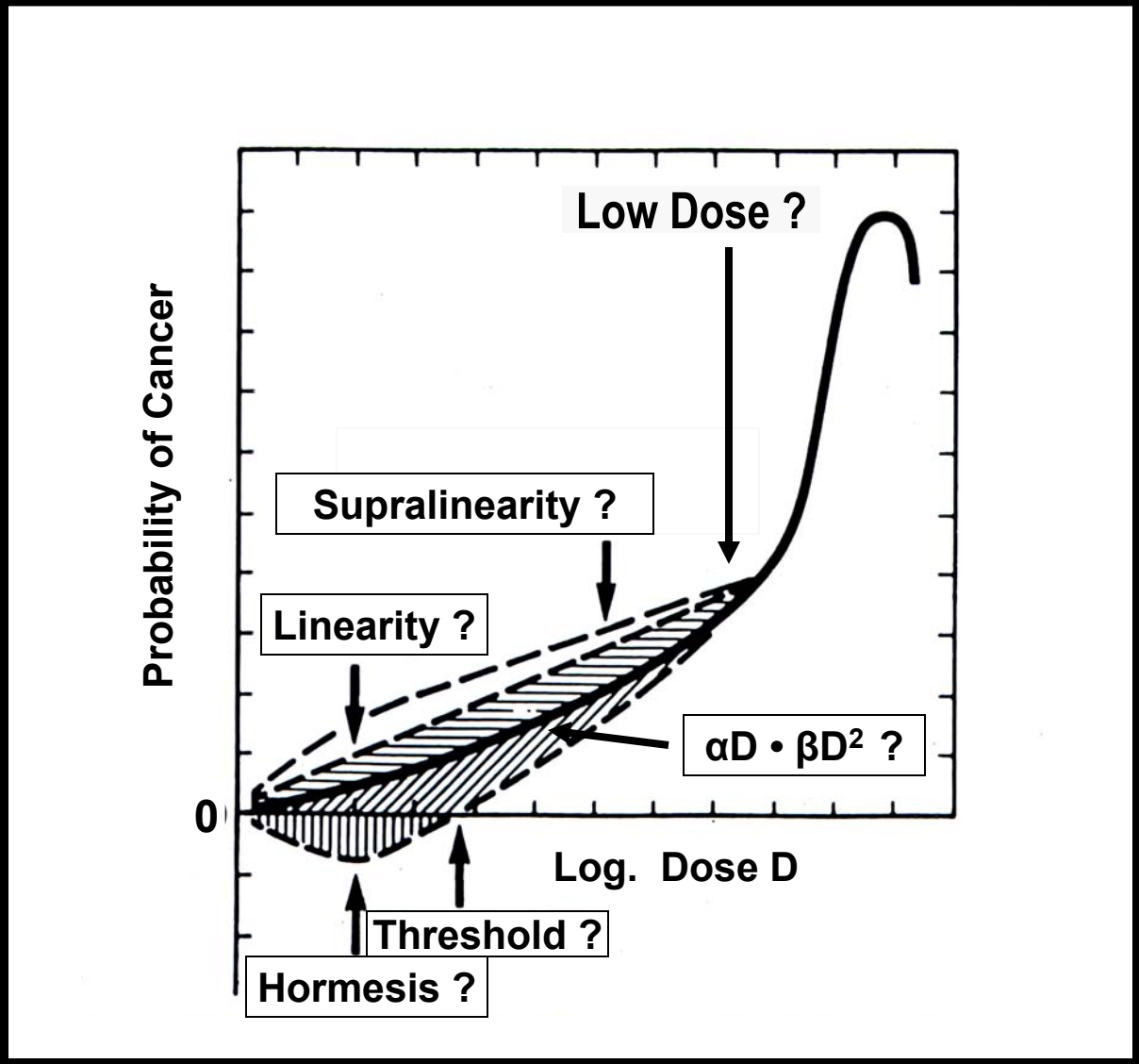
R = cancer probability in exposed tissue

D = absorbed dose

New research data contradict
the LNT hypothesis:

Low-level irradiation triggers
system responses
which express adaptive protection
against damage anywhere in the system,
- largely irrespective of cause of damage
be it radiogenic or non-radiogenic -.

Options of Low-Dose Induced Cancer Risk



The Critical Cell Concept and Its Application in the Assessment of Effects from Different Dose Rates and Different Radiation Qualities

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Nowhere else has hematology and radiobiology been brought together so well and so creatively as around E. P. Cronkite at Brookhaven National Laboratory. Beginning with the measurement of radiation-induced changes in the structure and cellular composition of the hemopoietic system, he was the first to proceed to unravel the kinetic parameters of hemopoiesis by employing [^{3}H]thymidine ([^{3}H]TdR) and autoradiography.[1] His studies over many years on the control of hemopoiesis, and especially on granulopoiesis and lymphopoiesis, were stimulated by constant and intimate contact with clinical medicine. Of course, the question of radiation effects from ^{3}H and other radionuclides incorporated into the genetic material inevitably arose. Under the chairmanship of Eugene Cronkite, Committee 24 of the National Council on Radiation Protection (NCRP), on which the senior author has served, was set up to work out guidelines for the use of radiation protection dosimetry in the incorporation of [^{3}H]TdR.[2] How was one to proceed with the problem of detriment generated by radionuclides that were heterogeneously distributed within a fraction of proliferating cells, or were eventually distributed among resting cells? After long deliberation, the question was finally addressed in NCRP Report 63; in the process, this effort helped to advance a new concept of absorbed dose and its consequences with respect to late effects.[3] It was becoming increasingly clear at this time, from microdosimetric and other considerations, that the conventional concept of dose was inapplicable in the case of low-dose exposure.

In discussing this problem, we will briefly deal with the following three questions:

(a) In the case of low-dose exposures, what and how big is the apparent critical volume of the individual cell "target" which gives rise to late effects such as cancer?

(b) What is the fate of this critical volume in the low-dose-exposure case?

(c) How does this critical volume react to being hit by different-sized energy packages, or "hit sizes"?

[a] Von Humboldt Fellow; on leave from Brookhaven National Laboratory, Upton, N.Y.
[b] Guest Scientist; on leave from the University of California, Irvine, Calif.

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Health Phys. 52: 663 – 669, 1987

● *Mechanisms*

INTRACELLULAR STIMULATION OF BIOCHEMICAL CONTROL MECHANISMS BY LOW-DOSE, LOW-LET IRRADIATION

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and

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***Abstract*—Non-specific generation of intracellular free radicals in excess of normal levels, e.g. by the acute radiation absorption event in cells, has led to a delayed and temporary inhibition of thymidine kinase. The enzyme activity reaches a minimum at 4 h even after a low-level exposure with full recovery soon thereafter. This process appears to represent a biochemical response to an initial physical event, but must be distinguished from the response of the DNA repair enzyme system. A reduction of cellular thymidine kinase activity is expected to cause a temporary reduction of DNA synthesis and may be of advantage to the cell. Such a response may be regarded as an instance of radiation hormesis in the sense that such a compensatory response to the stimulus of irradiation may confer protection against a repeated increase in free radical concentration whether by renewed radiation exposure or by metabolism in general. An improvement of the efficiency of repair or an increased level of free radical detoxification should be of benefit to both the individual cell and to the organism as a whole.**

1. INTRODUCTION

IRRADIATION of mammals at a low dose causes mainly single absorption events and these occur only within a

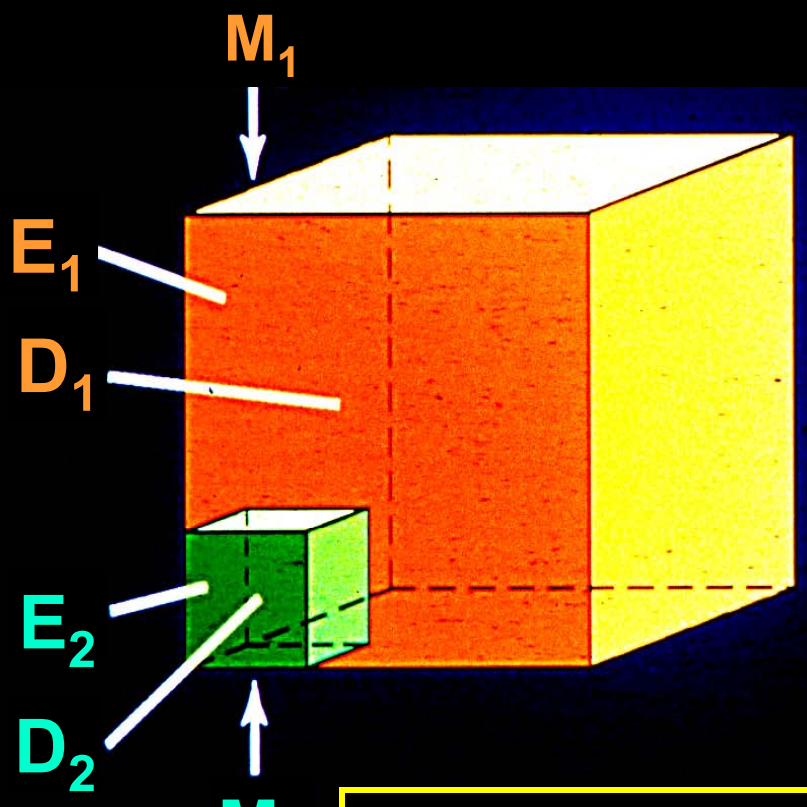
2. EXPERIMENTAL METHODS

These studies were carried out in mice (Za81; Fe84). The test systems involve the metabolic pathway of thy-

Absorbed Dose D

expresses concentration

not amount of energy E in mass M



$$D = \frac{E}{M};\ 1\ Gy = \frac{1\ J}{1\ kg}$$

$D_1 = D_2$

$E_1 > E_2$

Which mass should be chosen for stating dose ?

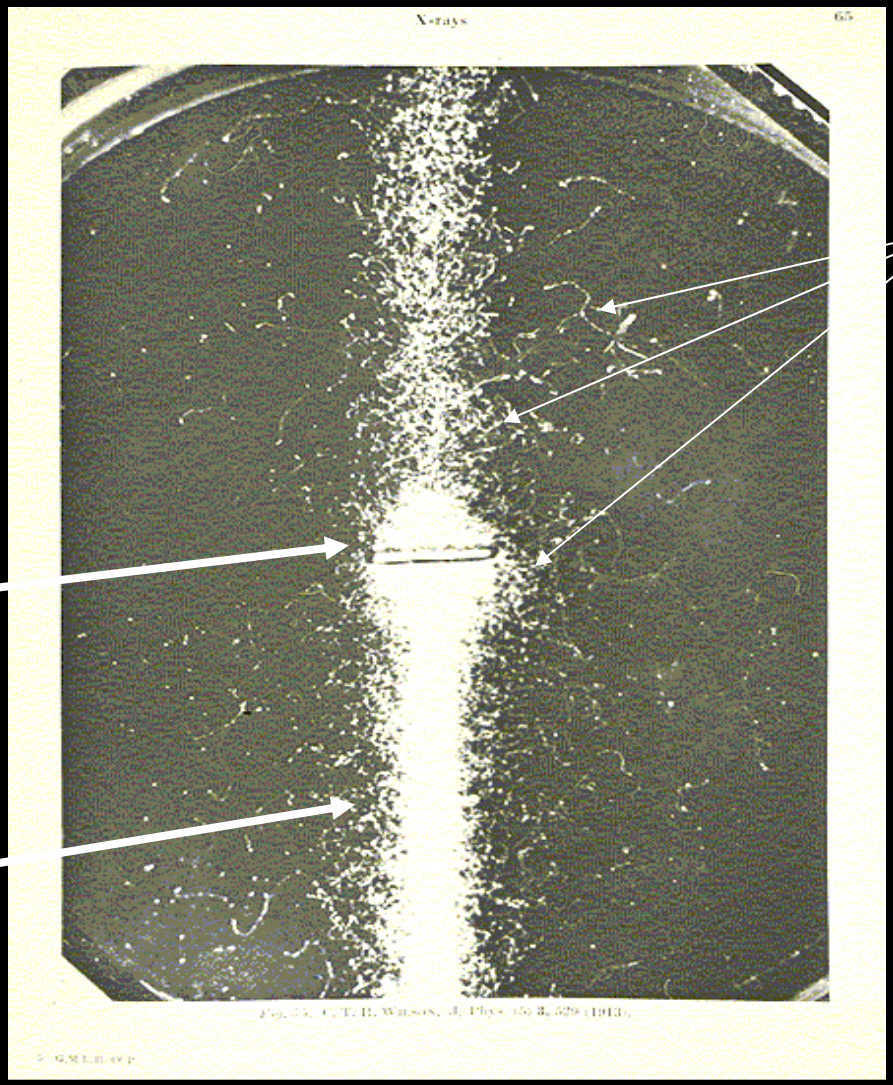
Ionizing Radiation→Energy Deposition Events

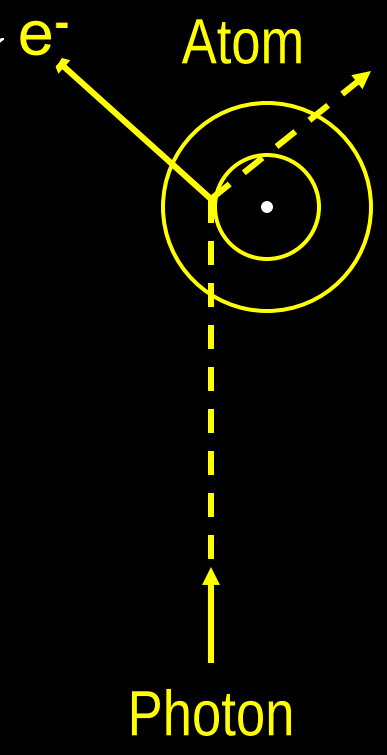
Wilson cloud chamber, here mainly Compton electrons

