HEALTH EFFECTS OF CELLULAR MUTATION REPAIR RESPONSE TO RADIATION:

LOW DOSE HORMESIS AND HIGH DOSE CARCINOGENESIS

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Bishop, M., et al. "Cancer," Chapt. 21 in "The Molecular Biology of the Cell." 1989
UNSCEAR 1994. Annex B-"Adaptive Responses to Radiation of Cells and Organisms"
Wei, Q, et al. "DNA Repair and Aging in Basal Cell Carcinoma." Proc. Nat'l Academy of Science 90:1614. 1993

POSITIVE HEALTH EFFECTS OF LOW-LEVEL RADIATION
...AND WHY

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The increased incidence of cancer observed during the fifties in atomic bomb survivors that received high-level radiation was consistent with our knowledge of radiochemistry and the newly discovered molecular structure of DNA. The damage to DNA and the risk of cancer were both proportional to radiation dose. Since some mutations of DNA initiated cellular changes that could be promoted and induce cancer, it was reasonable in the absence of low-level data, to postulate a linear, no threshold model as an upper limit to the risk of cancer induction. Though epidemiologic surveys in the United States, Brazil, India, and China consistently observed less mortality and less cancer in high background populations than in low background populations, these findings were discounted because of lack of individual dosimetry, strict controls, unreliable public health data, and inadequate consideration of confounding factors. The threshold of 1000 rad for development of bone cancer in the radium dial painters was simply ignored.[1]

Recently, however, the positive health effects of decreased mortality and decreased cancer in human populations exposed to low-level radiation have been observed in large populations with high statistical power and careful consideration of controls: US Nuclear Shipyard Worker Study[2] , US-Japan Atomic Radiation Effects Research Foundation (RERF)[3], Canadian Breast Cancer Fluoroscopy Study[4], and the University of Pittsburgh Residential Radon Study[5].

The UNSCEAR 1994 Report provides extensive documentation of many cellular repair mechanisms, including the immune system, that are stimulated by low dose radiation. Nevertheless, a positive health effect is considered implausible. "As to the biological plausibility of a radiation-induced adaptive response, it is recognized that the effectiveness of DNA repair in mammalian cells is not absolute... An important question, therefore, is to judge the balance between stimulated cellular repair and residual damage."[6]

This reasoning focuses upon the DNA mutations produced by radiation and ignores the normal presence of a very high background of equivalent DNA mutations unrelated to radiation. Each day intrinsic human metabolism produces 240,000 (10^4/cell/h) DNA mutations in each cell of our body[7]. During youth and middle age these are repaired effectively and cancer occurs infrequently. A low radiation dose of 20 rem stimulates repair by 50-100% and on that day adds only 400 mutations (20 mutations/cGy)[8] to the equivalent intrinsic 240,000 mutations occurring in each cell. However, a high dose of 200 rem *depresses* repair by approximately 40-50% while adding only 4000 mutations to the daily normal background of 240,000 similar mutations.

It is the reduced ability of our cellular repair processes to correct the very high background of intrinsic metabolic mutations that increases the risk of developing cancer. Genetic impairment of DNA repair capacity results in death from cancer at an early age[9]. Loss of DNA repair capacity that occurs with aging increases the risk of developing cancer[10]. Similarly, high-dose radiation impairment of the cell's homeostatic repair functions also increases the risk of developing cancer[11]. *The health effects of radiation are determined by the dose response of cell furctions including multiple repair processes, not by the relatively few DNA mutations produced, even by high-level radiation doses.*

The use of *biologically based* mathematical models that include both the very high intrinsic background of DNA mutations and the repair mechanisms that are stimulated by low-level radiation and depressed by high-level radiation, generate predictions of cancer incidence that are in agreement with the epidemiologic observations of the positive health effects of low-level radiation and the negative health effects of high-level radiation[5,11]. The prediction of cancer risk by the *biologically based* model of Dr. Bogen is remarkably similar to the diagrammatic prediction of health effects by Dr. T.D. Luckey based upon over a thousand experiments and epidemiologic observations throughout the world[12].