e^- track in H_2O → ~ 25 ROS per keV

attenuating metal plate

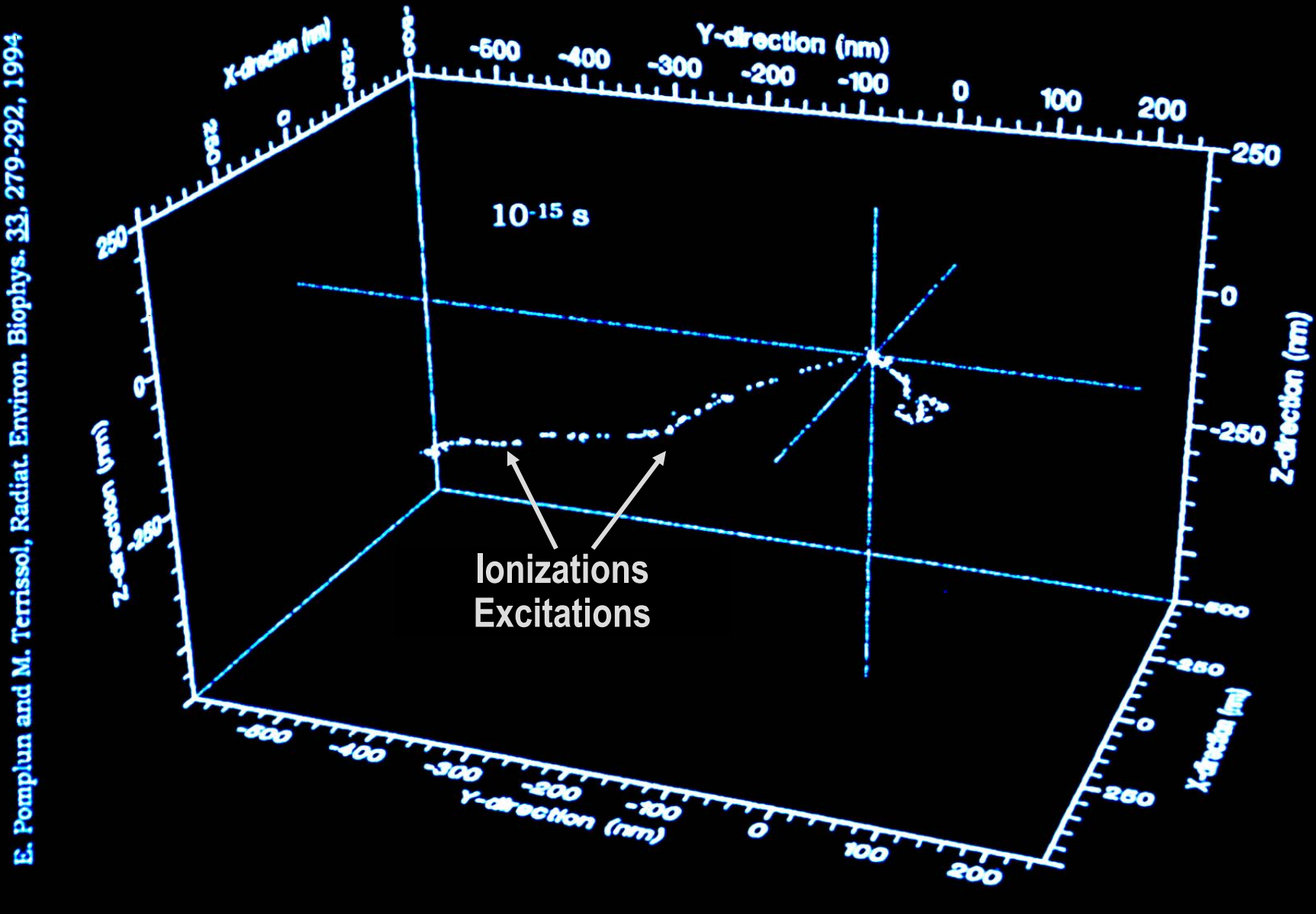
x-ray beam from below



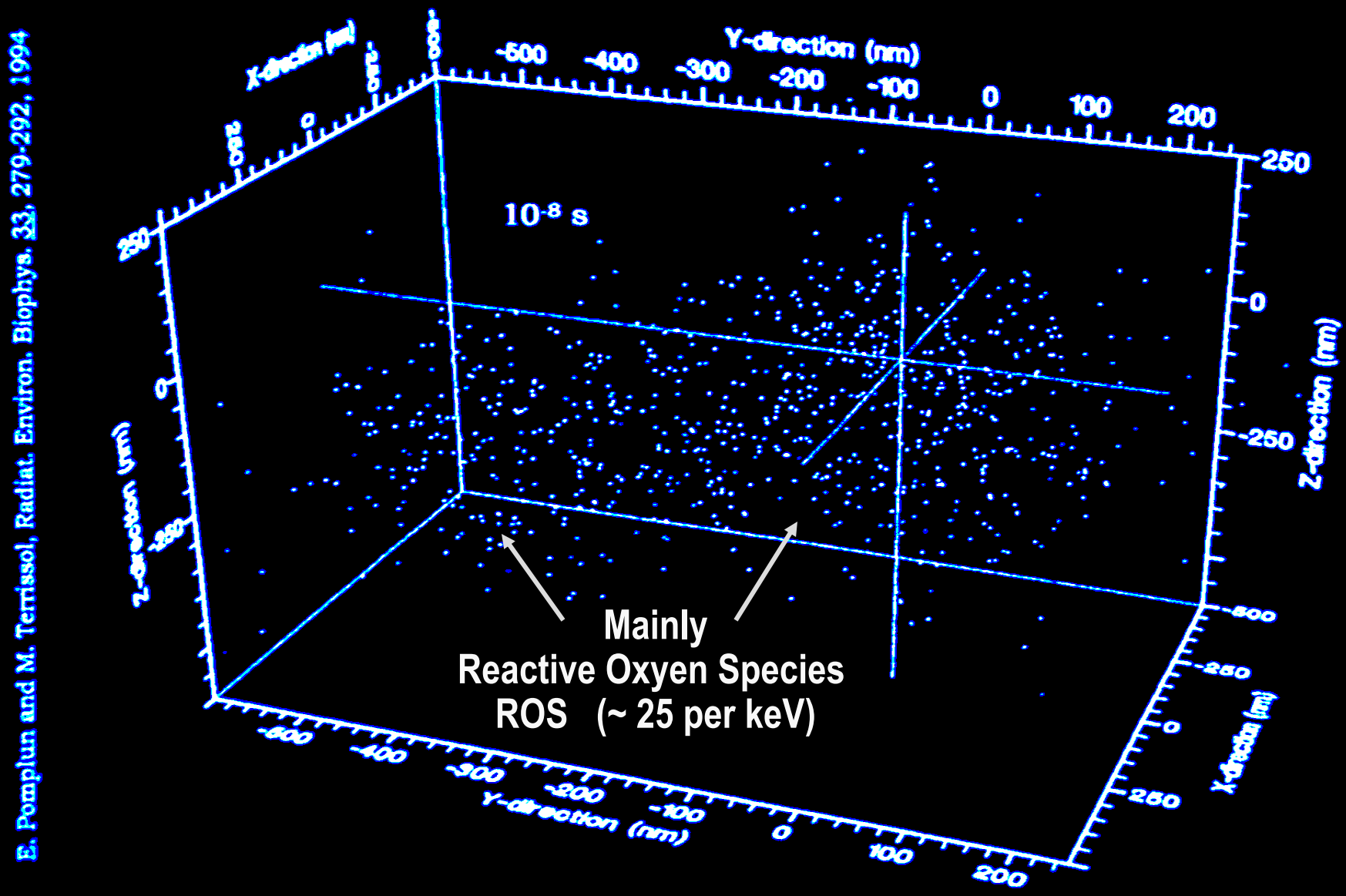


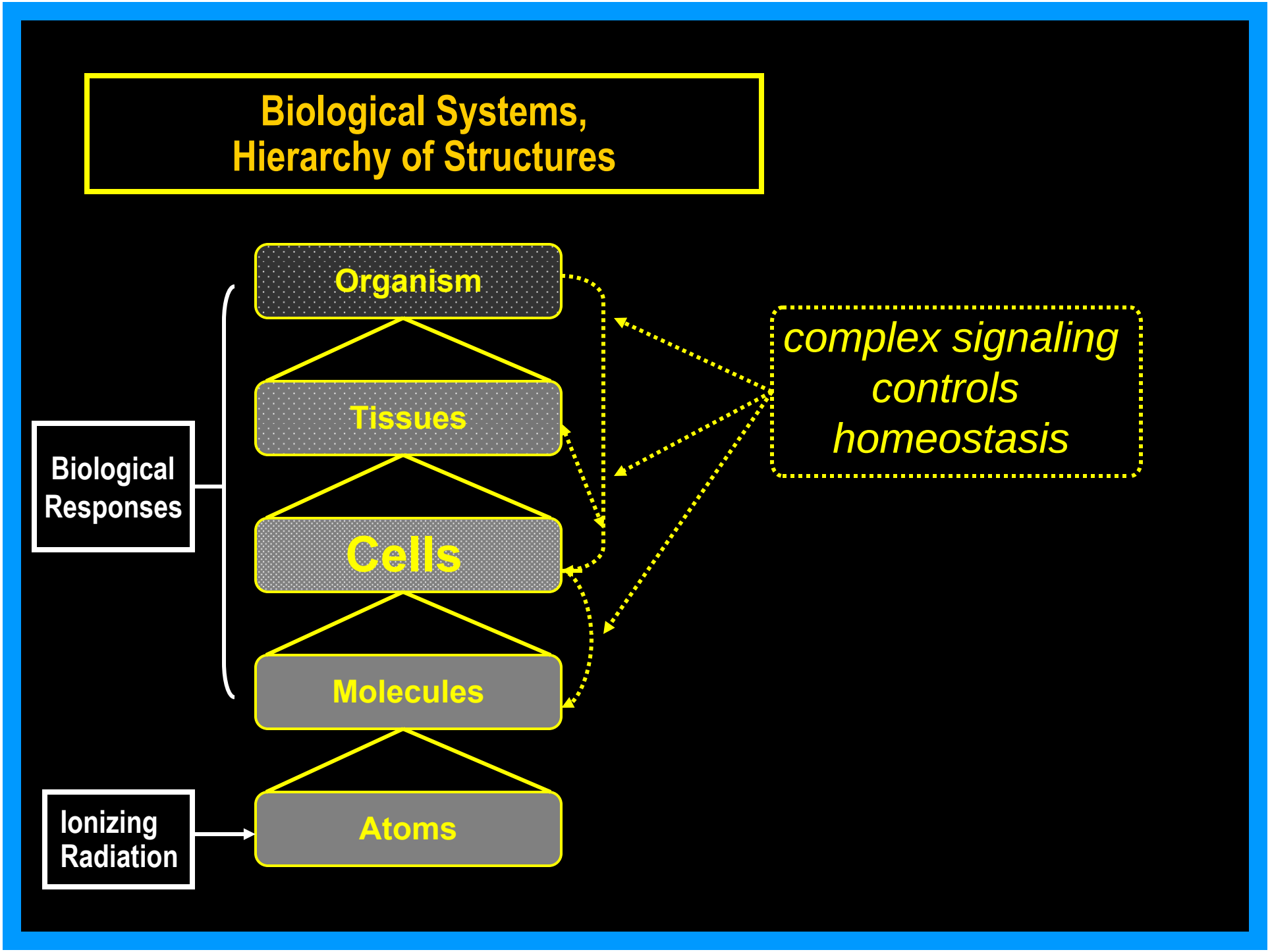
Wilson CTR, J. Phys., 1913

Electron Track in Water at 10^{-15} sec



Electron Track in Water at 10^{-8} sec

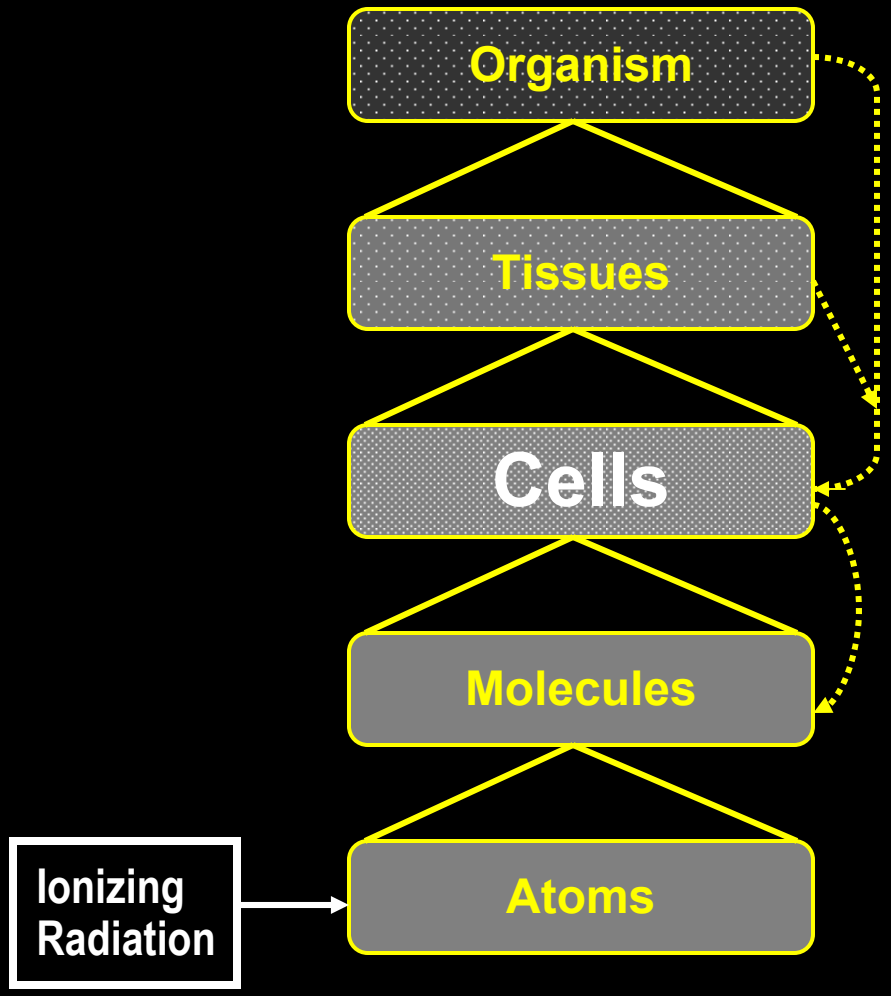



Biological Systems,
Hierarchy of Structures
Organism
Tissues
Cells
Molecules
Atoms
Biological Responses
Ionizing Radiation
complex signaling controls homeostasis

Scheme of Biological Systems

Various Levels of Organization

From Matter to Life



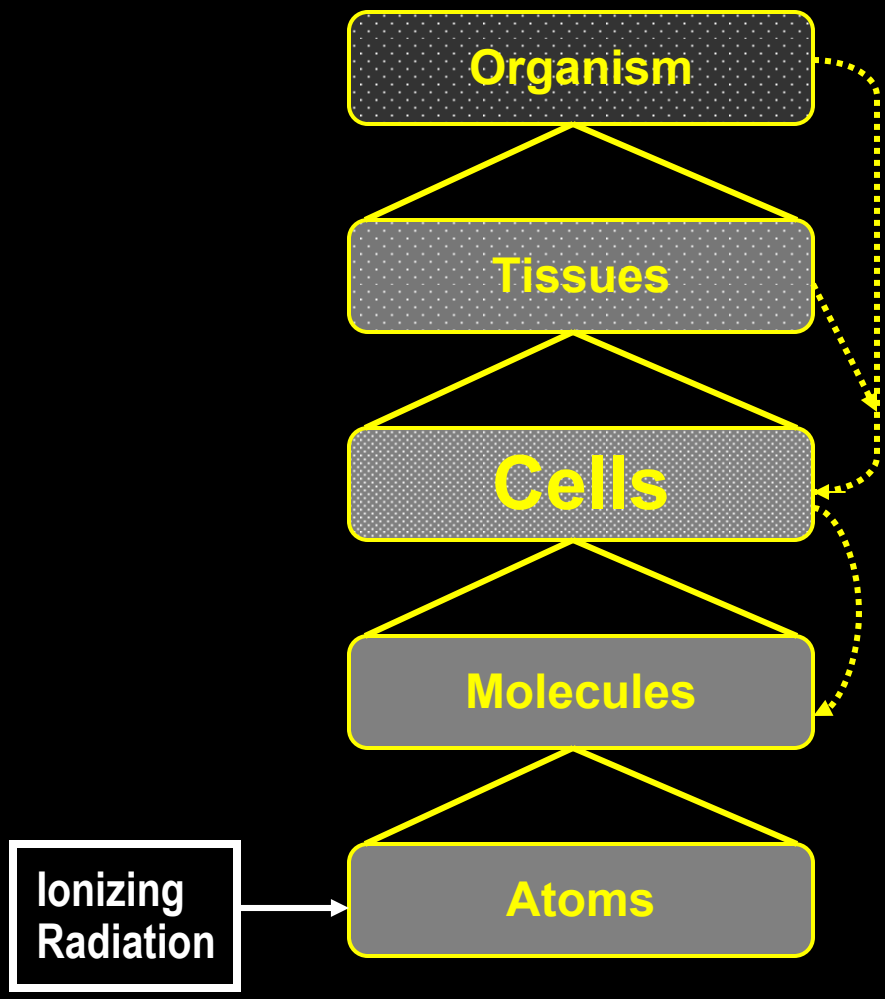
Living Organism

Cells are Fundamental Units of Life Triggering Tissue Effects

Building Blocks of Life

Complex Adaptive Systems
Hierarchy of Structures

From Matter to Life



Living organism

Complex signaling

Cells are fundamental units of life, determine tissue effects

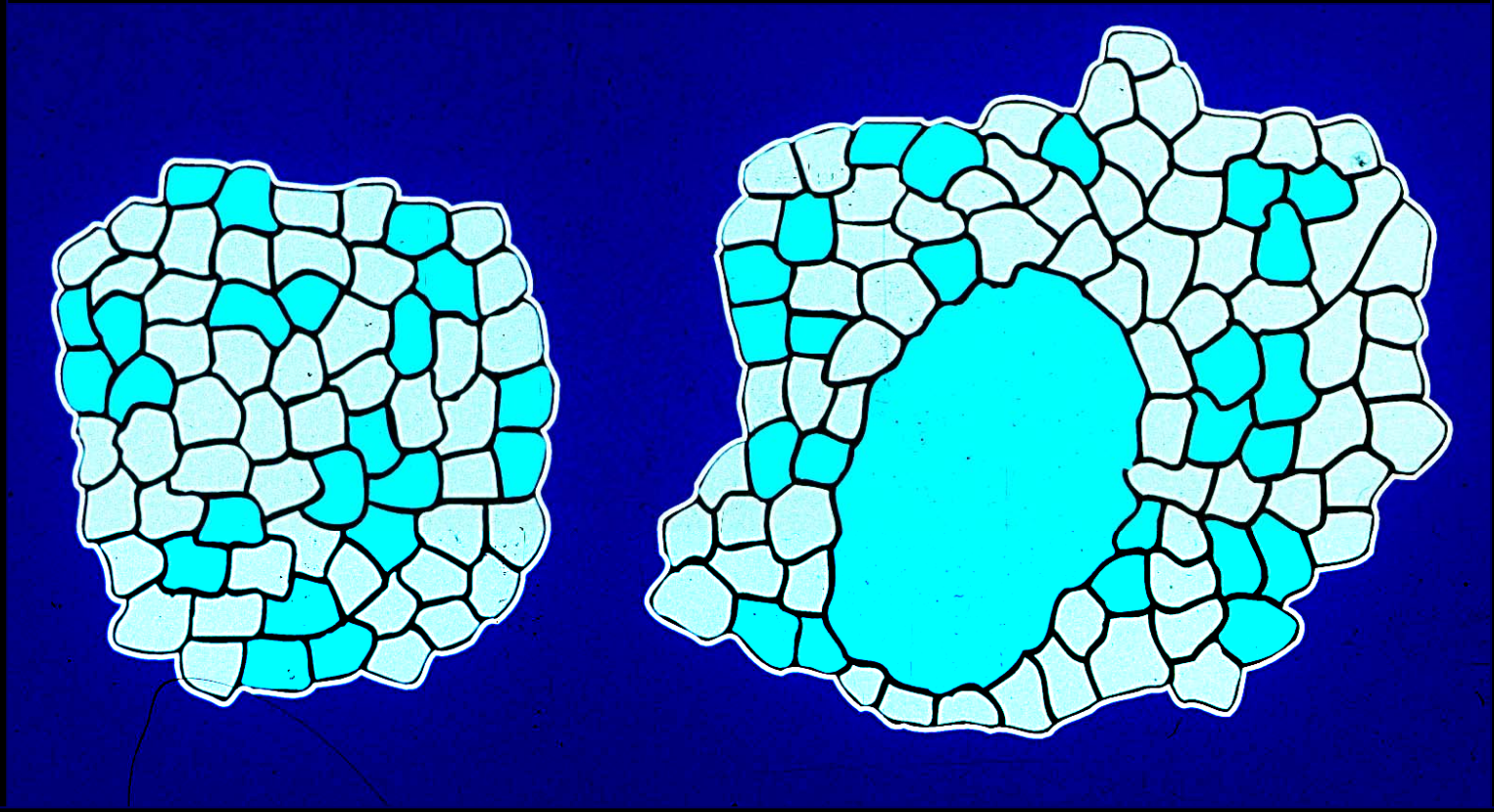
Building blocks of life

Biologically Reacting Target: Tissue Cell

Cell is fundamental unit of life.

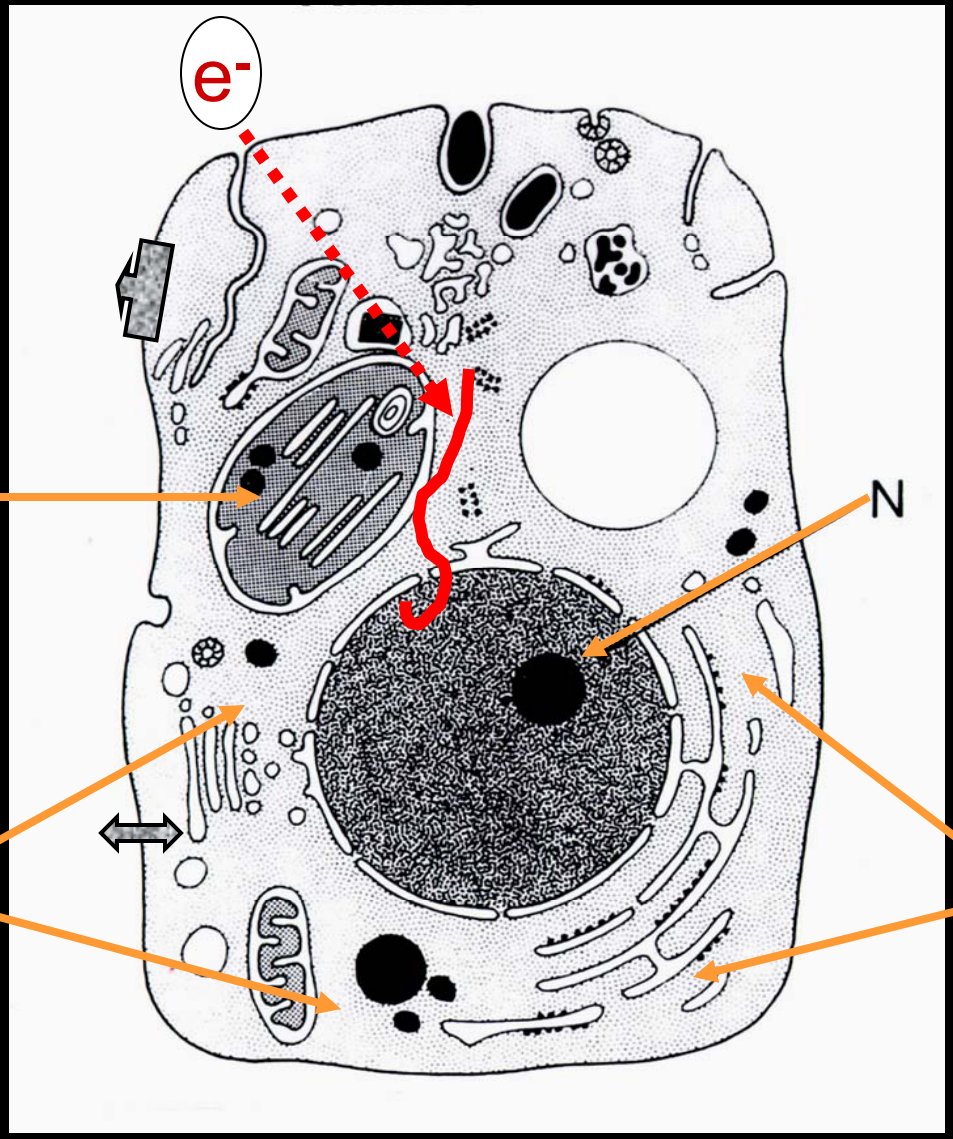
Cells communicate and interact in tissue.

Malignant tumors develop from one cell.



average cell mass = 1 ng = micromass (12.6 µm ∅ sphere)

Animal Cell Hit by Electron



Mitochondrium generates energy (has own DNA)

Nucleus = site of genetic material (DNA)

Cytoplasm

Cytoplasm

Average cell mass = 1 ng

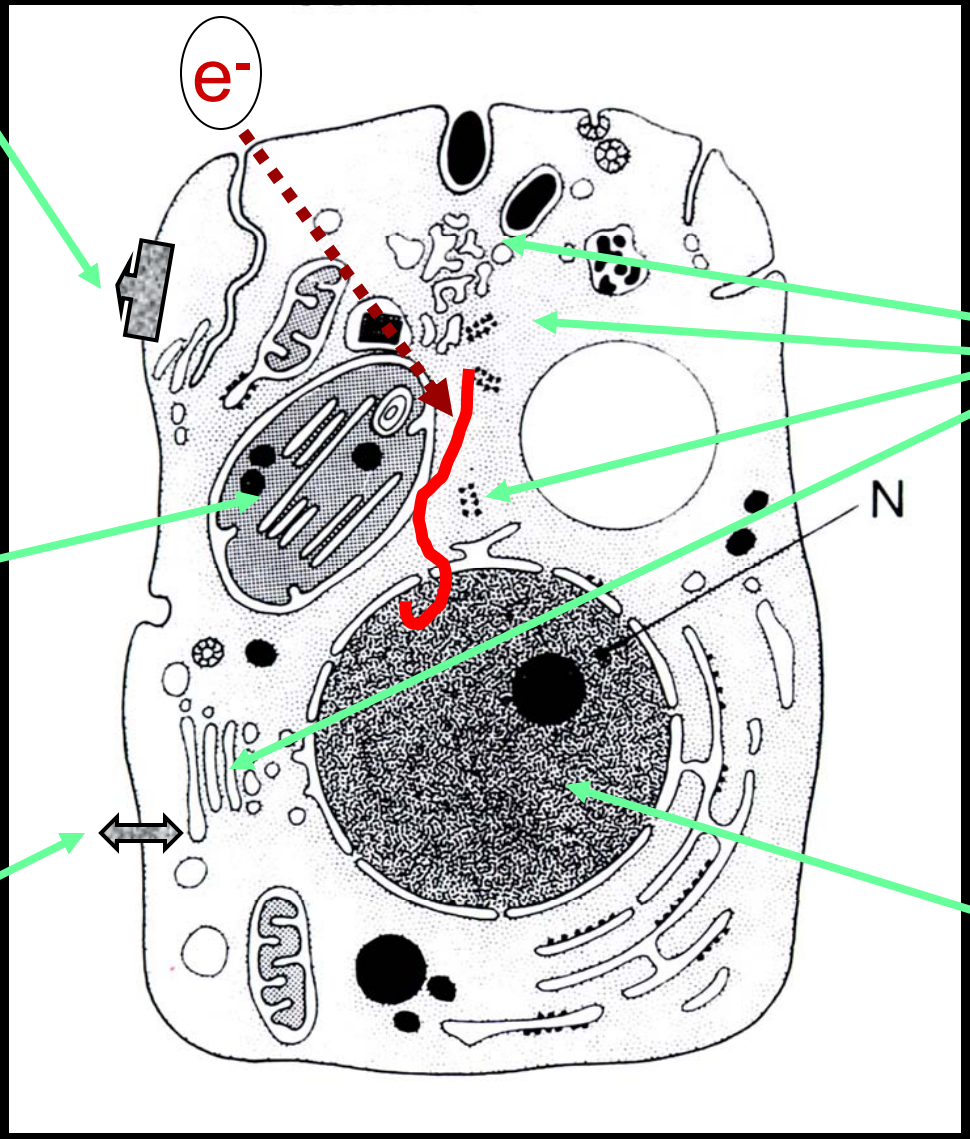
N = Nucleus ($\bar{x}$ 8 µm ∅)

Cell Hit by Electron Track (~ 6 keV/ng ~ 1 mGy)

Receptors
for binding
signal-
substances

Mitochondrium
generates
energy
(has own DNA)

Channels
for ions
and molecules



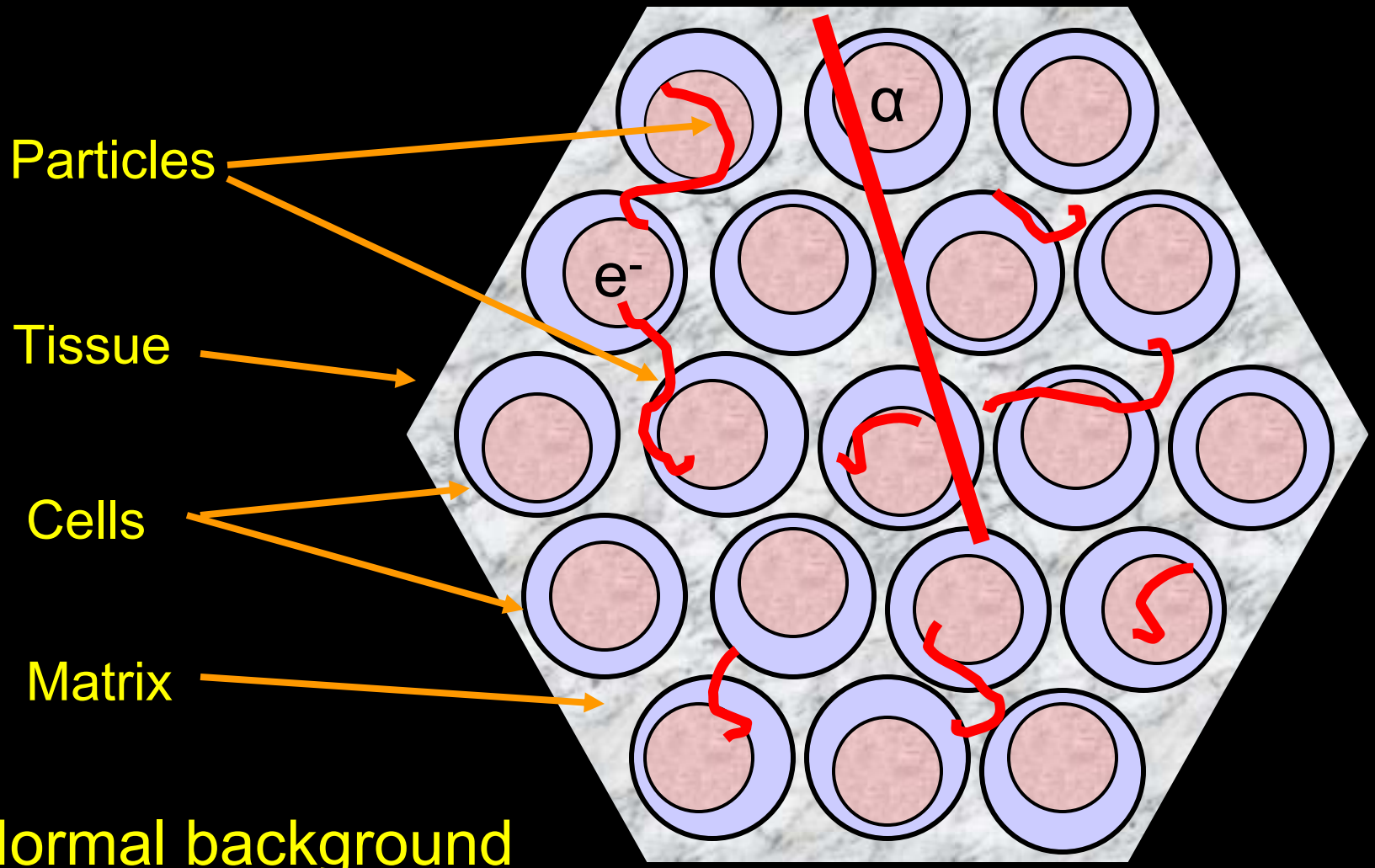
Cytoplasma
with structures
and biolog. tools
(enzymes)
for
energy provision
and substrate-
- synthesis,
- catabolism
- transport

Nucleus
with genes
(DNA)

Average Cell Mass = 1 ng

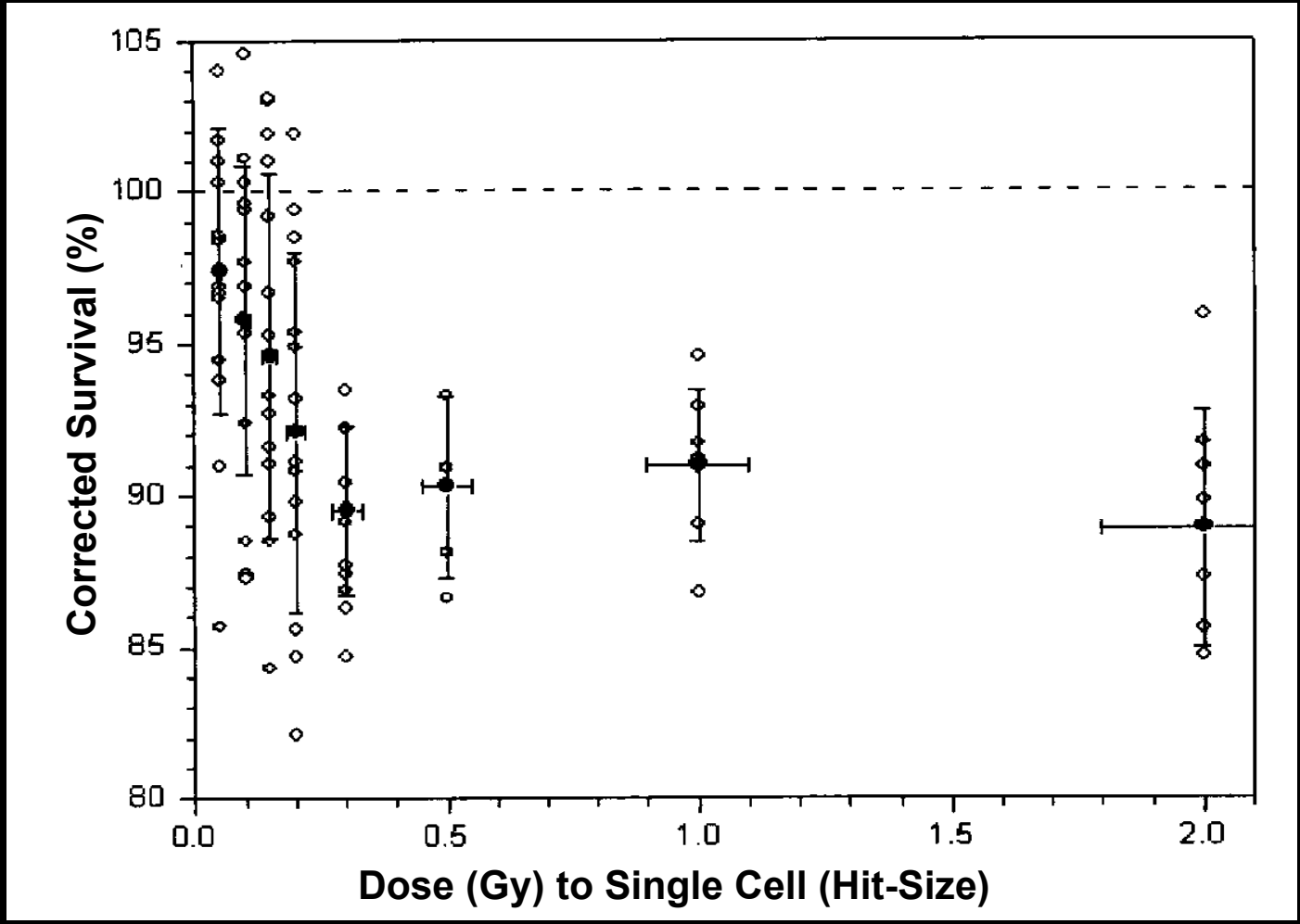
N = Cell Nucleus ($\bar{x}$ 8 µm ∅)

Particle Distribution in Tissue



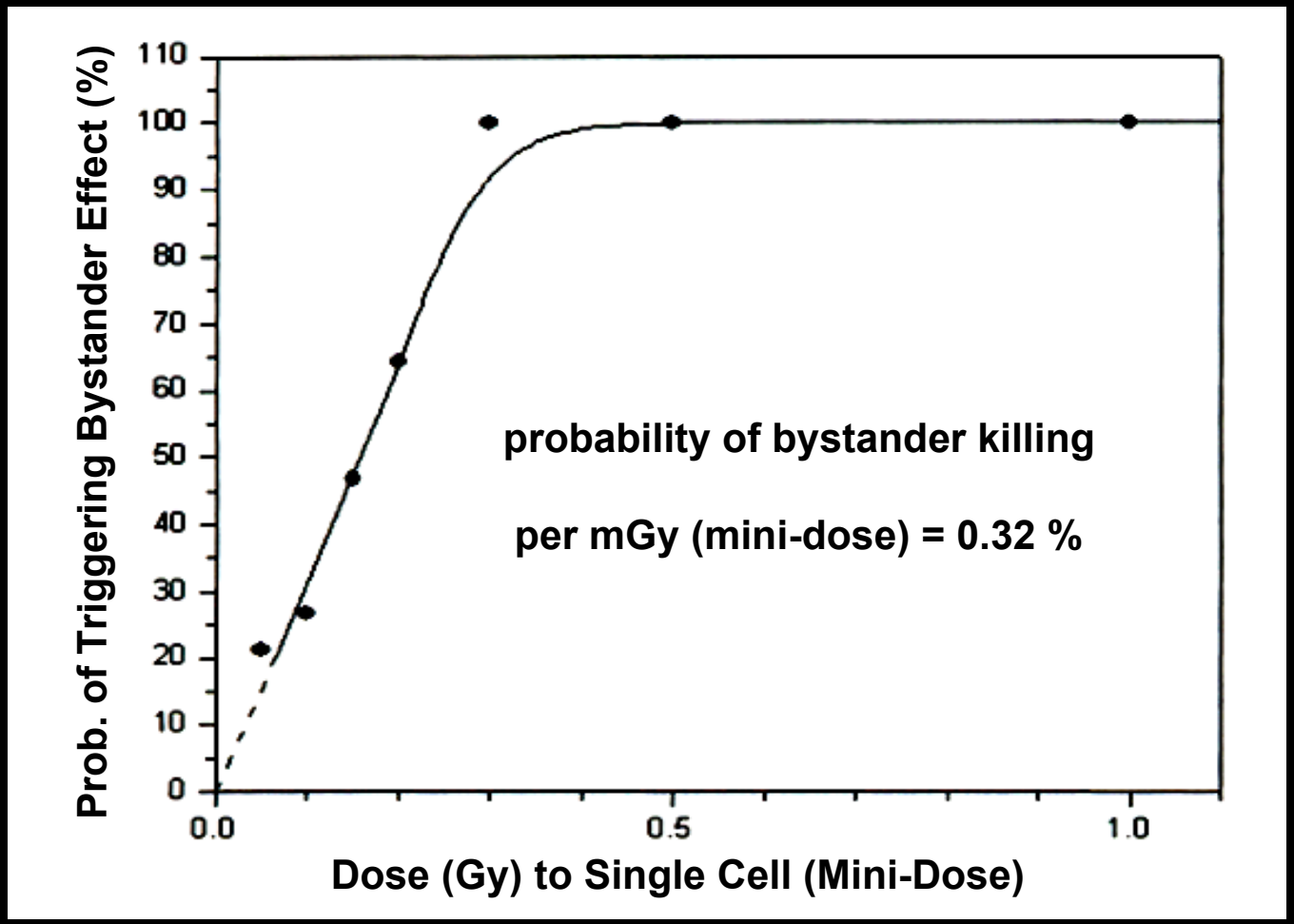
Normal background brings about 1 – 2 e^- hits per ng mass per year

Bystander Killing Effect from Single Cell
C_K X irrad. of 1 cell in dish with ~160 cells



Schettino G. et al., Radiat. Res. 163: 332 - 336, 2005

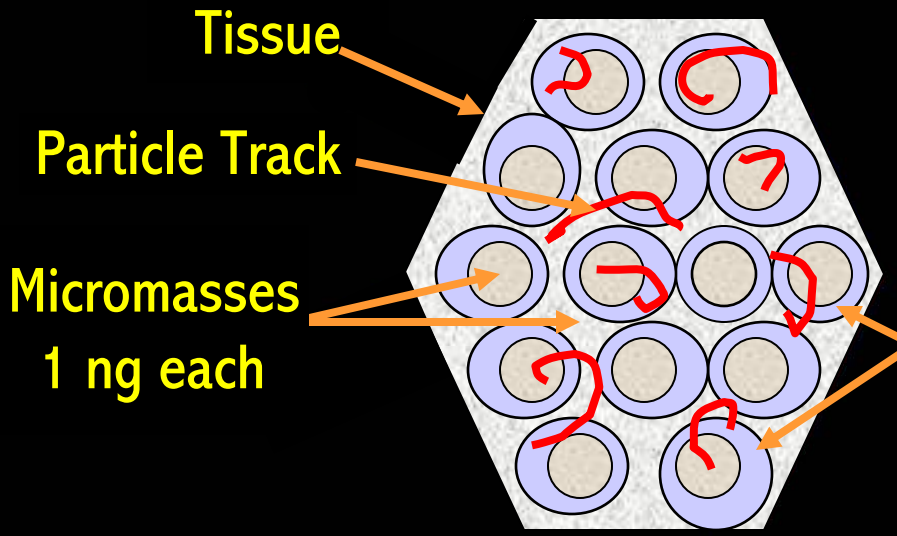
Probability of Bystander Effect (V79 cells)
after single irradiation to single cell (C_K x rays)



Schettino G. et al., Radiat. Res. 163: 332 - 336, 2005

From Absorbed Dose (D) to Total Energy (E)

absorbed in exposed micromasses



M = Mass of exposed tissue

N_E = No of exposed micromasses

N_H = No of track hits in micromasses

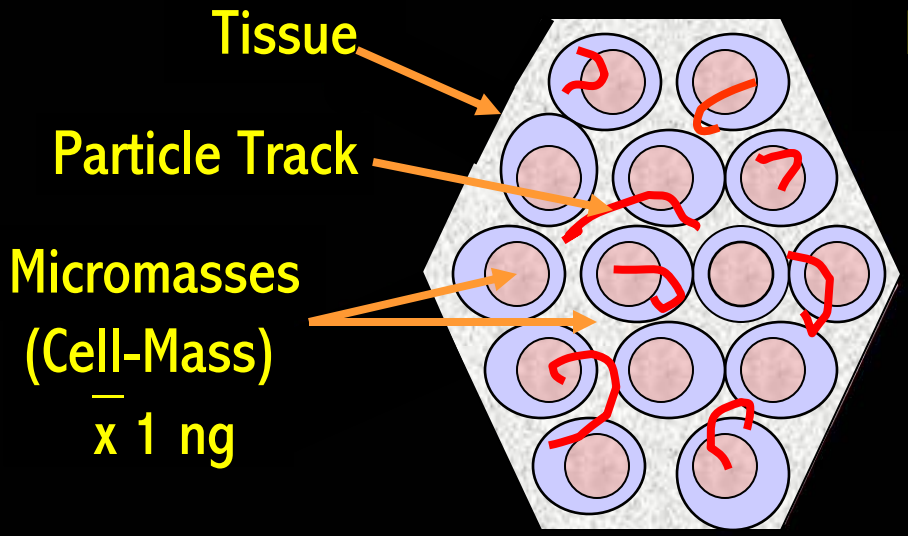
z_1 = Energy absorbed per hit in micromass (Specific Energy)

$$E / M = \bar{D} = [\ \bar{z}_1 \bullet N_H\ ] / N_E$$

Dose expresses multiple hits, N_H, of $\bar{z}_1$ per N_E

Bond et al., Int. J. Radiat. Biol., 1988

Absorbed Dose D:
Sum of Energy Absorbed in Exposed Micromasses



E/M = Energy per Tissue Mass

N_E = No of exposed micromasses

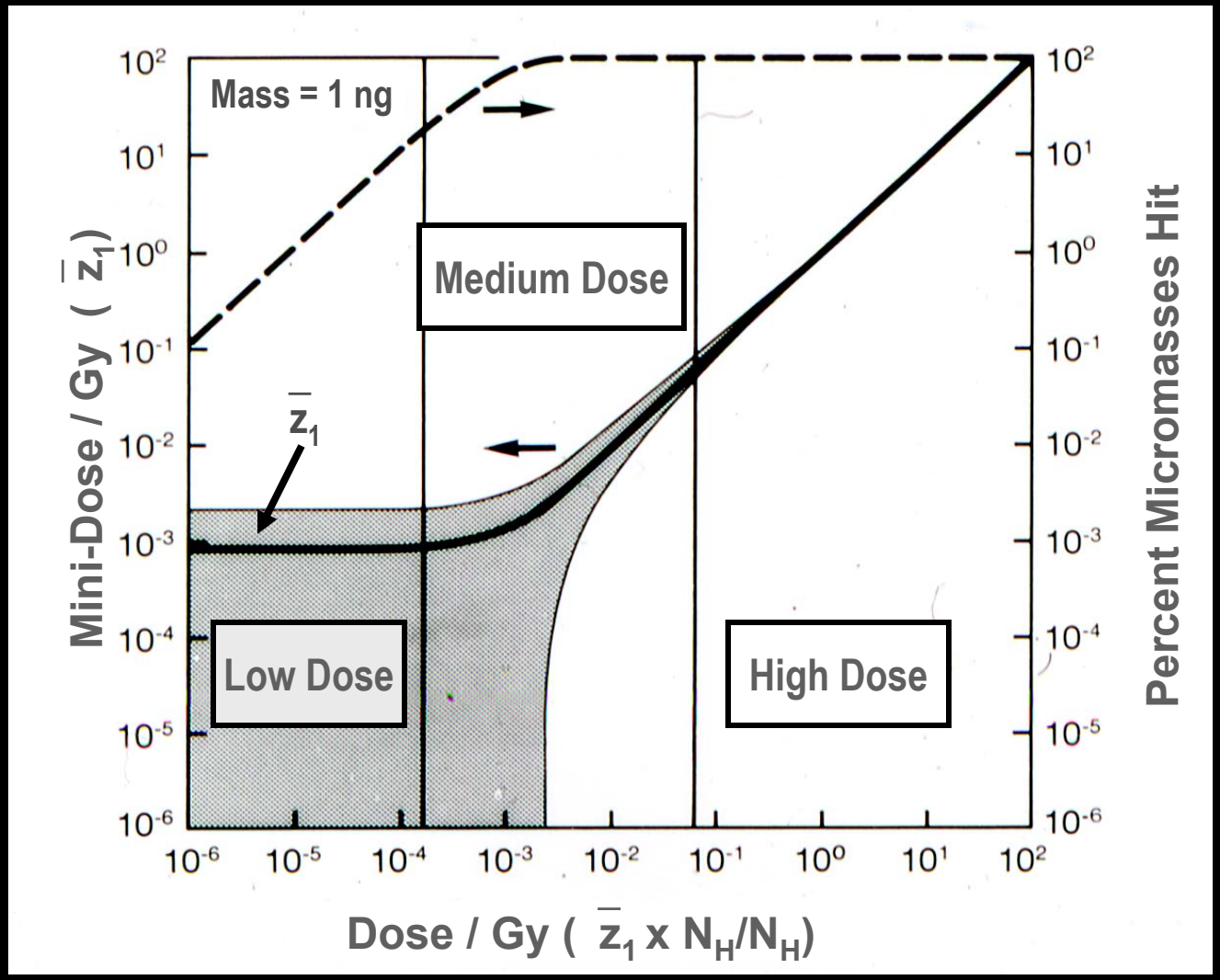
N_H = No of microdose-events (hits) in exposed micromasses

z_1 = Energy abs. per micromass per microdose-event (hit)

$$\sum z_1/N_E = E/M = D = [\sum z_1/N_H] \bullet [N_H/N_E]$$

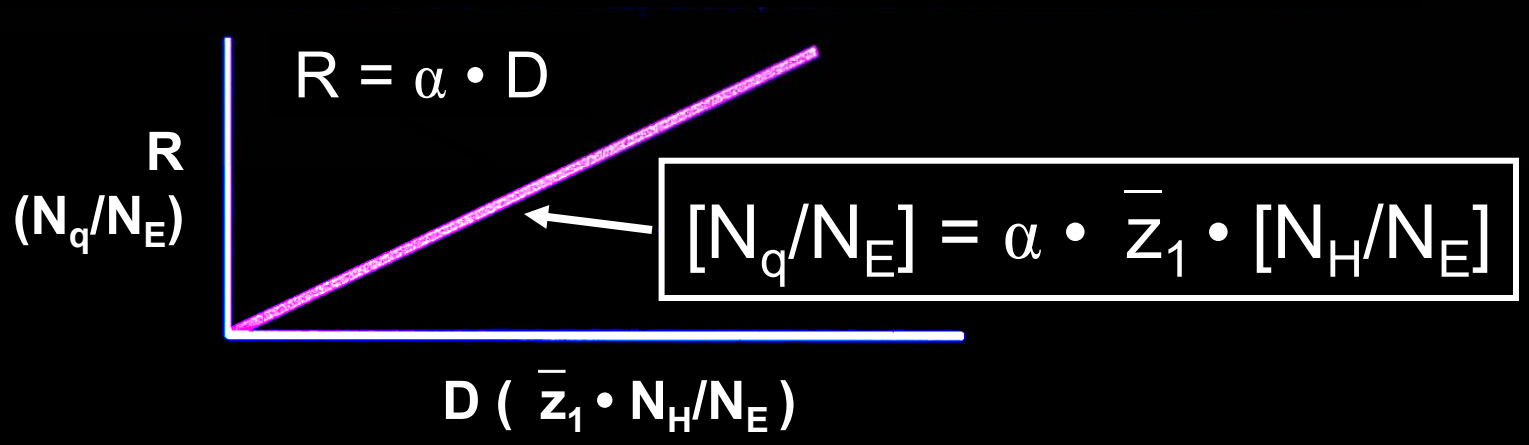
$$D = \bar{z}_1 \bullet [N_H/N_E]$$

Mini-Dose and Dose, of 250 kVp X-Rays ?



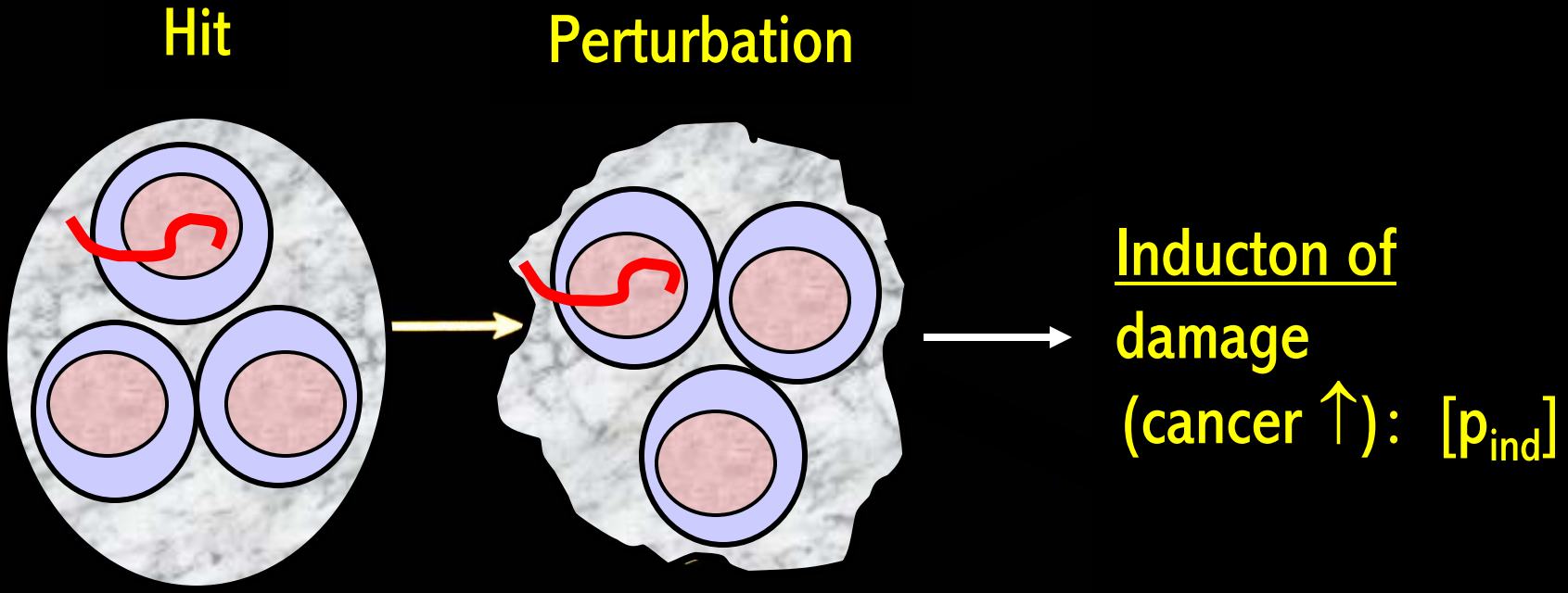
Modified from: ICRU Report 36, 1983, 1993

The Dose-Risk Function → Hit-Number-Effectiveness-Function

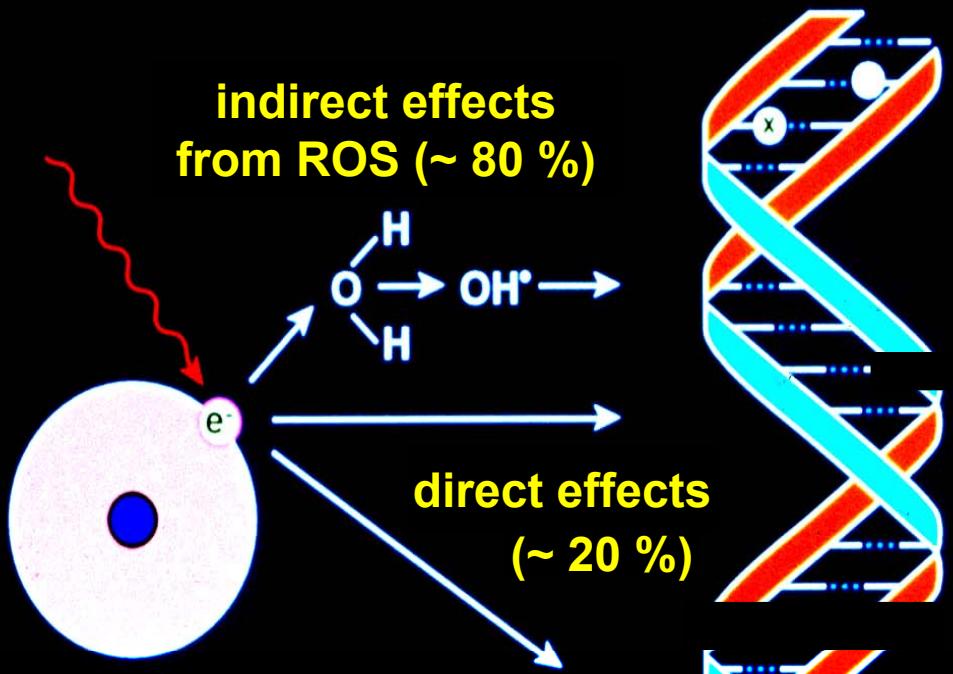


N_q = number of cancer-transformed cells
N_E = number of exposed micromasses
$\bar{z}_1$ = mean energy per hit per micomass (mGy)
N_H = number of z_1 hits in micromasses
α = constant of proportionality

Effect of Energy Deposition in Cells and their Neighbors



Radiation Effects on DNA



base loss
base change
(~10/0.01 Gy)

single strand breaks
SSB (~ 10/0.01 Gy)

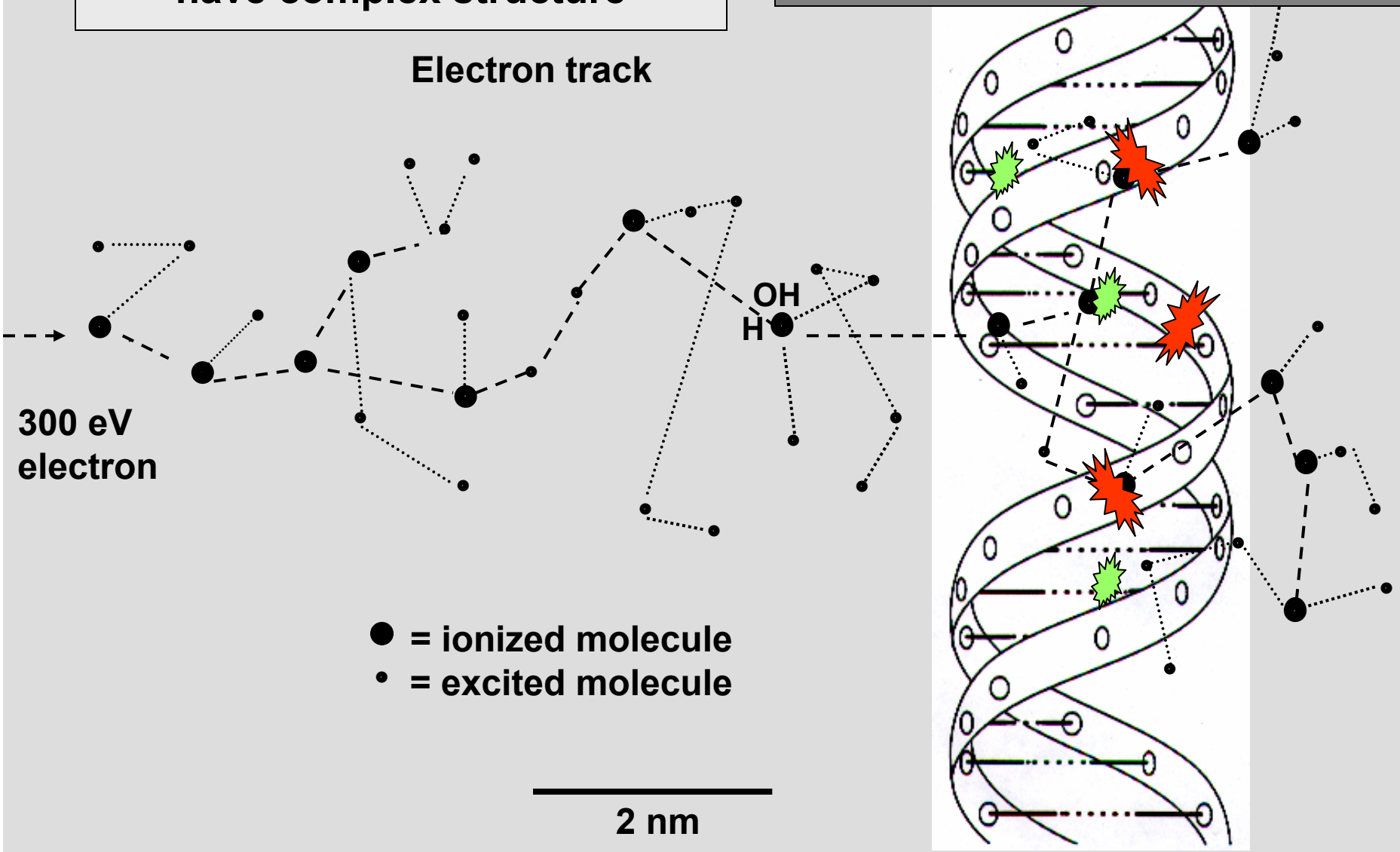
double strand breaks
DSB (~ 0.4/0.01 Gy)

cross links
(~ 1-2/0.01 Gy)

Repair of DNA damage begins immediately and may last from minutes to hours to days.