The key to science is the necessary agreement of both imagination and observation. As Professor of Theoretical Physics Richard P. Feynman put it, "It does not make any difference how beautiful your guess is. It does not make any difference how smart you are, who made the guess, or what his name is - if it disagrees with experiment it is wrong. That is all there is to it"[13].

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   (b) Ward JF. DNA damage produced by ionizing radiation in mammalian cells: Identities, mechanisms of formation, and repairability. Prog. Nucleic Acid Res. Mol. Biol. 35:95(1988).

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12. Luckey TD. Radiation Hormesis, CRC Press, Boca Raton, FL (1991).

13. Feynman RP. *The Character of Physical Law*. MIT Press, Cambridge, MA (1965).

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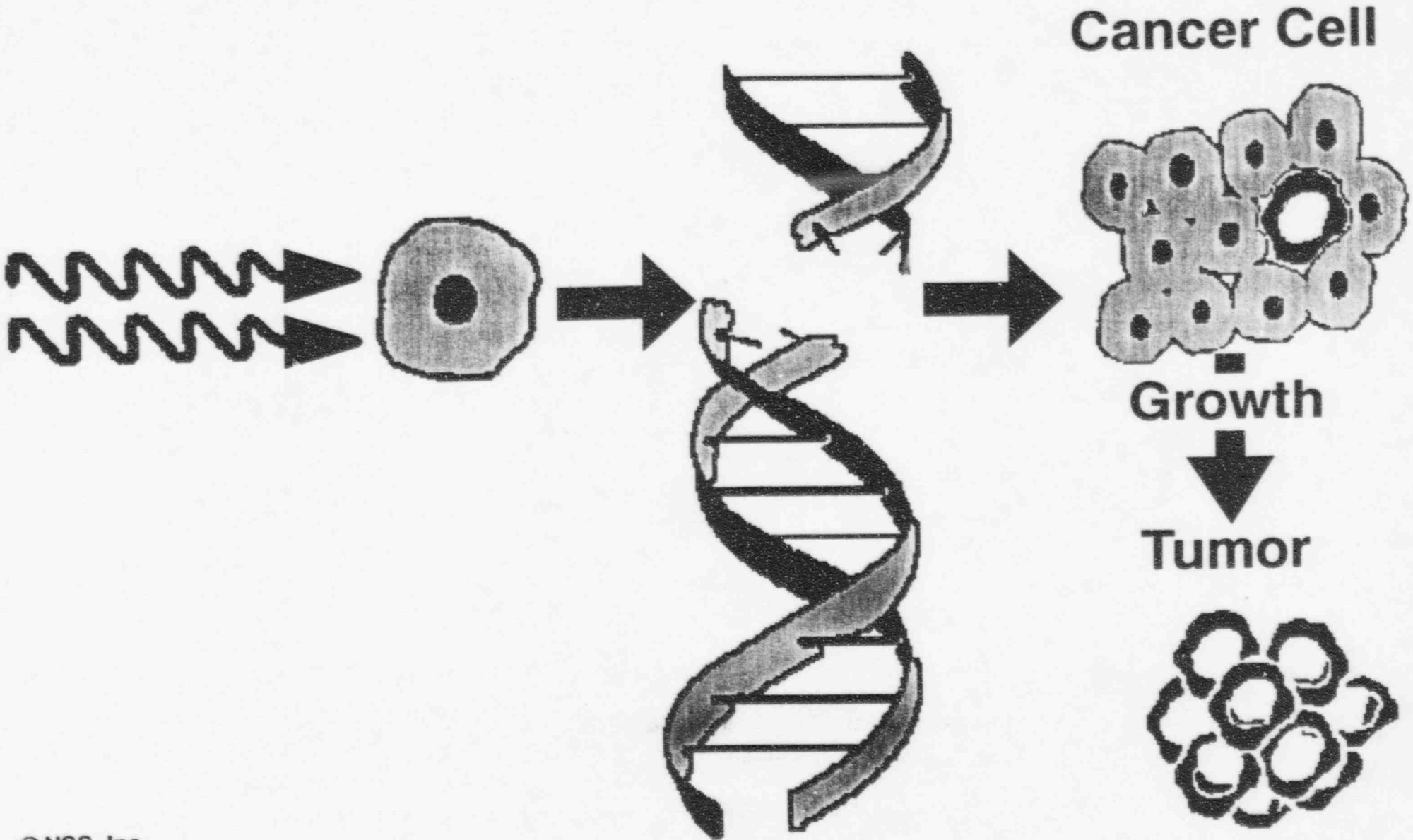
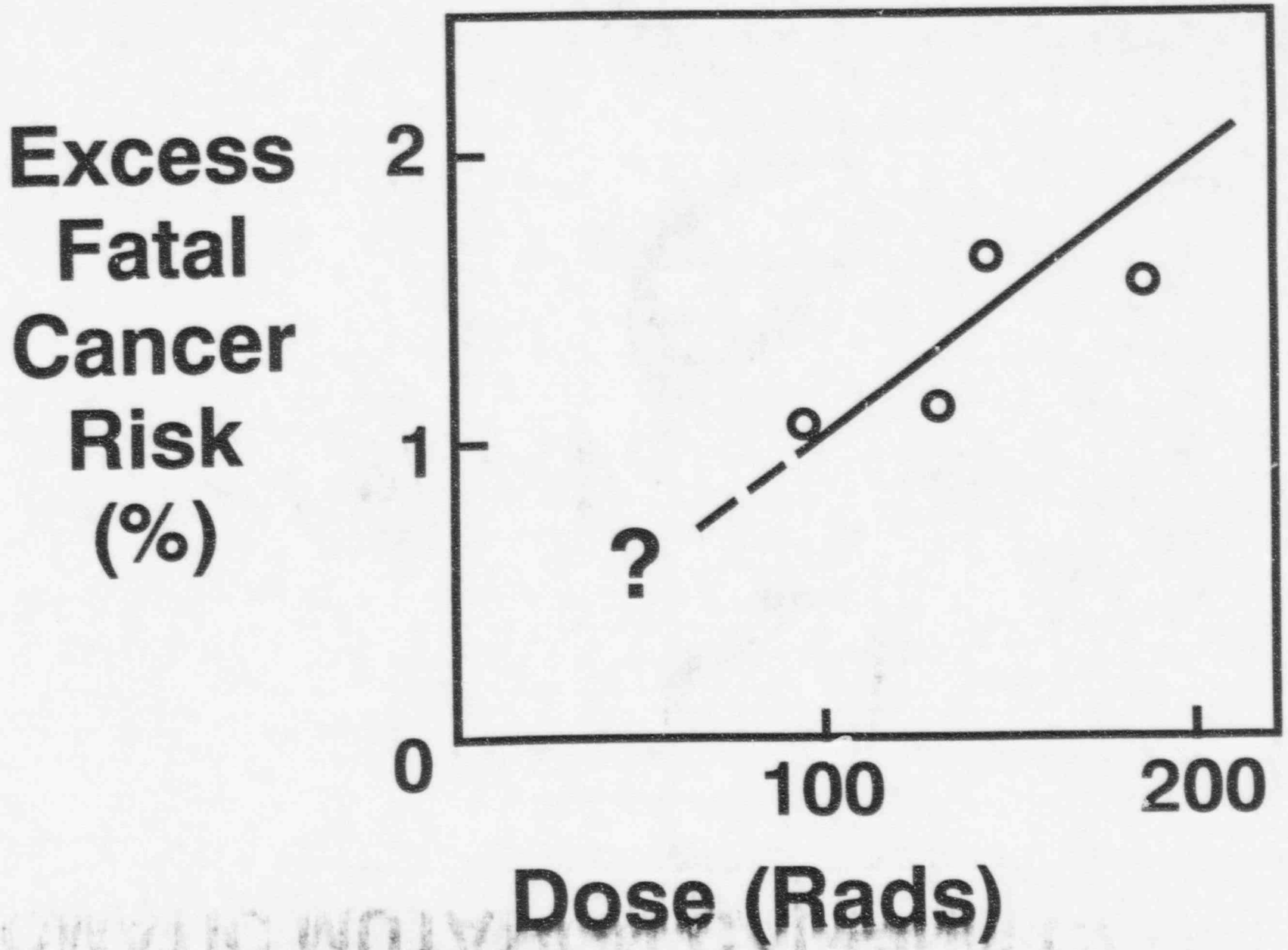
SOMATIC MUTATION-CAUSING CANCER