Clustered DNA Damage

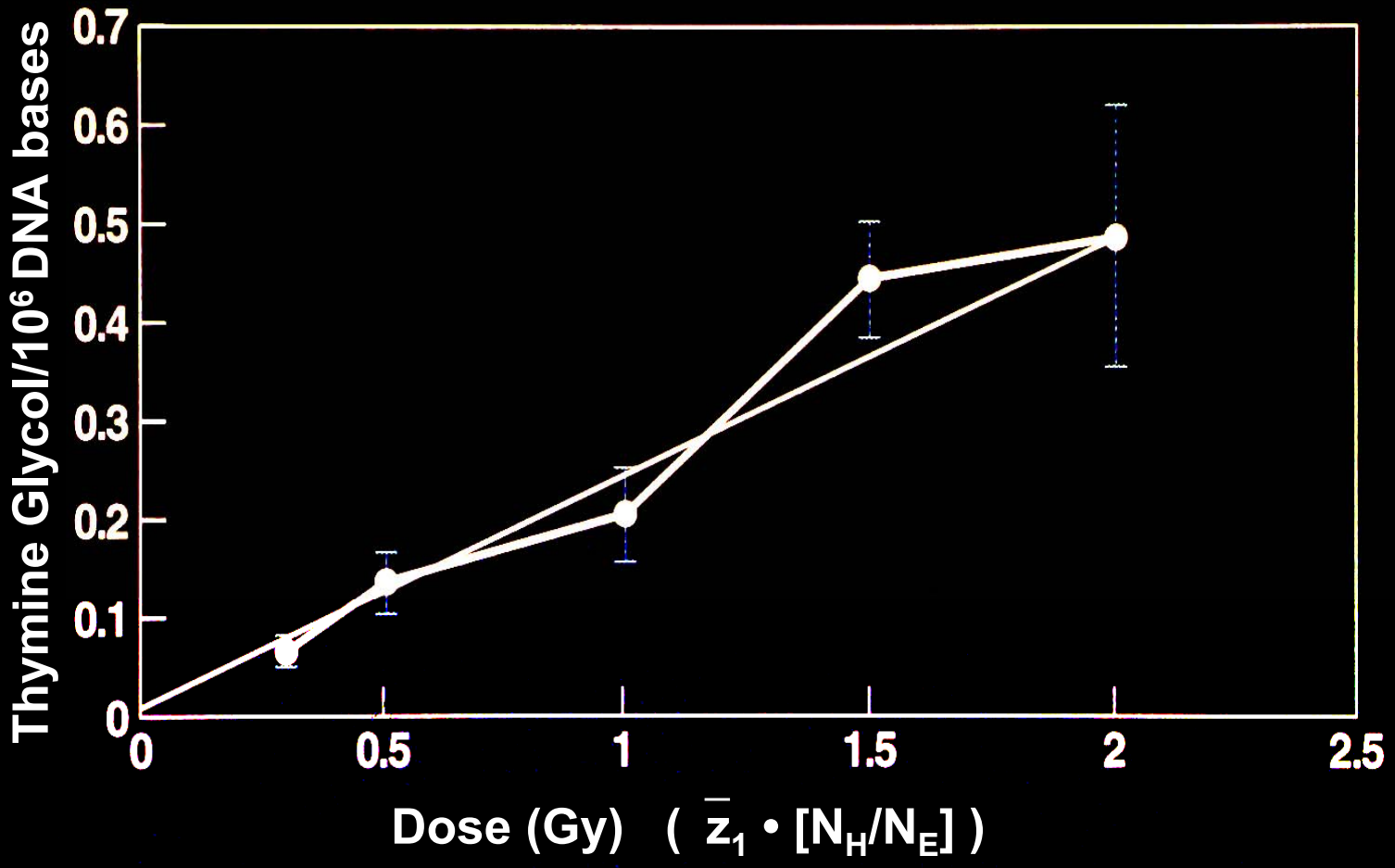
~ 25 - 40 % of DSBs from x-rays have complex structure



Goodhead D, pers. comm., 21. 08. 2003

DTG 21.8.03

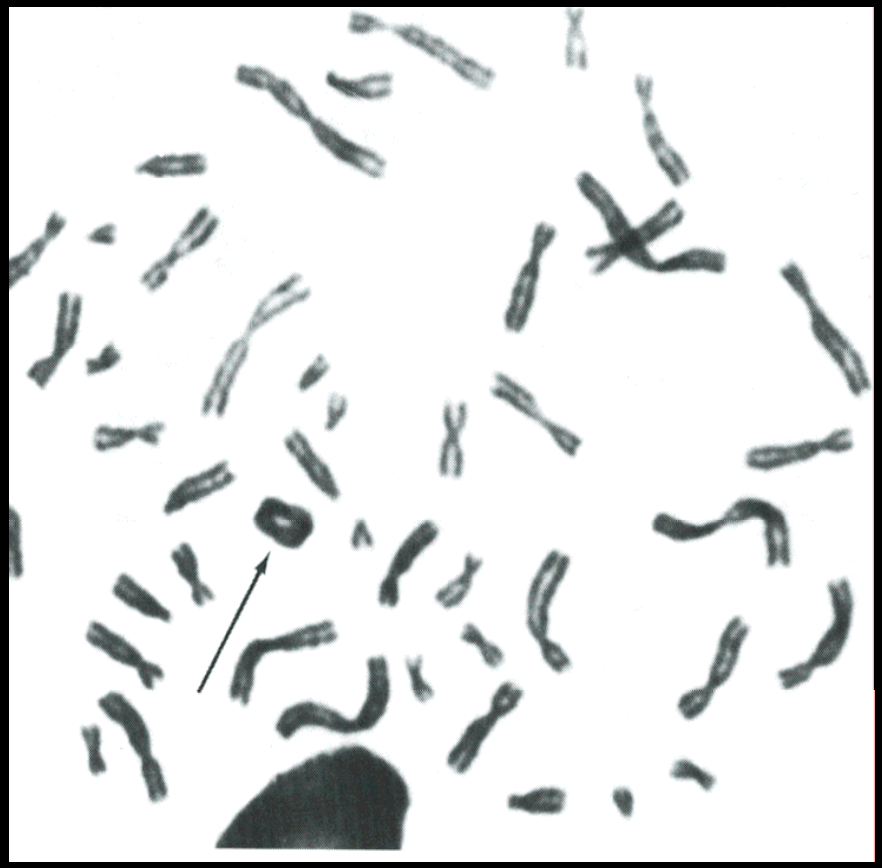
Radiation-Induced DNA Base Changes
in ^{137}Cs γ-irradiated T_1 cells in culture



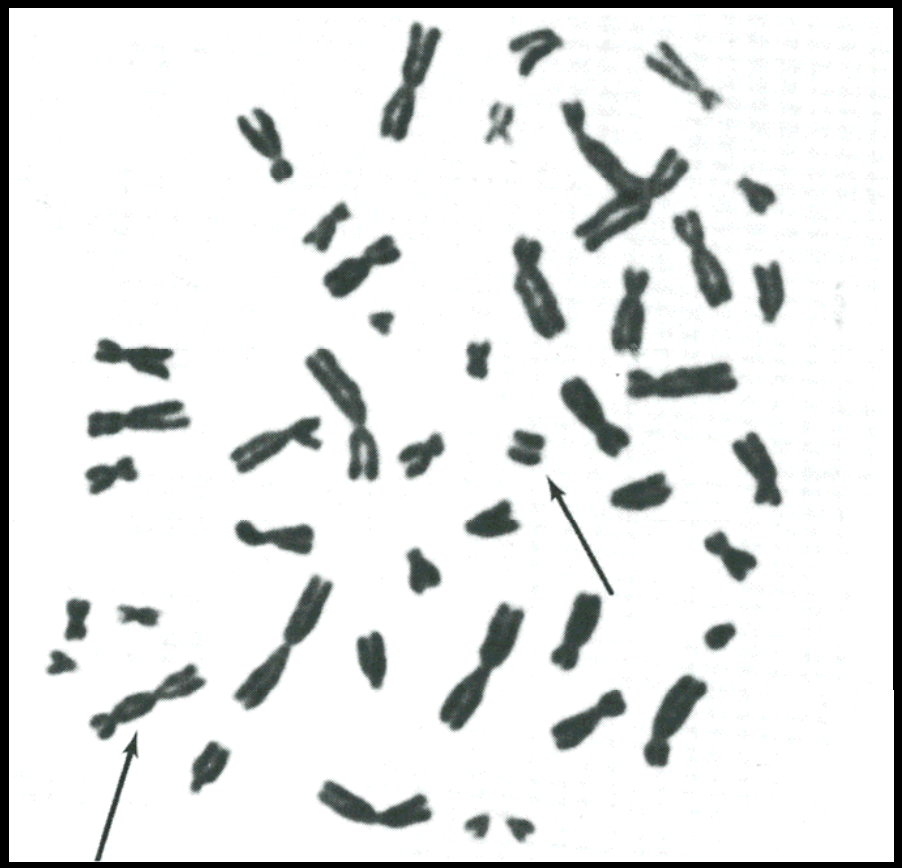
Radiation-Induced Chromosome Aberrations

in human leukocytes

ring chromosome

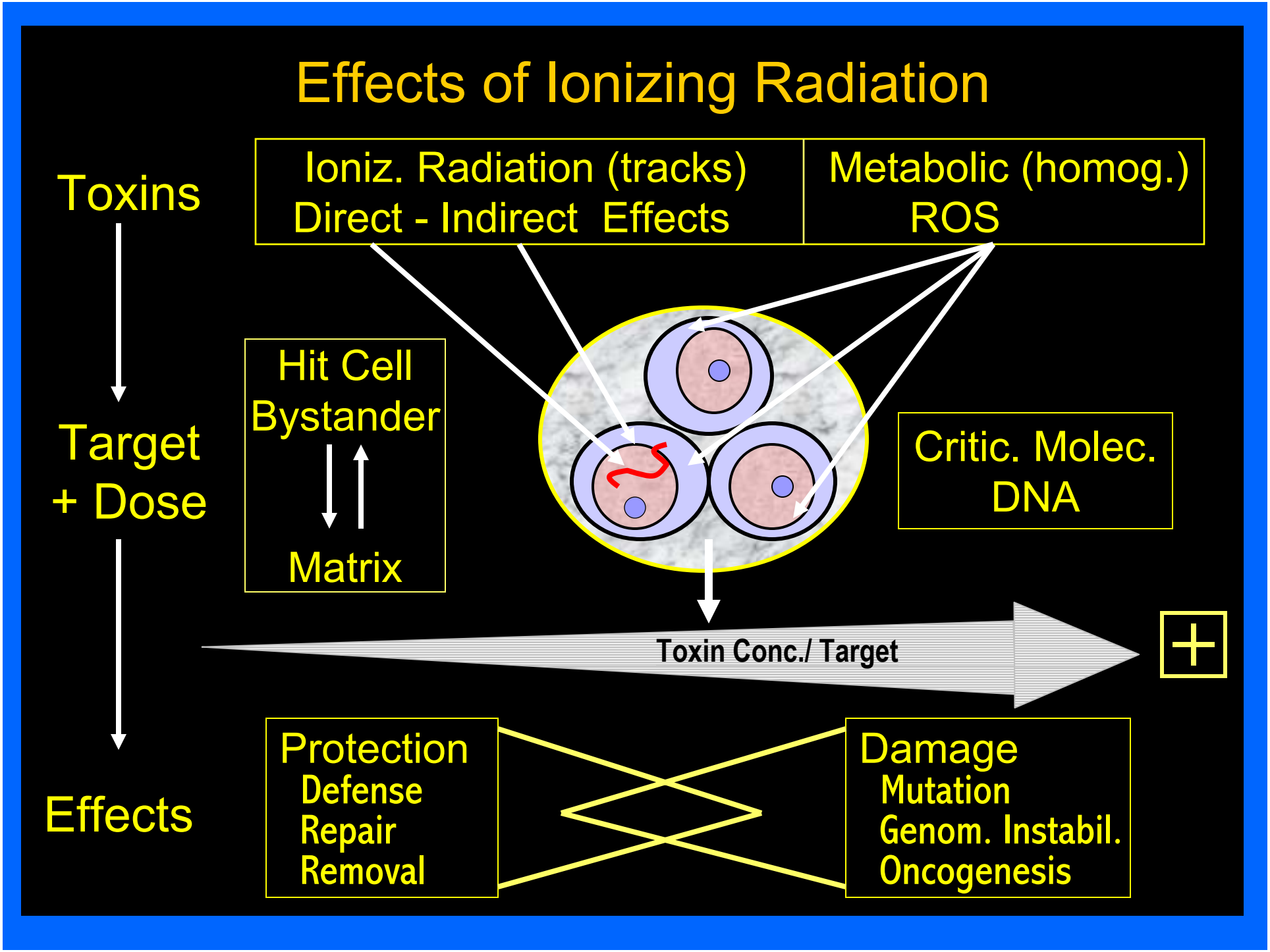


dicentric, fragment chromosome

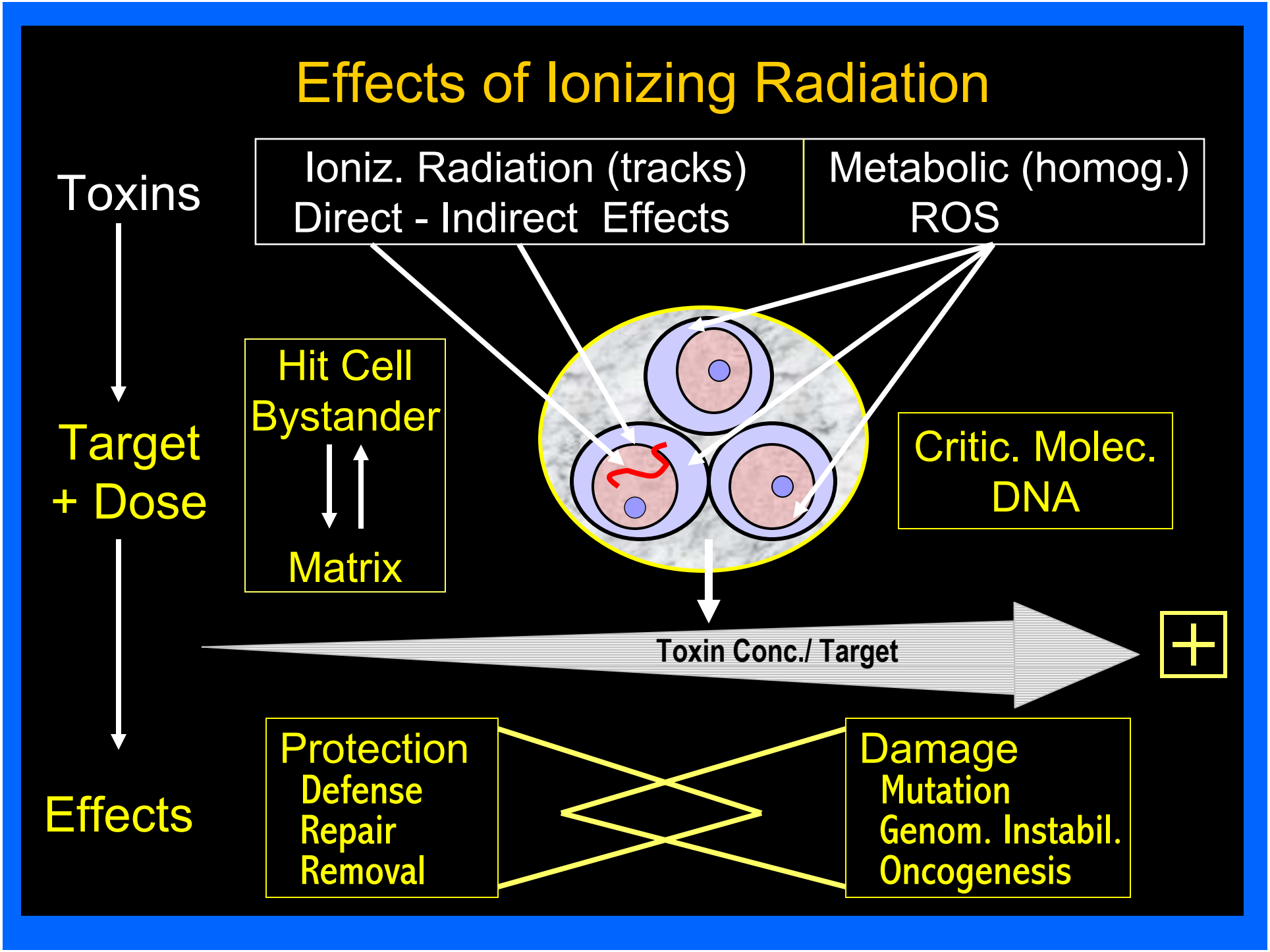


Hall E., Radiobiology for the Radiologist, Lippincott et al., 2000

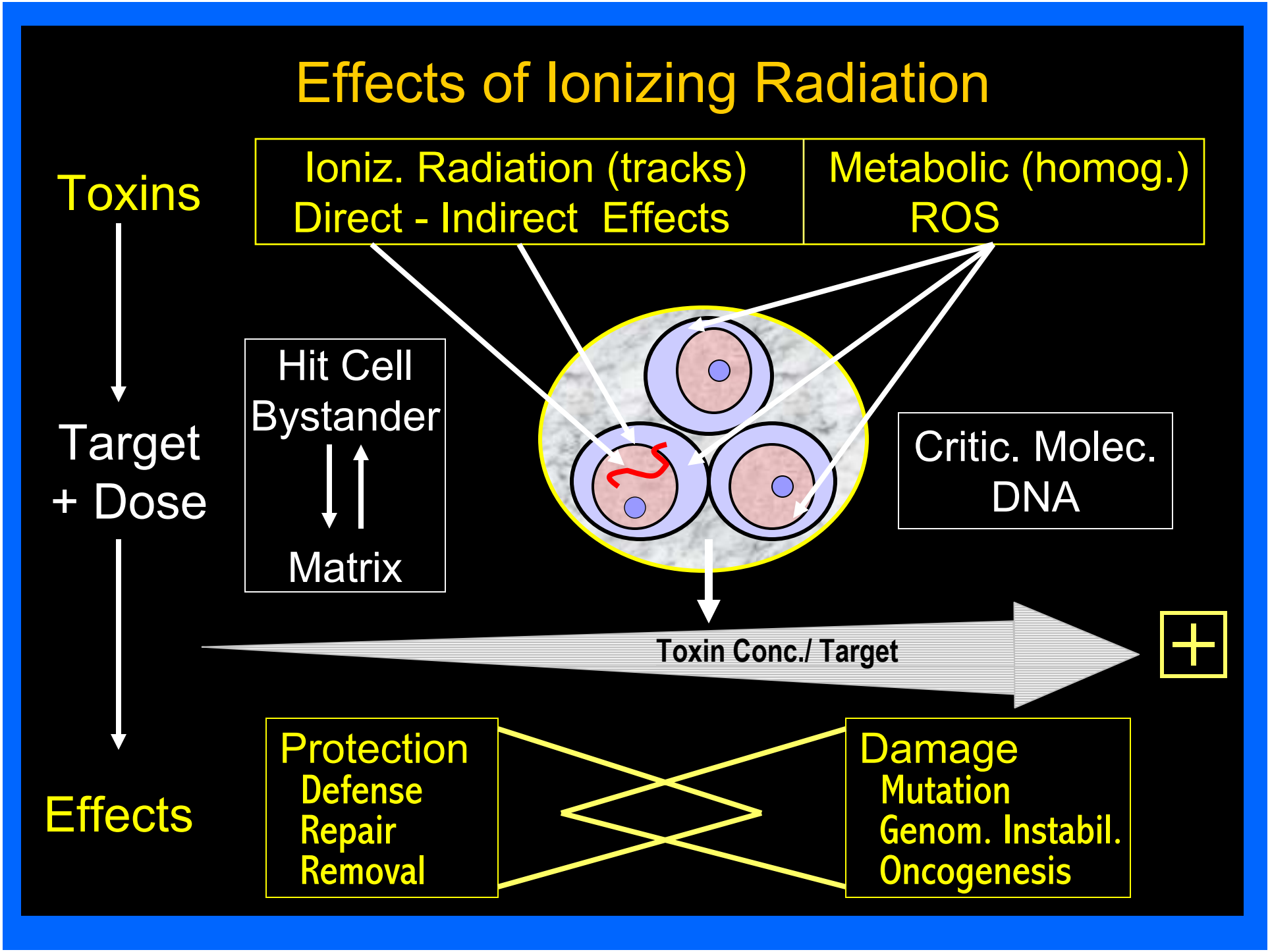
Effects of Ionizing Radiation



Effects of Ionizing Radiation

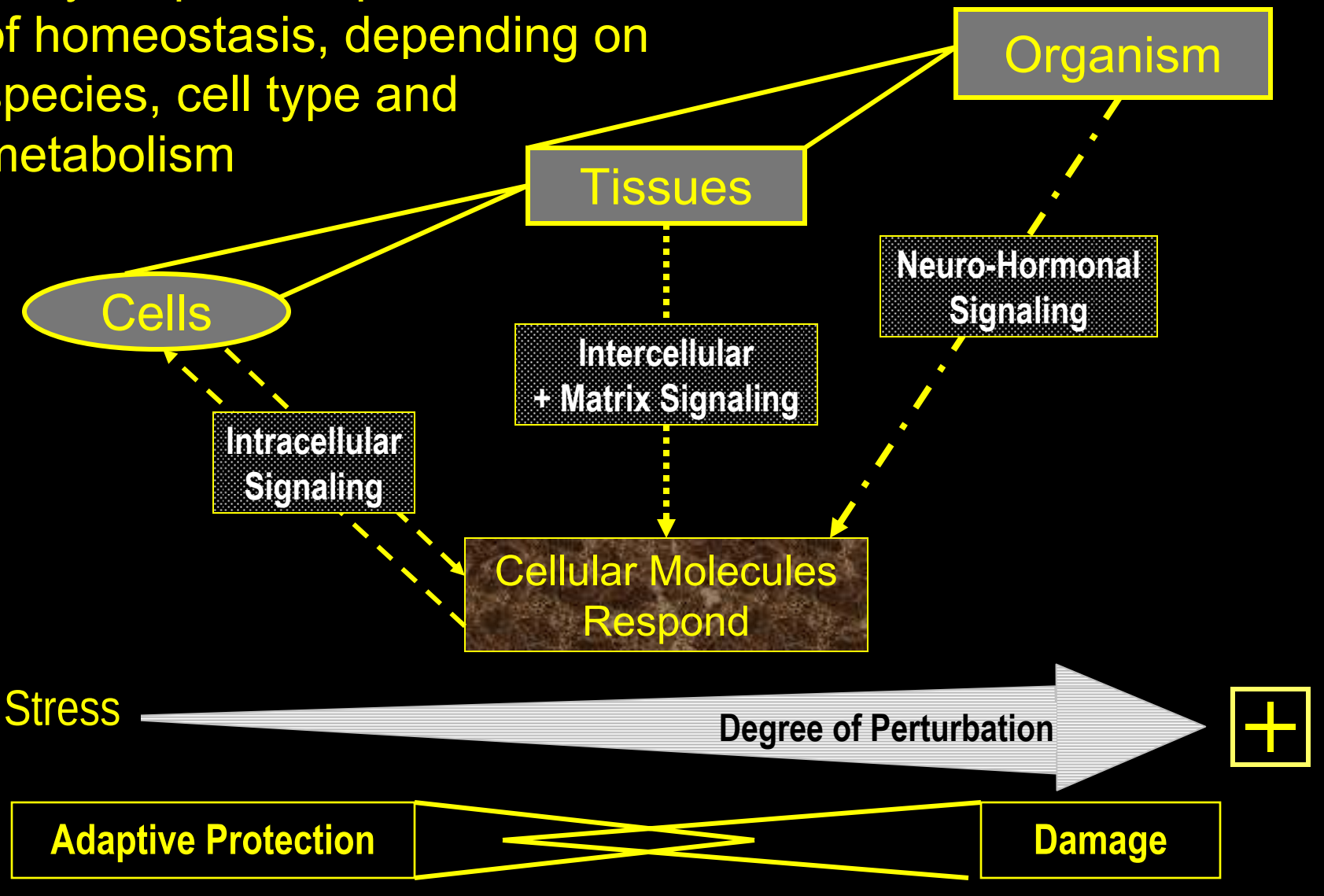


Effects of Ionizing Radiation



Biological Systems are Complex and Adapting

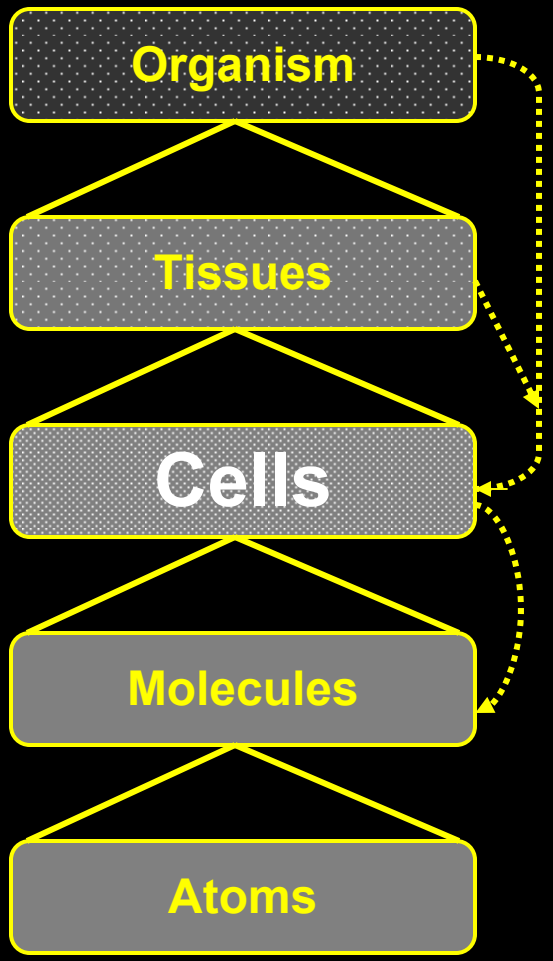
They respond to perturbations of homeostasis, depending on species, cell type and metabolism



Scheme of Biological Systems

Various Levels of Organization

From Matter to Life



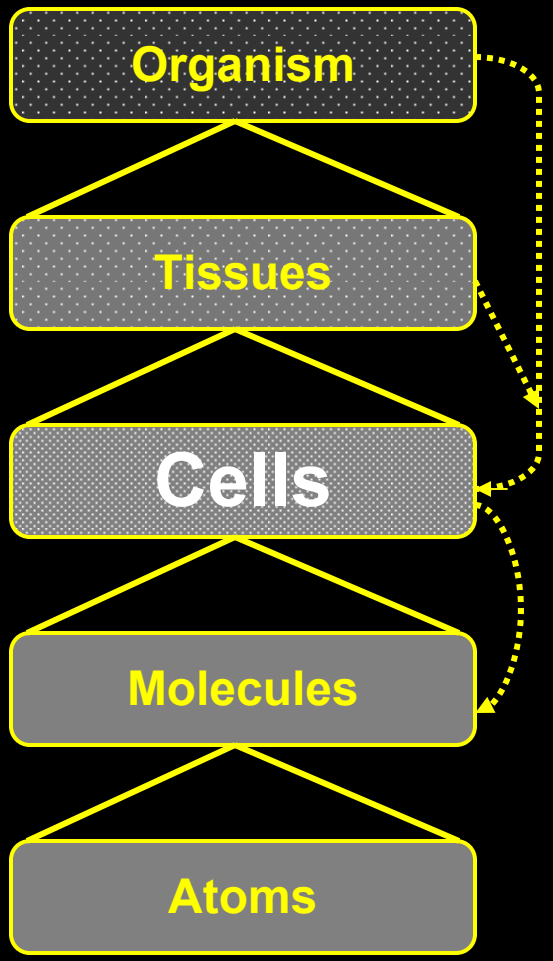
Living Organism

Cells are Fundamental Units of Life Triggering Tissue Effects

Building Blocks of Life

Complex Adaptive Systems at Various Levels

From Matter to Life

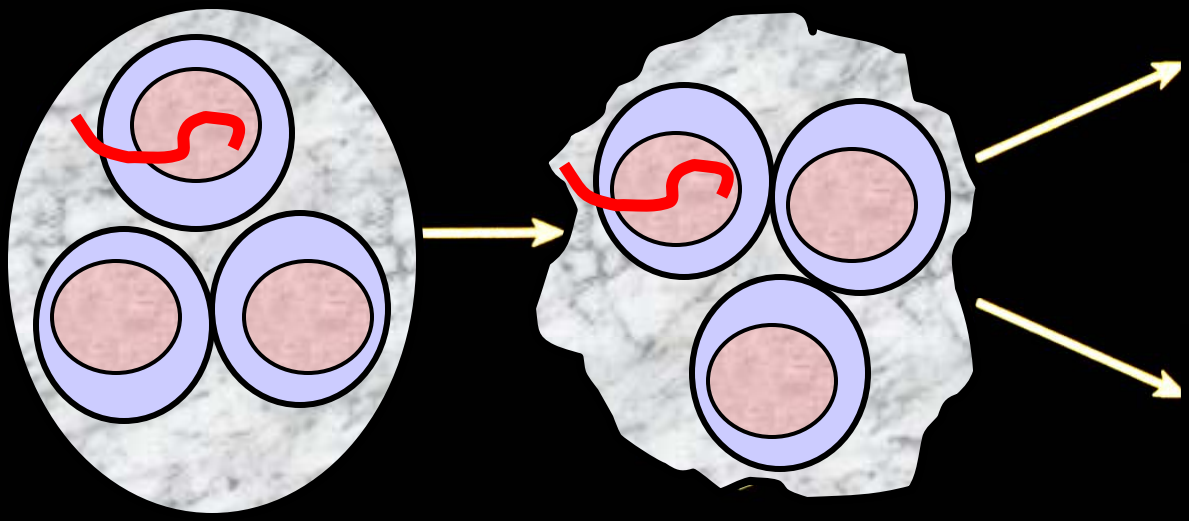


Living Organism

Cells are Fundamental Units of Life Triggering Tissue Effects

Building Blocks of Life

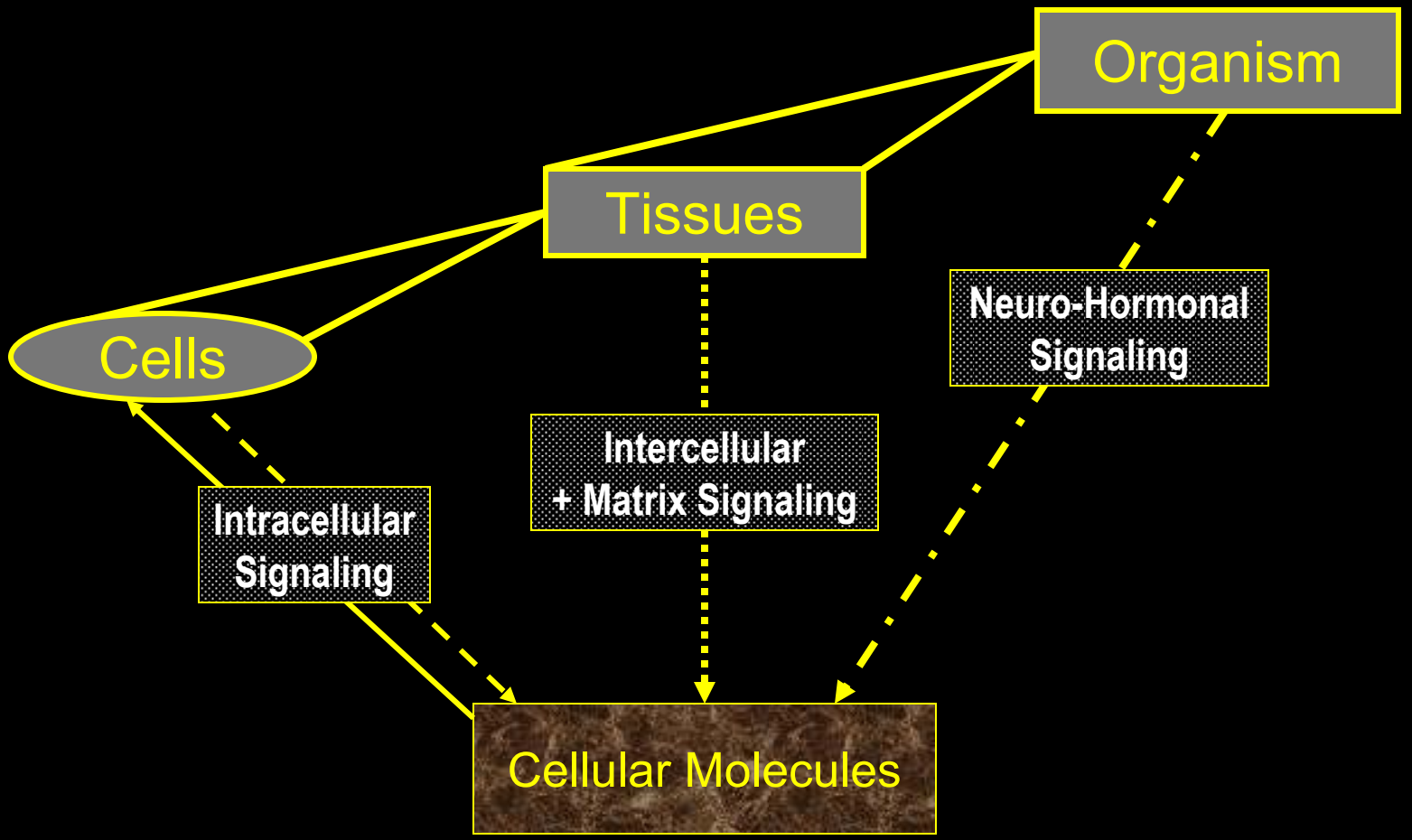
New research shows dual effect of low doses of ionizing radiation in cells and their neighbors

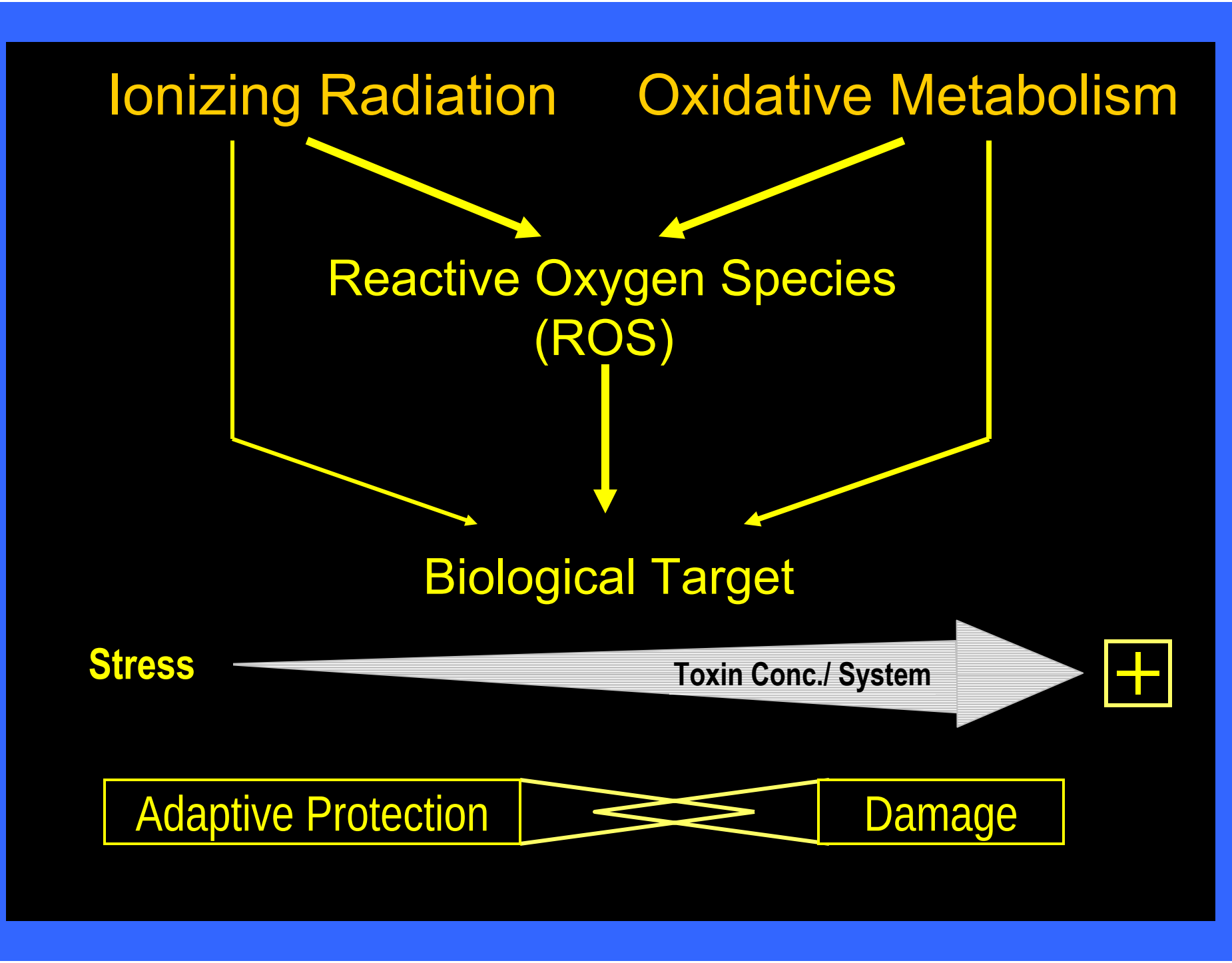


Induction of damage (cancer ↑): $[p_{ind}]$

Activation of protection (cancer ↓): $[p_{prot}]$

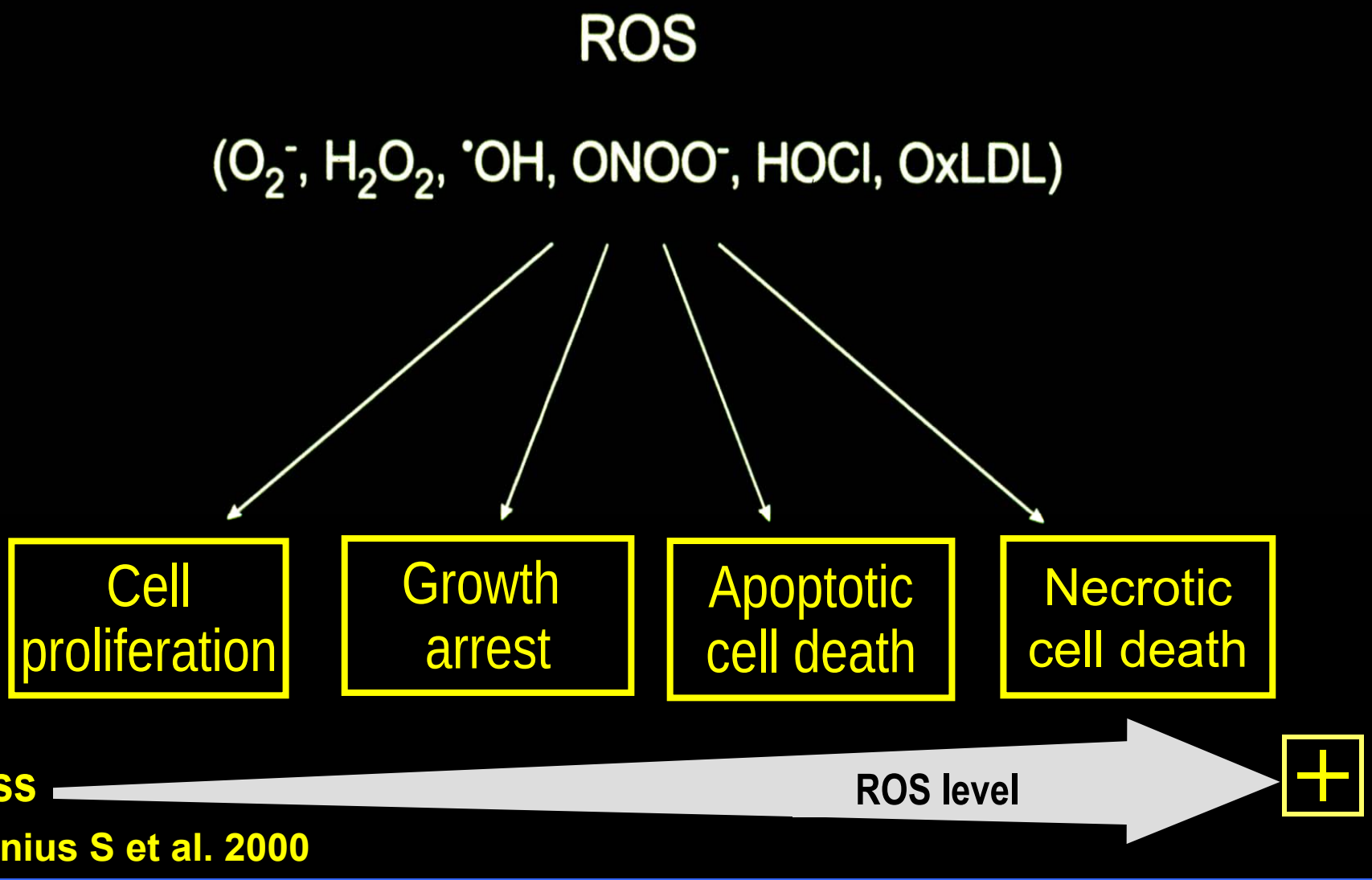
Biological Systems




Ionizing Radiation
Oxidative Metabolism
Reactive Oxygen Species
(ROS)
Biological Target
Stress
Toxin Conc./ System
+
Adaptive Protection
Damage

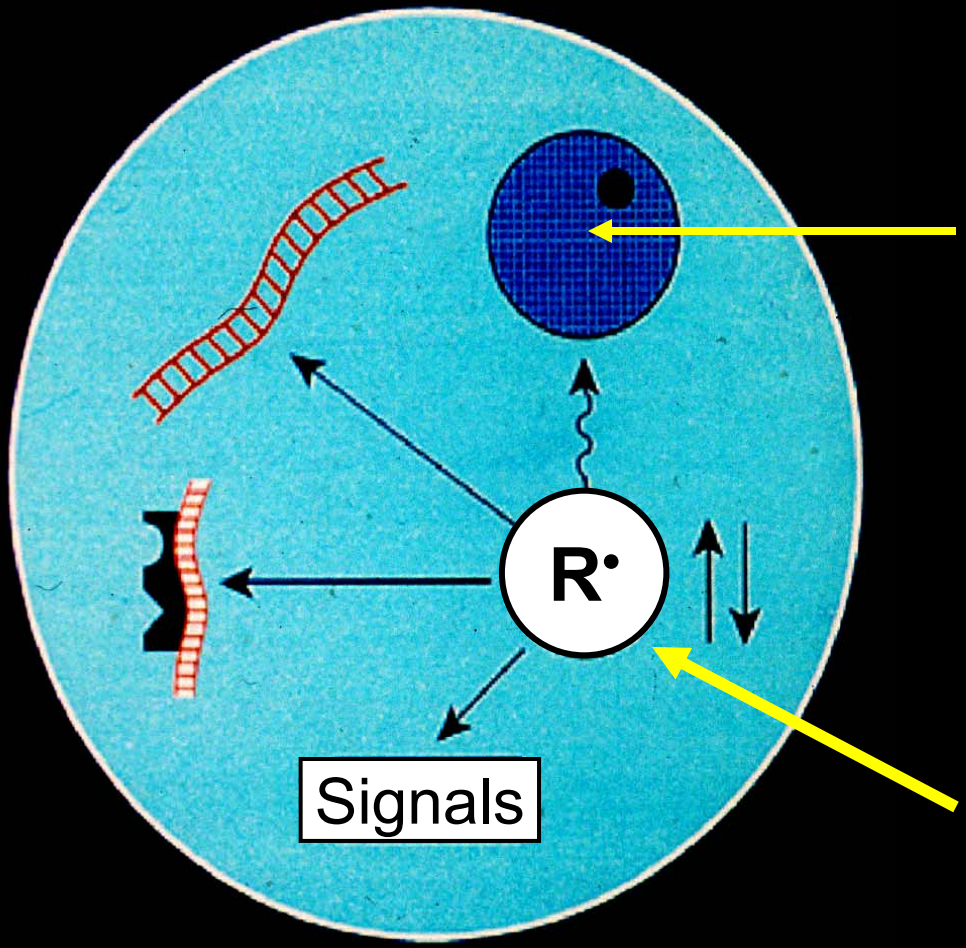
Reactive Oxygen Species (ROS)

cause effects depending on ROS concentration



Orrenius S et al. 2000

Reactive Oxygen Species (ROS) by Metabolism



Normal Cell

Pollycove M, Feinendegen LE
Hum. Exp. Toxicol, 2003

~ 10^9 ROS ($R^{\bullet}$)
per cell per day →
~ 10^6 DNA alterations,
with ~ 0.1 DSB

Lipid peroxidation

Protein-carbonylation

Cytoskeletal disruption

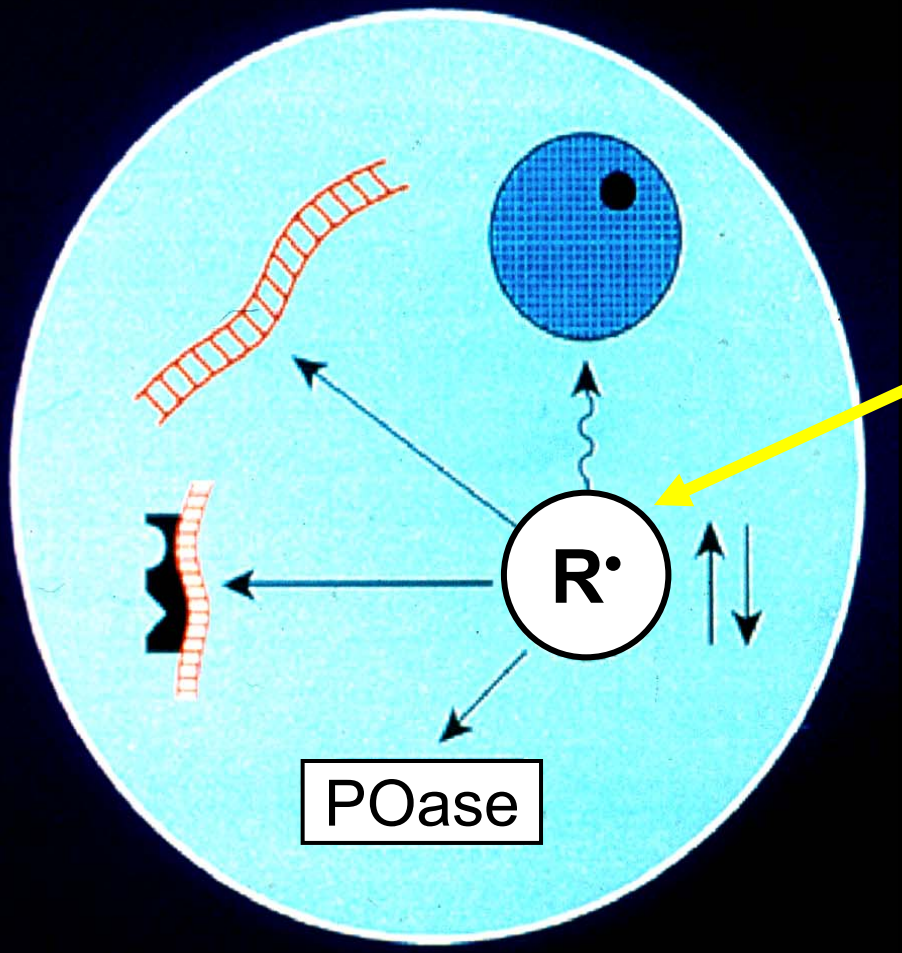
Perturbs Ca^{2+} homeostasis

Interfers with cell signaling

Activates apoptosis

Orrenius S et al., 2000

ROS Arise from Normal Metabolism



Normal Cell

In cytoplasm

~ 10^9 ROS ($R^{\bullet}$)

arise endogenously per day at a rate that depends on metabolism, and also occur in minibursts

Adapted from Pollycove M, Feinendegen LE 2003

Oxidative Stress May Causes Damage and Adaptive Protection (AP)

System AP: ↑ Antioxidant reactions:
G-SH; SOD; Catalase → *Protection*

↑ DNA repair → *Damage reduction*

↑ Apoptosis → *Damage removal*
↑↓ Cell proliferation → dto + *amplification ?*

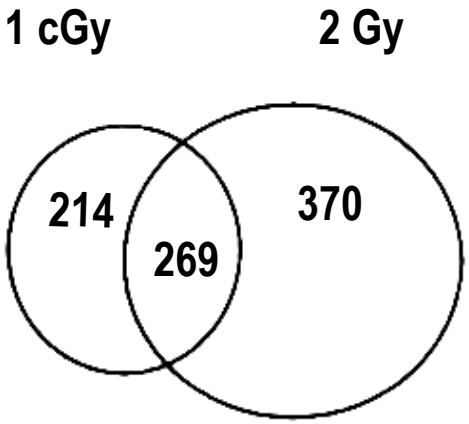
Damage: ↑ Oncogenic transform. → *Cancer*

Often accompanied by ↑ or ↓ gene expression

Finkel and Holbrook, Nature 2000

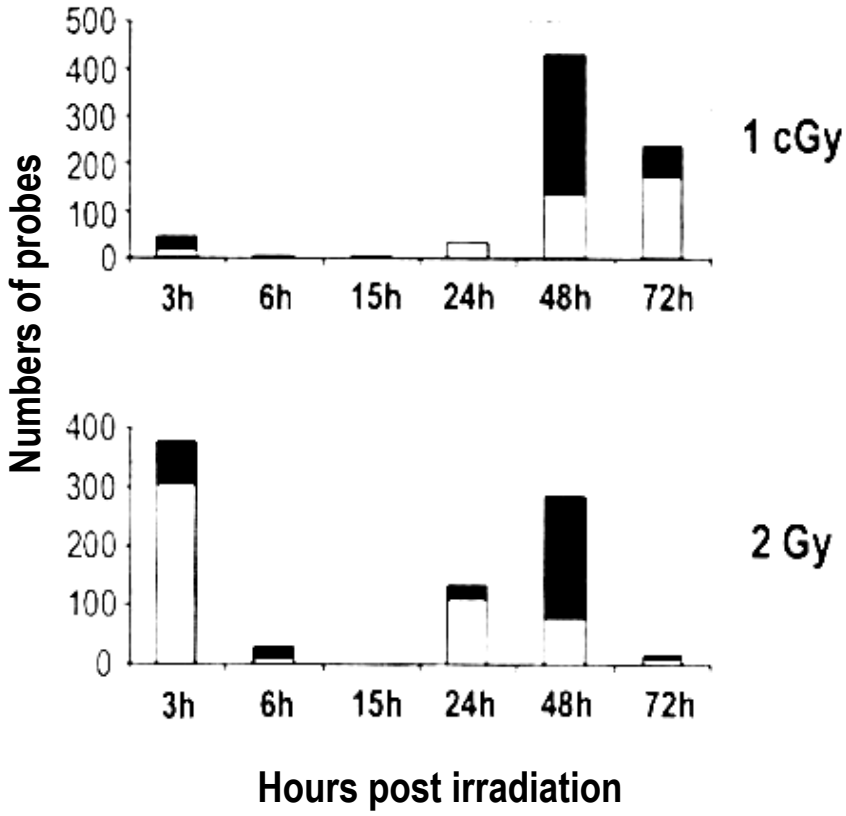
Gene Expression in cDNA Microarray Analysis
in low and high dosed normal human keratinocytes

Distribution of 853 genes modulated by γ radiation



Black Column: Gene Repression
White Column: Gene Induction

Gene modulation at different times



Franco N et al., Radiat. Res. 163: 623 – 635, 2005

Radiation-Induced Gene Expressions

human fibroblasts in culture, 90 % in G_2-phase
at 1, 2, 4, 24 hrs after 2 cGy (LD) and 4 Gy (HD)
of 7168 genes tested 2345 responded

Gene category	P value *	
	2 cGy	4 Gy
Cell signaling	**0.0002**	0.141
Signal transduction	**0.011**	0.705
Development	**0.002**	0.441
Response to DNA damage	**0.035**	0.324
Cell Proliferation	0.546	**0.009**
Apoptosis	0.568	**0.047**

*** P values < 0.05 give significant diffences from all other groups**

L-H Ding et al., Radiat. Res., 2005

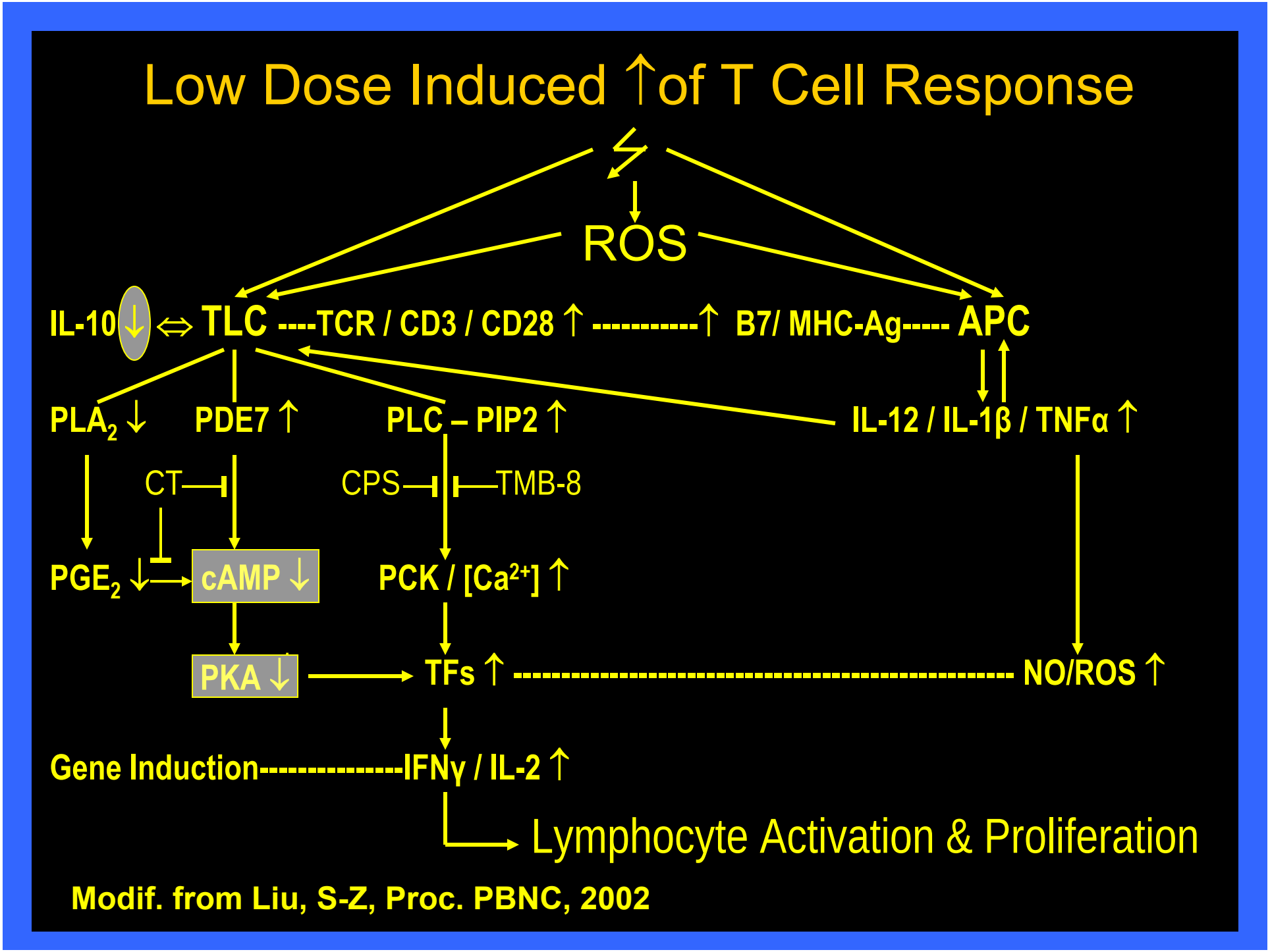
Radiation-Induced Gene Expressions

human fibroblasts in culture, 90 % in G_2 -phase at 1, 2, 4, 24 hrs after 2 cGy (LD) and 4 Gy (HD)

of 7168 genes tested 2345 responded

LD only		16
LD and HD both		47
	in opposite direction 13	
	earlier at LD than HD 9	
	greater at LD than HD 25	
HD only		148
LD and HD, dose-dependent		228

L-H Ding et al., Radiat. Res., 2005


Low Dose Induced ↑of T Cell Response
ROS
IL-10↓ ⇔ TLC ----TCR / CD3 / CD28 ↑ ----------↑ B7/ MHC-Ag----- APC
PLA2 ↓
PDE7 ↑
PLC – PIP2 ↑
IL-12 / IL-1β / TNFα ↑
CT
CPS
TMB-8
PGE2 ↓
cAMP ↓
PCK / [Ca2+] ↑
PKA ↓
TFs ↑ ---------- NO/ROS ↑
Gene Induction----------IFNγ / IL-2 ↑
Lymphocyte Activation & Proliferation
Modif. from Liu, S-Z, Proc. PBNC, 2002

Human Diploid Fibroblasts in Culture

DNA-DSB shown by γ-H2AX focus assay

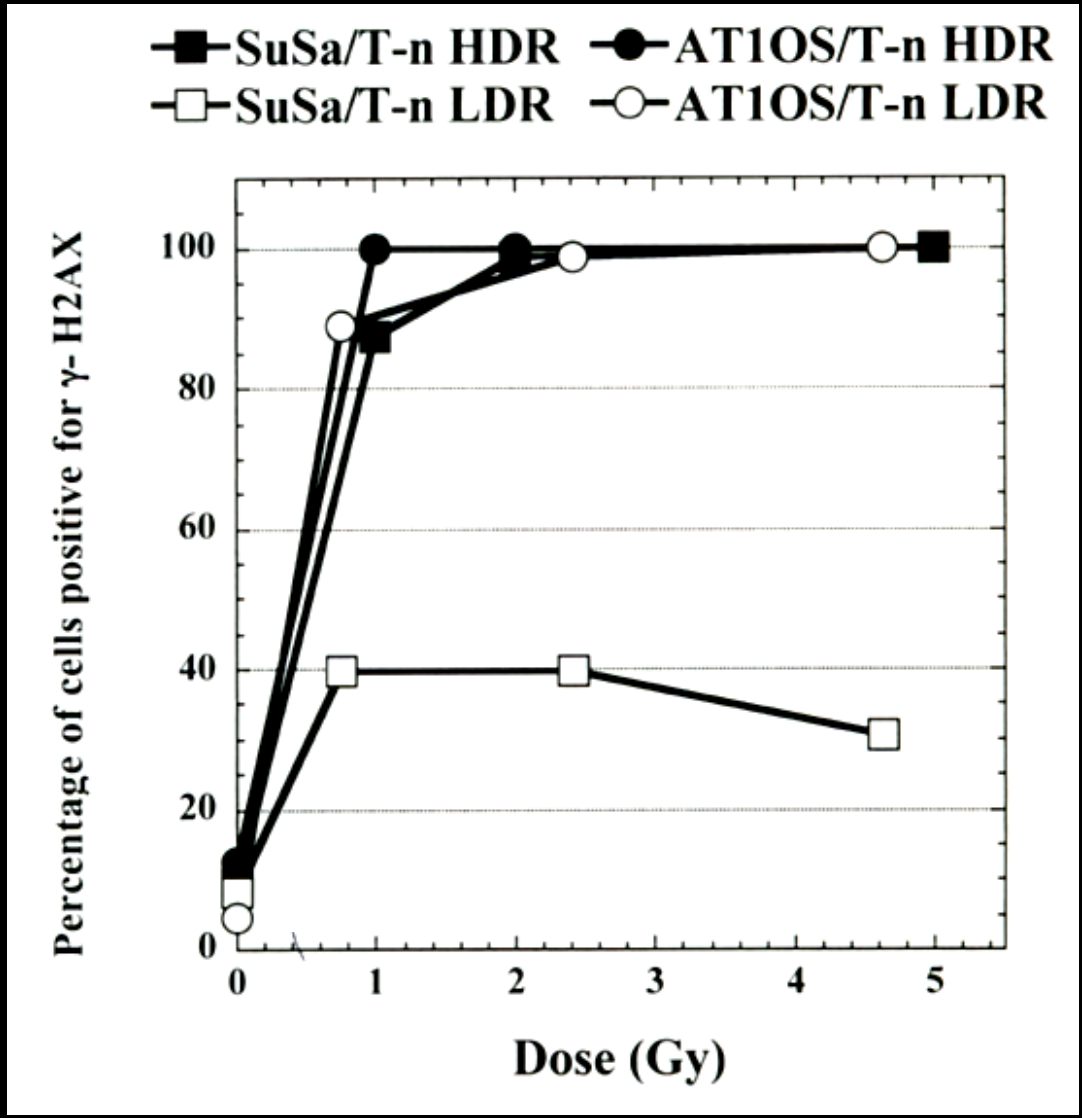
Normal cells
(SuSa/T-n)

Cells from AT patient
(AT1OS/T-n)

HDR = high dose rate
2 Gy/min;150 kV x-rays

LDR = low dose rate
0.3 mGy/min; ^{137}Cs γ
(~ 1 e^- hit /cell / min)

Nakamura H et al.
Radiat. Res. 165: 277, 2006



Human Diploid Fibroblasts in Culture

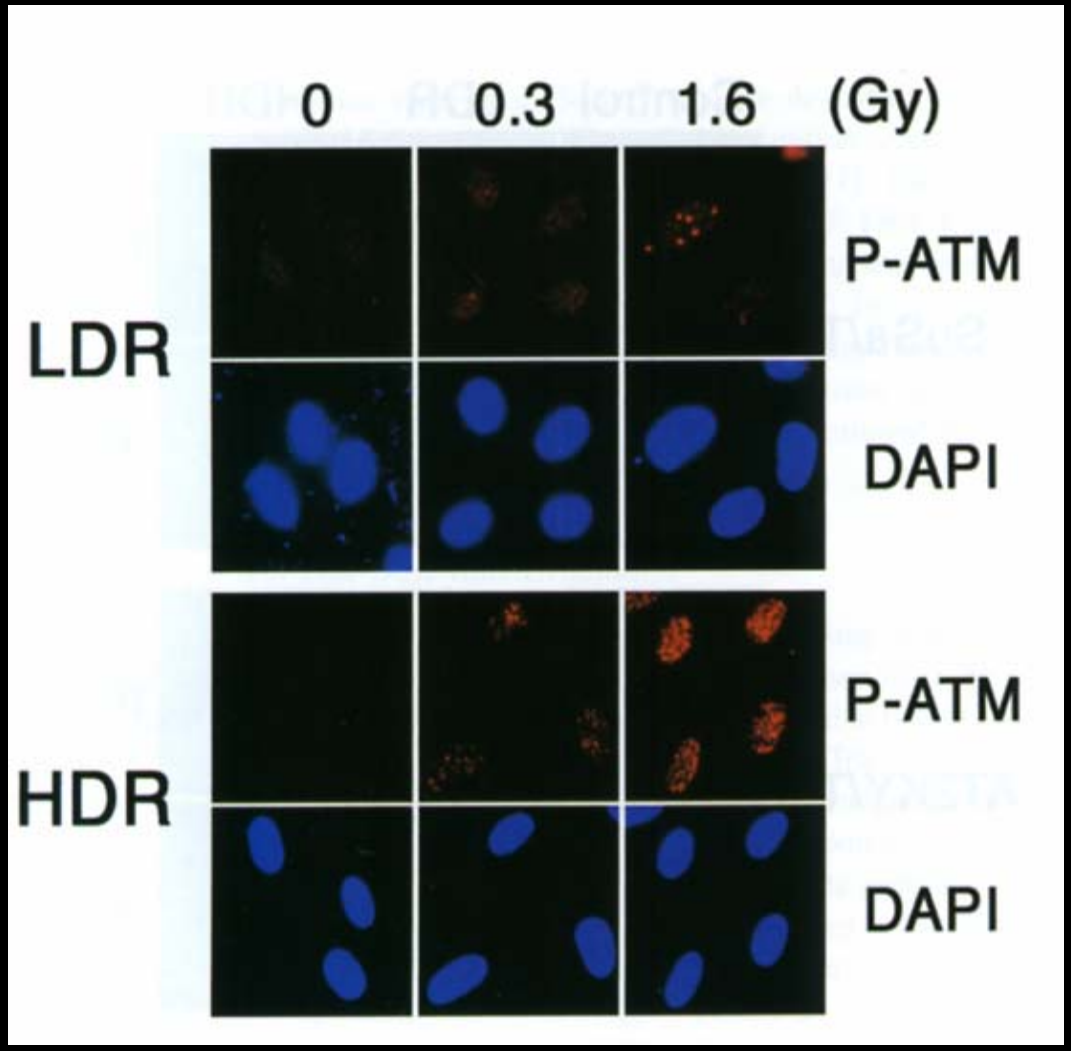
normal cells (SuSa/T-n)

LDR = low dose rate
0.3 mGy/min; ^{137}Cs γ
(~ 1 e^- hit /cell / min)

HDR = high dose rate
2 Gy/min;150 kV x-rays

P-ATM = phosph.-ATM

DAPI = nuclear stain



Nakamura H et al.
Radiat. Res. 165: 277, 2006

Low-Dose (low-LET) Induced Adaptive Protection Disappearing at High Doses

Response	*(Ref.)*	*D (Gy) at Max. Resp.*
1. Radical Detoxification		
–Prot.TdR-K (BM cells)	(Fei 95)	0.1
–Ind SOD (mitoch. brain)	(Yam 92)	0.5
2. DNA Damage Reduction		
–Red. Chr. Ab. (lymph.)	(PoR 83)	0.05
–Prot. Chr. Ab. (lymph.)	(Sha 87)	0.2
–DNA Recomb. (cult. cells)	(Leh 97)	0.25
3. DNA Damage Removal		
–Induct. Immune Comp.	(Mak 90)	0.1
– " " "	(And 92)	0.1
– " " "	(Sak 97)	0.1
–Apoptosis (thymocytes)	(Shu 96)	0.15
–Hypersens. (cult. cells)	(Joi 96)	0.2-0.4
4. Gene Expression		
–Thioredoxin (liver cells)	(Koj 98)	0.2-0.5
–c-fos (cult. cells)	(Pras 95)	0.25
–c-jun, c-myc, c-Ha-ras (cult. cells)	(Pras 95)	0.5

Adaptive protection also operates

against

spontaneous gene-, cell- and tissue damage

!

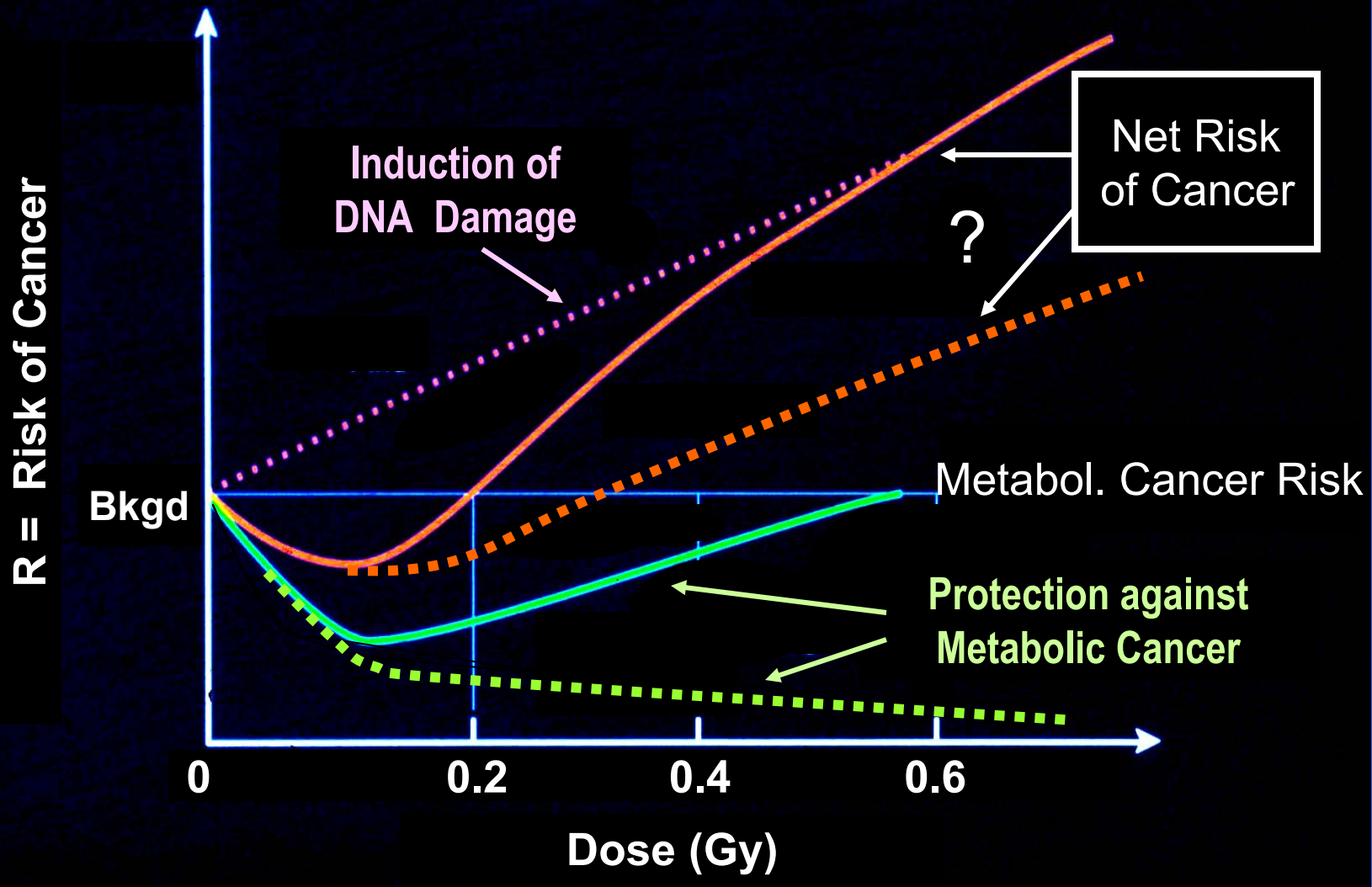
DNA double strand breaks per average cell

are about a thousand times more frequent

from normal metabolism

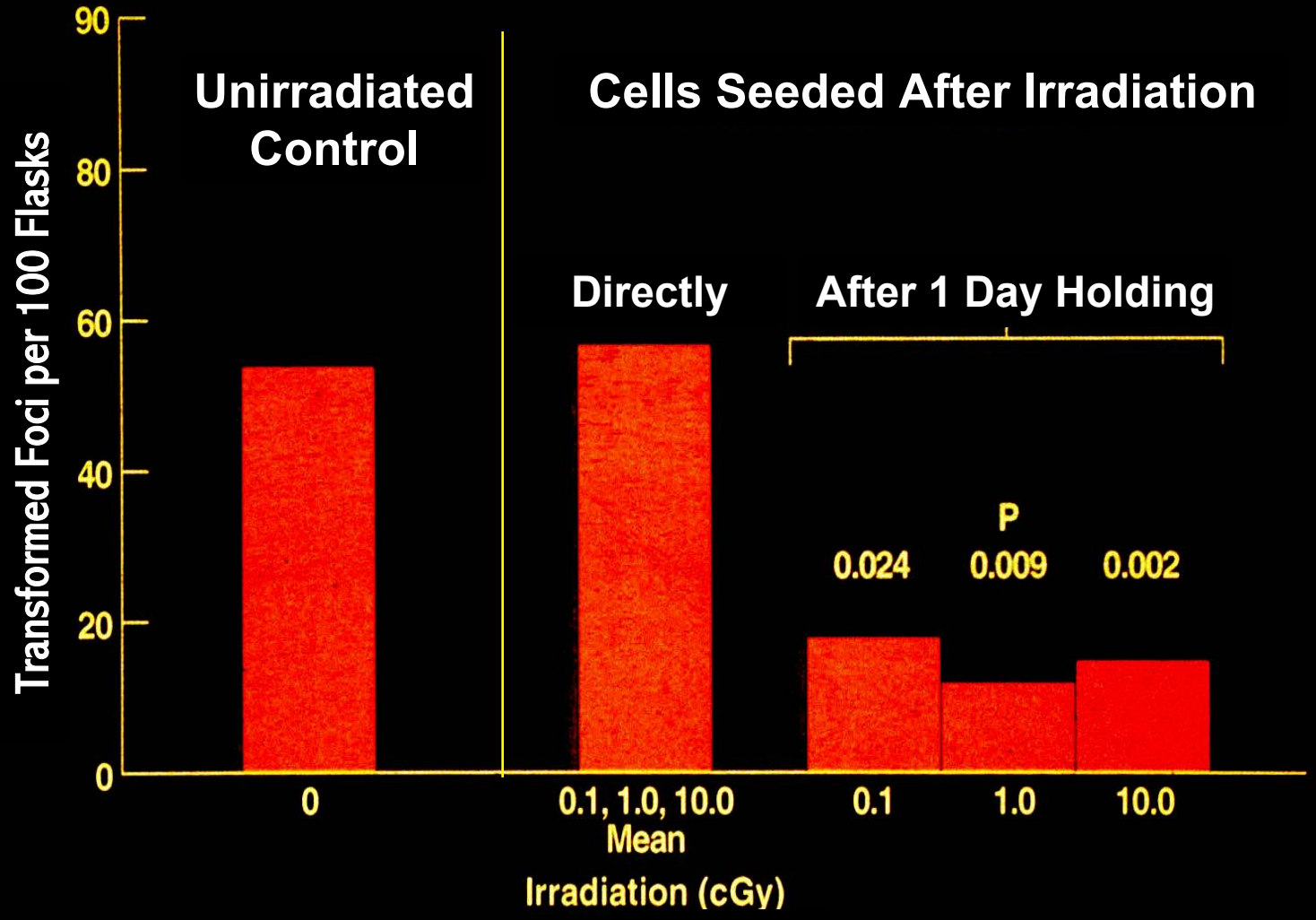
than from normal background radiation.

Dual Effect of Low-Dose (Low-LET) Radiation



Low-Dose Induced ↓ of Spontaneous Transformation

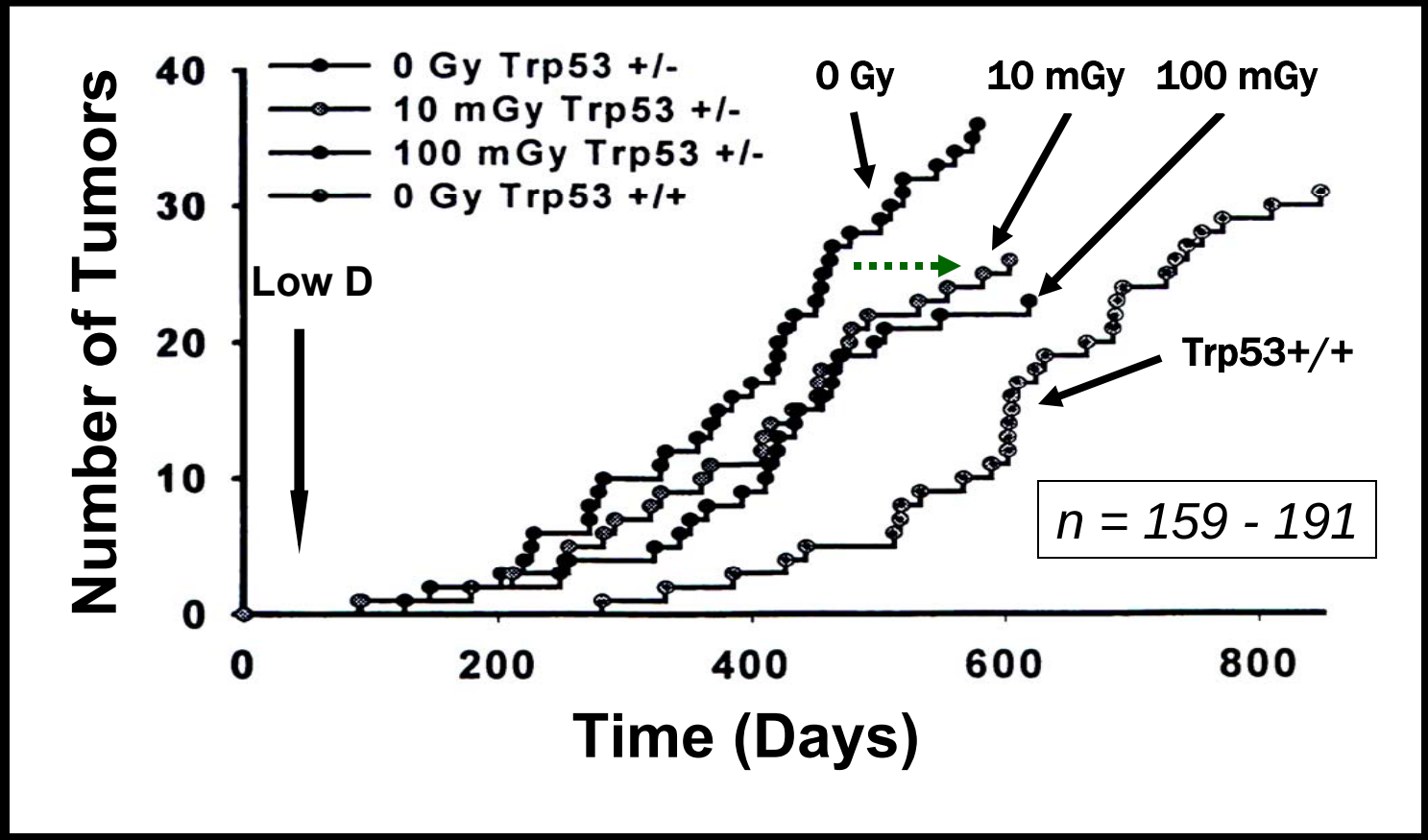
C3H10 T ½ cells after ^{60}Co γ-irrad. with 0.1, 1.0, 10 cGy, vs. control



Azzam El et al., Radiat. Res., 1996

Low-Dose Induced ↓ of Spont. Tumor

lymphoma in Trp 53 +/- mice after single WB γ-irrad. at age ~ 2 months



Mitchel REJ et al., Radiat. Res., 2003

Observed and Expected Solid Ca Deaths 1950 – 1997

among atomic bomb survivors

Dose Gy	No. People Observed	Solid Ca + Observed	Solid Ca + Expected
< 0.005	37458	3833 ± 62	3844 ± 62
0.005 - 0.1	31650	3277 ± 57	3221 ± 57
0.1 - 0.2	5732	688 ± 26	622 ± 25
0.2 - 0.5	6332	763 ± 28	678 ± 26
0.5 - 1.0	3299	438 ± 21	335 ± 18
1.0 - 2.0	1613	274 ± 17	157 ± 13
2.0 +	488	82 ± 9	38 ± 6
Total	86 572	9335 ± 97	8895 ± 30
Percent	100 %	10.8 %	10.3 %

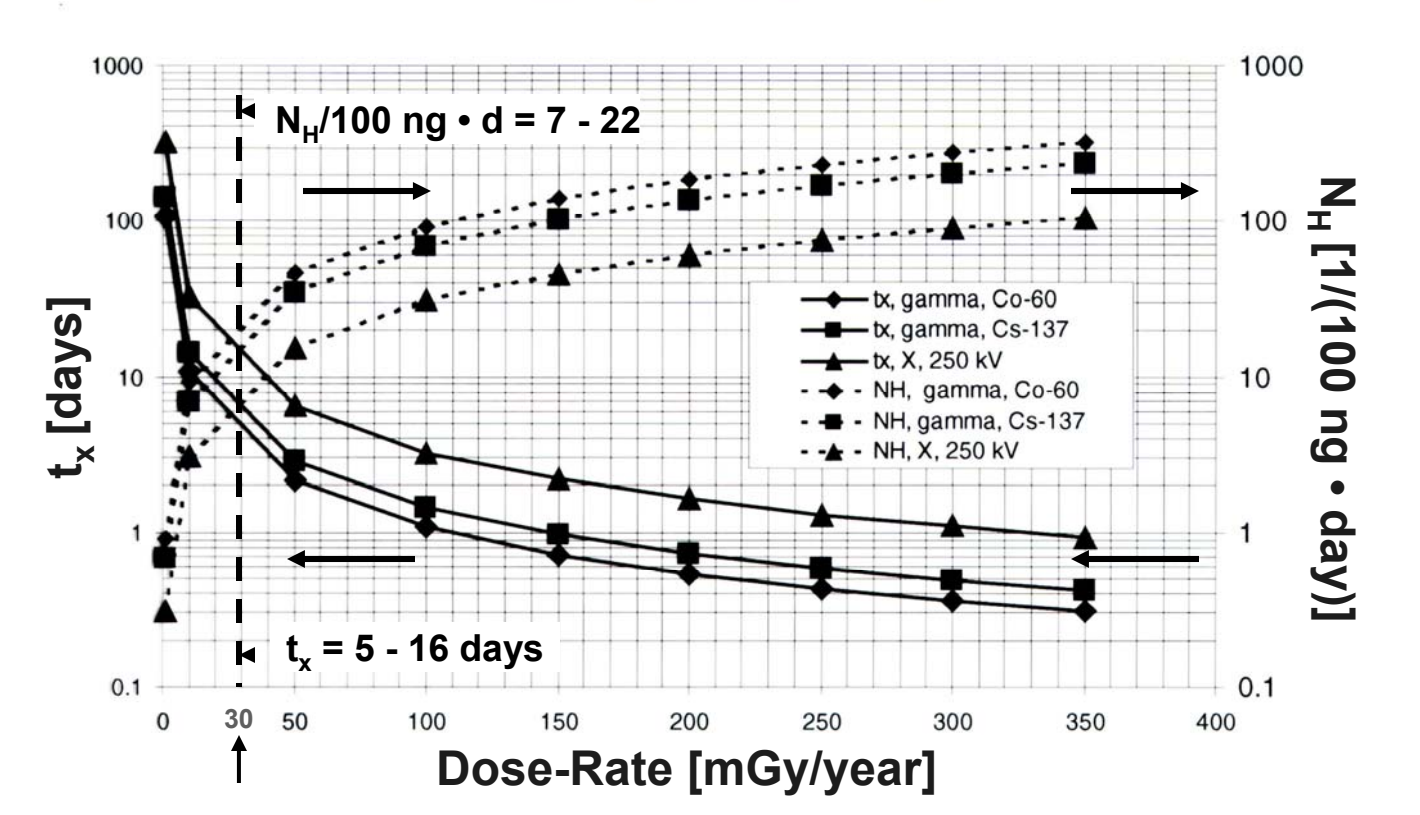
from Preston DL et al., 2003

Atkinson WD et al. published in 2004 the mortality among 51 367 employees of the UK Atomic Energy Authority, from 1946-1997.

The all cancer mortality
was significantly lower for radiation workers
than for non-radiation workers.

Atkinson WD et al., Occup. Environ. Med., 2004

Dose-Rate and Microdose-Hits

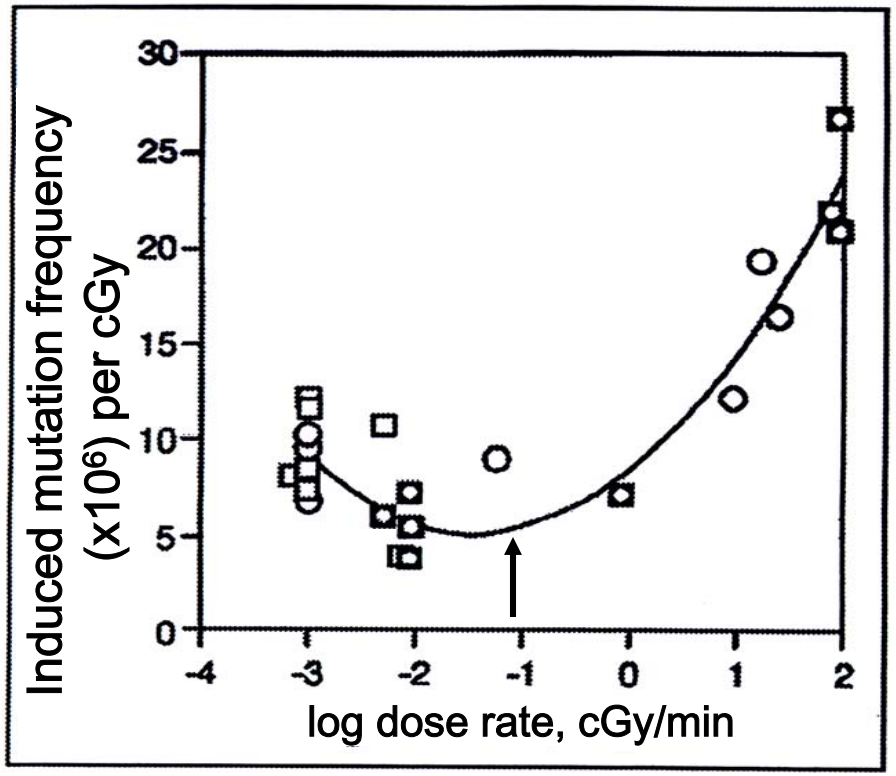


microdoses $\bar{z}_1$ in mGy: ^{60}Co-gamma radiaton 0.3 ~ 45 ROS
^{137}Cs-gamma radiation 0.4 ~ 60 ROS
250 kV x-rays 0.9 ~ 130 ROS

Feinendegen LE, Graessle DH, Brit. J. Radiol., 2002

Chronic Low Dose Rate Induced ↓ of Locus Mutations

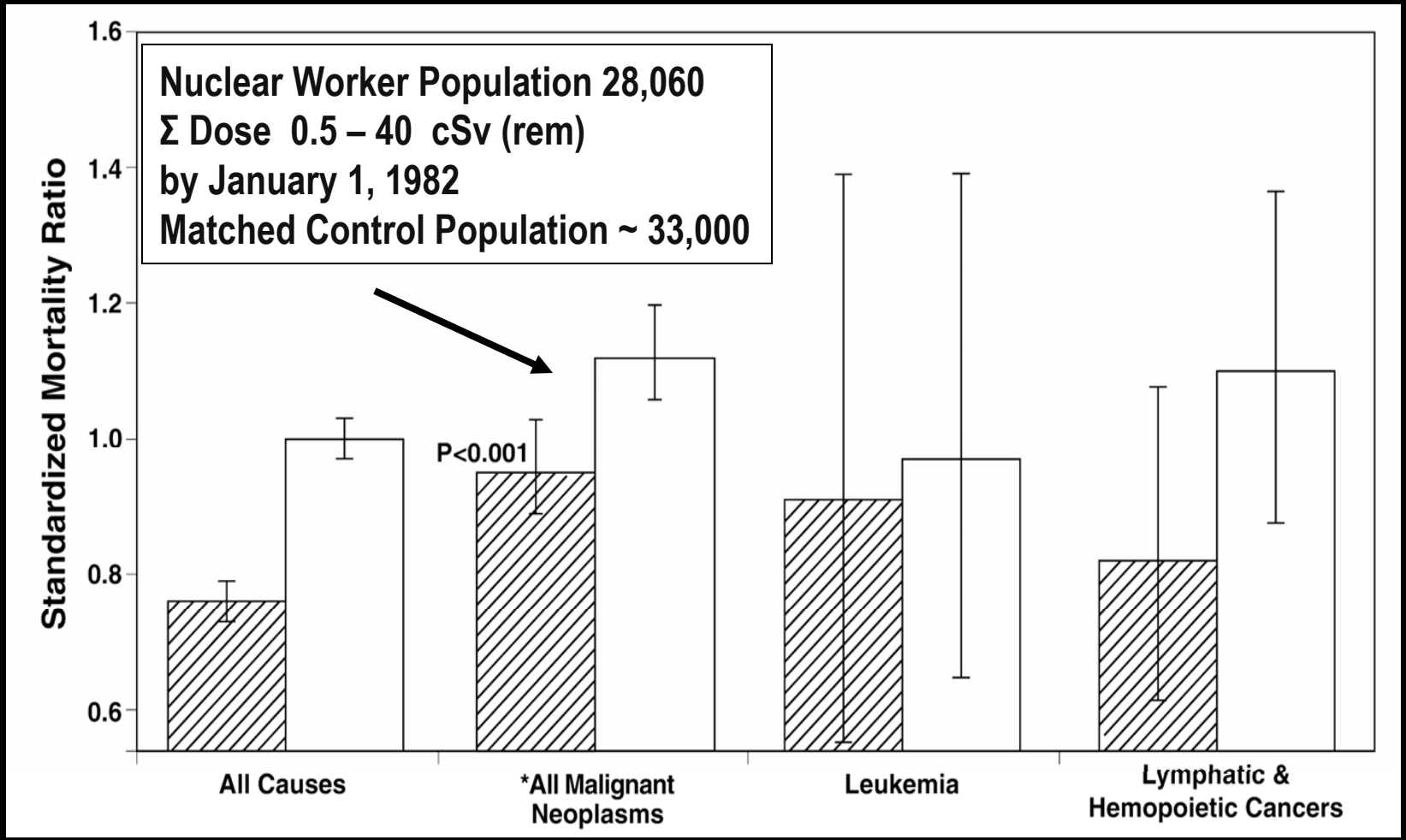
in vivo low-LET irradiation (^{137}Cs), mouse spermatogonia



0.1 cGy / min → 0.4 mGy–hits t_x : ~ 30 sec

Vilenchik MM, Knudson AG, PNAS, 2000

Health Effects of Low-Level Radiation in Shipyard Workers in the USA



Nuclear workers Non-Nuclear Workers 95% Confidence Limits

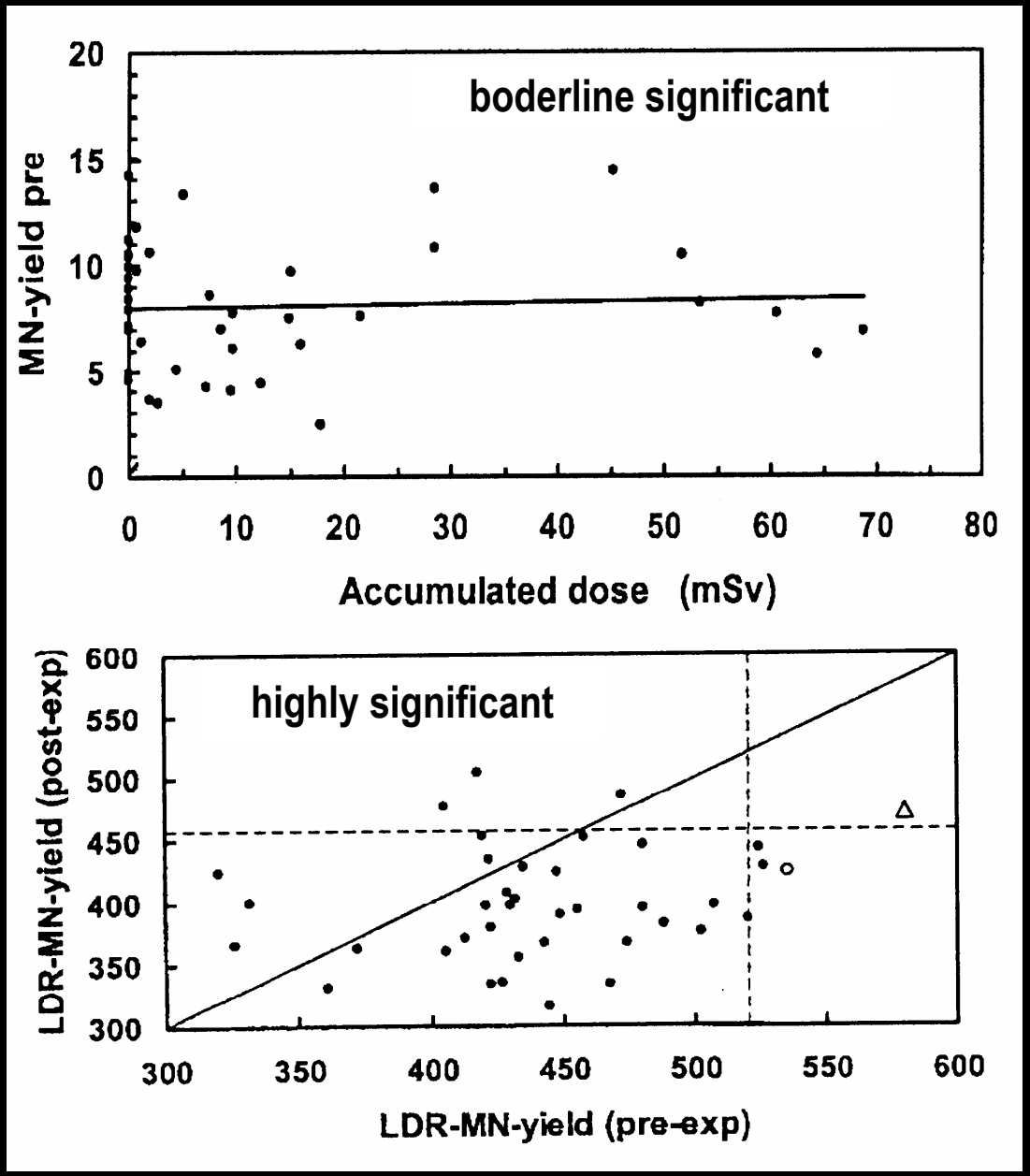
Data from: Matanoski GM, Tables 3.6 B,D; 4.1.A, Rep DOE, 6/1991, (DE-AC02-79EV10095)

DNA Damage

in human lymphoc.
of 41 exp.workers
(10 mSv γ irrad. ~
(33 x 0.3 mGy hit / ng)
in vivo

Enhanced DNA repair

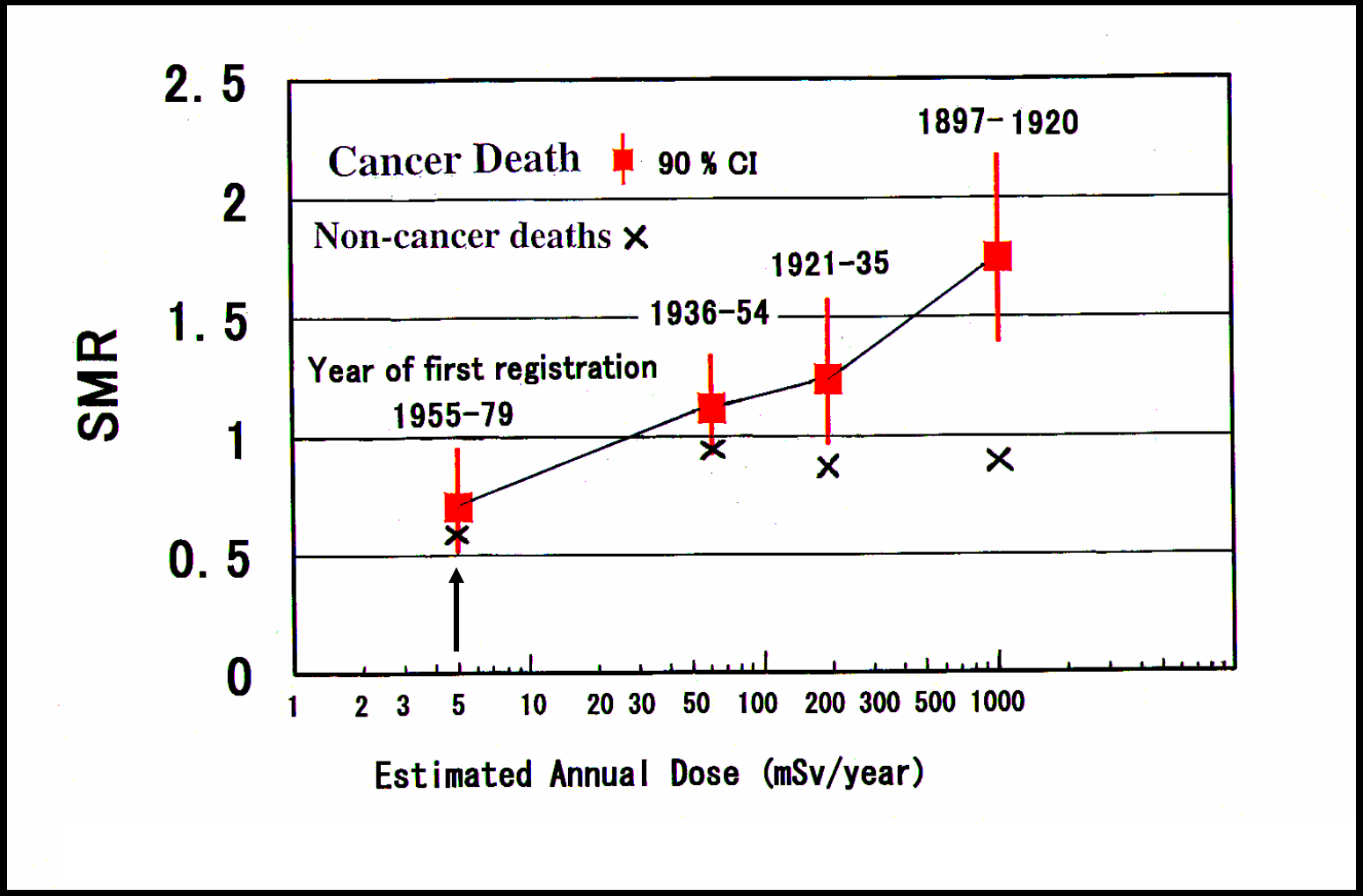
upon ^{60}Co irrad. in vitro
with 4 mGy / min
(0.3 mGy / ng / 4.6 sec)
accum. D = 3.5 Gy



Thierens H et al. , Int. J. Radiat. Biol., 2002

SMR for British Radiologists (100 Years Study)

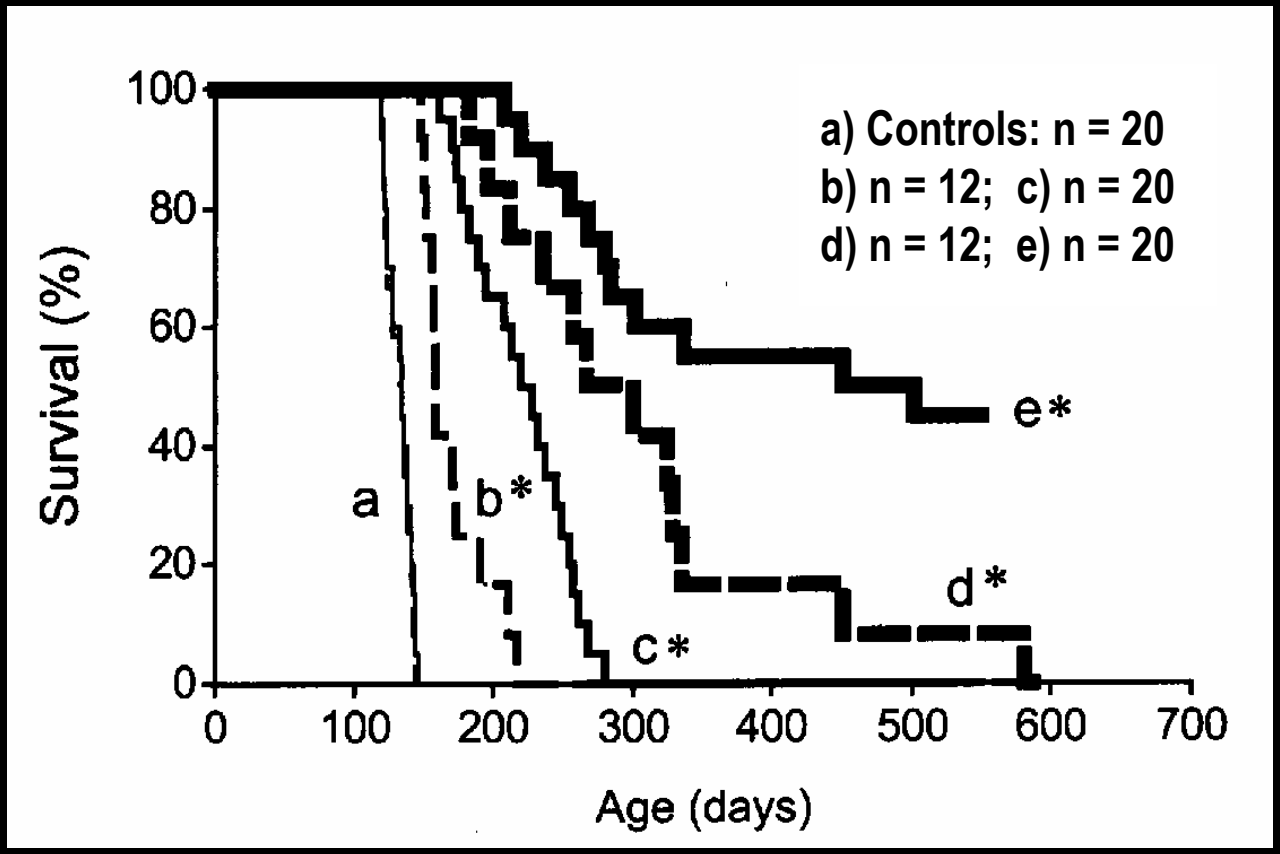
compared with medical practitioners



By Courtesy: Kaneko M, 2004; adapted from British J. Radiol., 2001

Chronic Low γ Dose Rate Induced ↑ of Life Span

Mice with defect in apoptosis-regulating *Fas* gene (MRL-*lpr/lpr* mice)



b) 0.35 mGy / hr begin at 7 weeks for 5 weeks; c) dto but for life.

d) 1.2 mGy / hr begin at 5 weeks for 5 weeks; e) dto but for 521 d

Ina Y, Radiat. Res. 163: 418-423 (2005)

Chronic Low γ Dose Rate Induced ↑ of Health

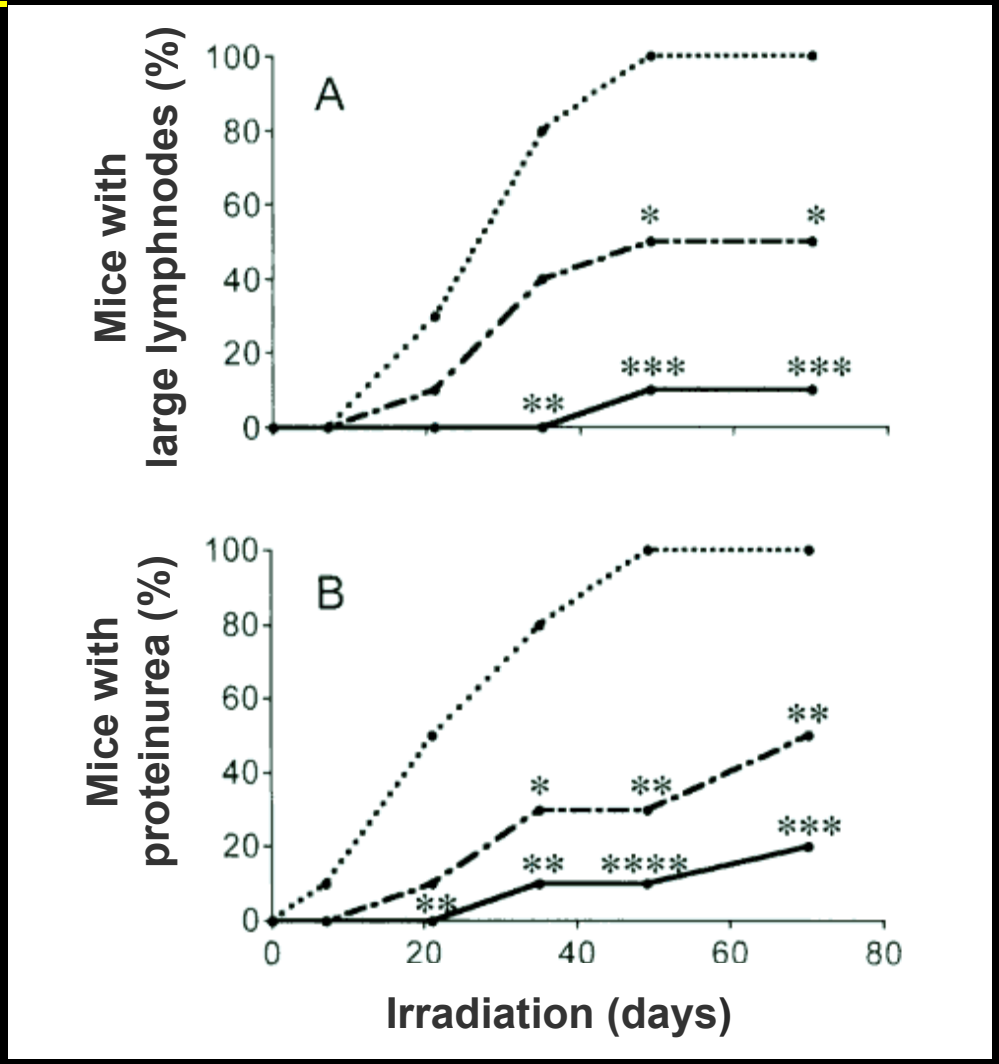
Mice with defect in apoptosis-regulating *Fas* gene (MRL-*lpr/lpr* mice)

These mice develop multiple severe diseases and die early

In panels A and B:

Upper curves: no irradiation
Middle curves: 0.35 mGy/hr
Lower curves: 1.2 mGy/hr chronic irradiation

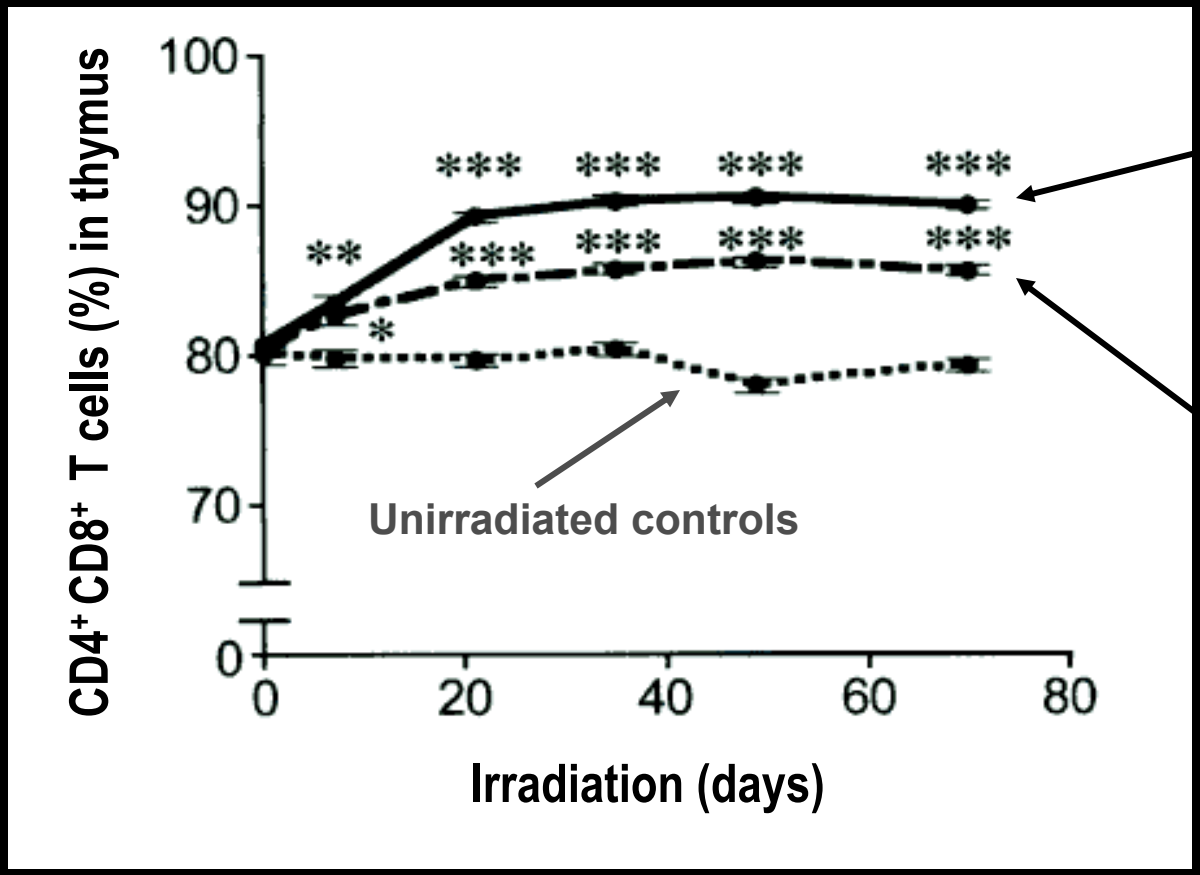
* = p (A) < 0.01; ((B) < 0.05
** = p (A) < 0.001; (B) < .0.01
*** = p (A) < 0.0001; (B) < 0.001
**** = p (B) < 0.0001



Ina Y, Radiat. Res. 163: 418-423 (2005)

Low γ Dose Rate (^{137}Cs) Induced ↑ of Immune Cells

mice with defect in apoptosis-regulating *Fas* gene (MRL-*lpr/lpr* mice)



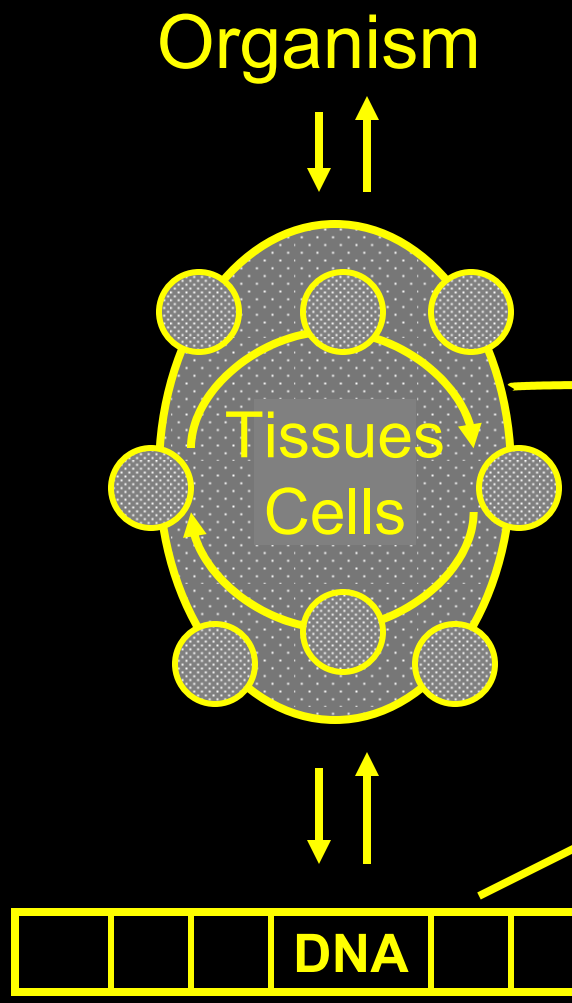
middle curve: chronic irrad. 0.35 mGy/hr; upper curve: dto 1.2 mGy/hr.

* = p < 0.01; ** = p < 0.001; *** = p < 0.0001

Ina Y, Radiat. Res. 163: 418-423 (2005)

Summary

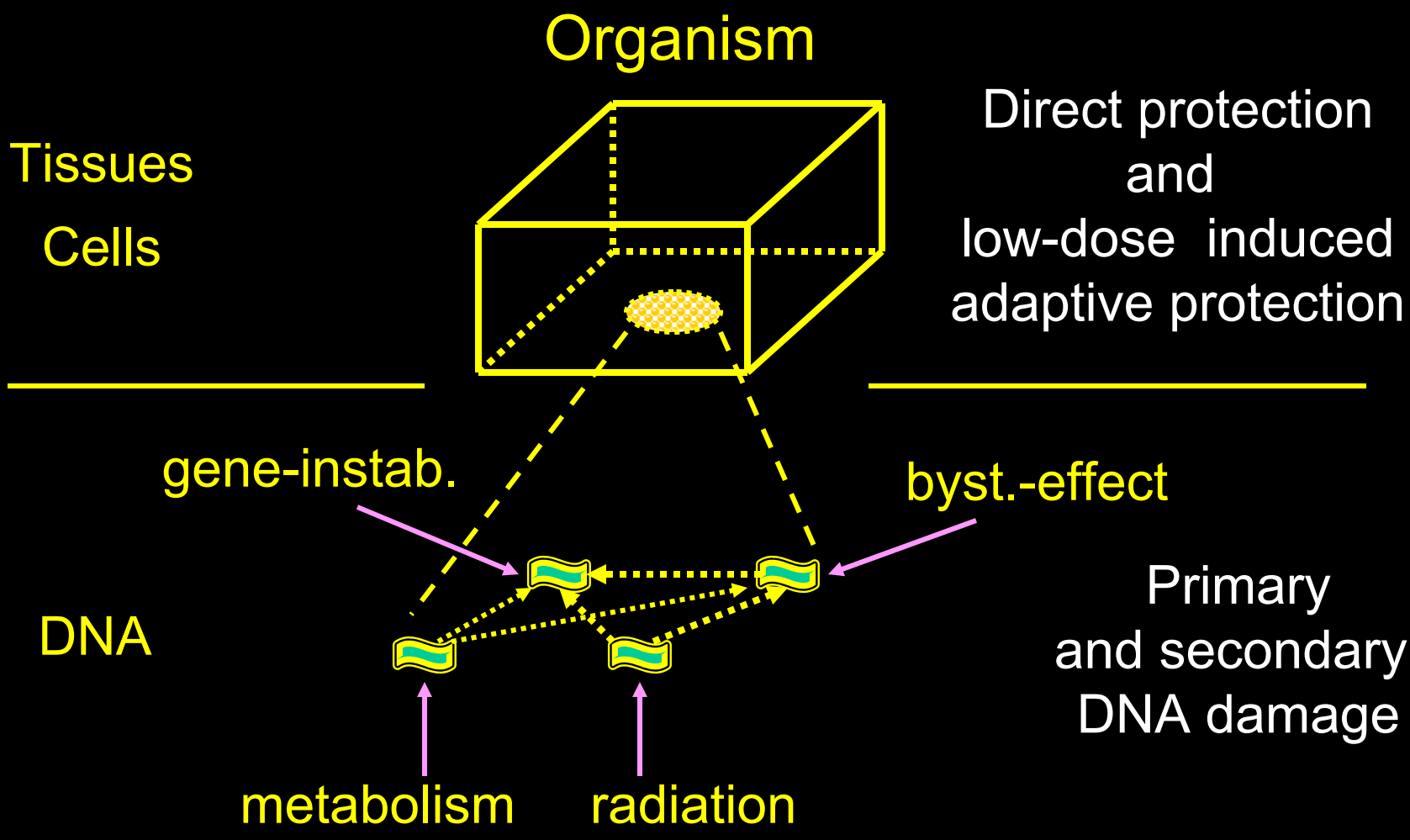
Biological systems exposed to ionizing radiation



Direct protection,
and low-dose induced
adaptive protection
block damage propagation
not linearly with dose

Low-dose induced
primary DNA damage
rises linearly with dose

System Response to DNA Damage



Dose Rate Effects
chronic exposure to tritiated water in mice

Thymic Lymphoma Induction

t.l. only increases when dose rate is above 1 mGy / day

($\bar{x}$ ~ 1 mGy-hits; t_x < 1 day)

- -

Life Shortening

l.s. only begins when dose rate is above 1 mGy / day

($\bar{x}$ ~ 1 mGy-hits; t_x < 1 day)

$\bar{z}_1$ = ~ 5.7 keV / ng ~ 1 mGy

Yamamoto O. et al., Int. J. Rad. Biol. 1998

Dose Rate Effects

chronic whole body ^{60}Co γ-irradiation mice

Life Prolongation

life span increased by 8 % with ~ 1 mGy / day

($\bar{x}$ ~ 0.3 mGy-hits; t_x ~ 8 hr)

- -

Delay of Leukemia

I. appeared significantly delayed with ~ 1 mGy / day

($\bar{x}$ ~ 0.3 mGy-hits; t_x ~ 8 hr)

Lorenz E., Am. J. Roentg. Rad. Ther. 1950

$\bar{z}_1$ = ~ 2 keV / ng ~ 0.3 mGy