Excess
Fatal
Cancer
Risk
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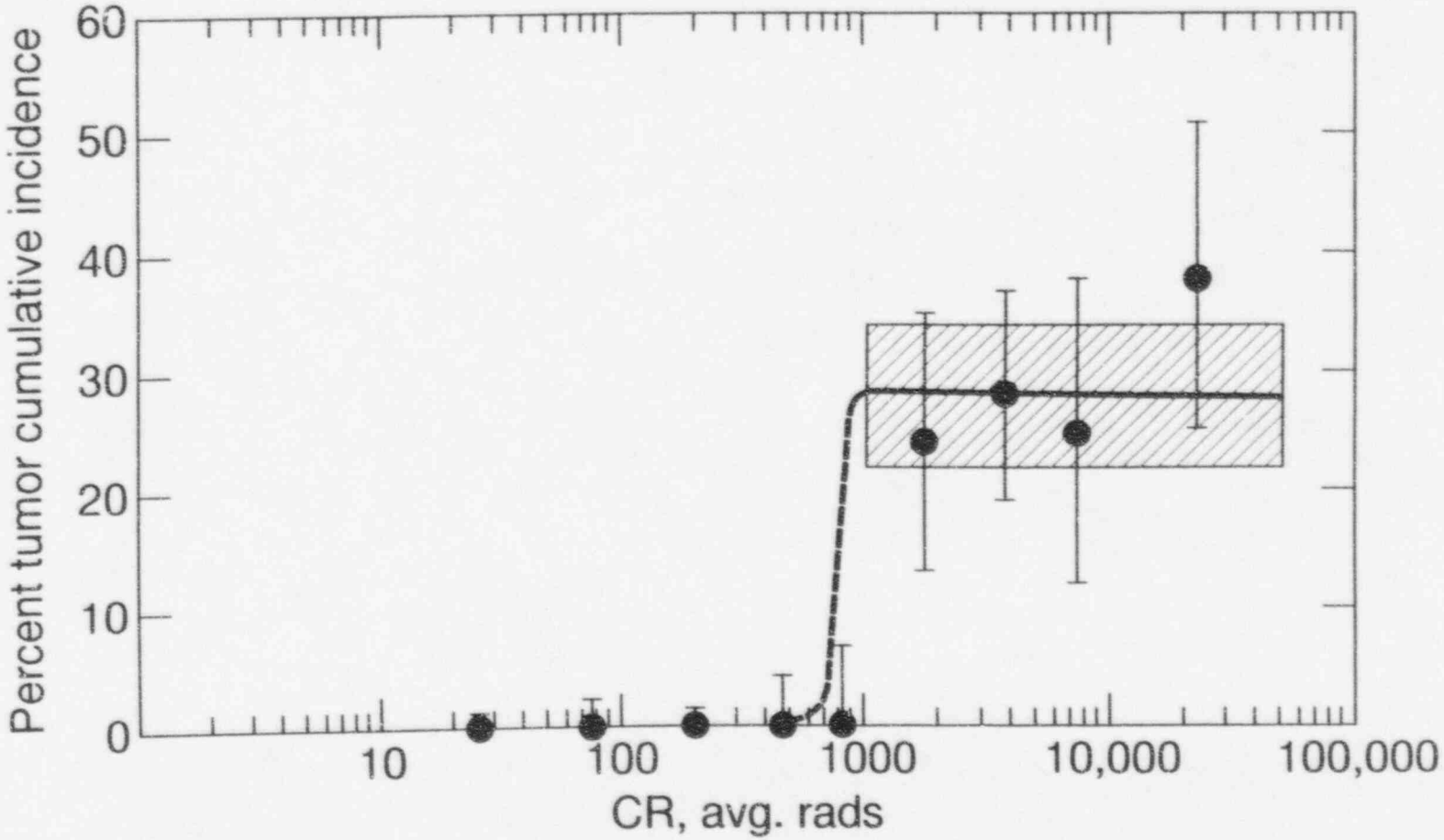
100
200
Dose (Rads)

RADIUM MALIGNANCIES



LNT MODEL FIT TO RADIUM MALIGNANCIES

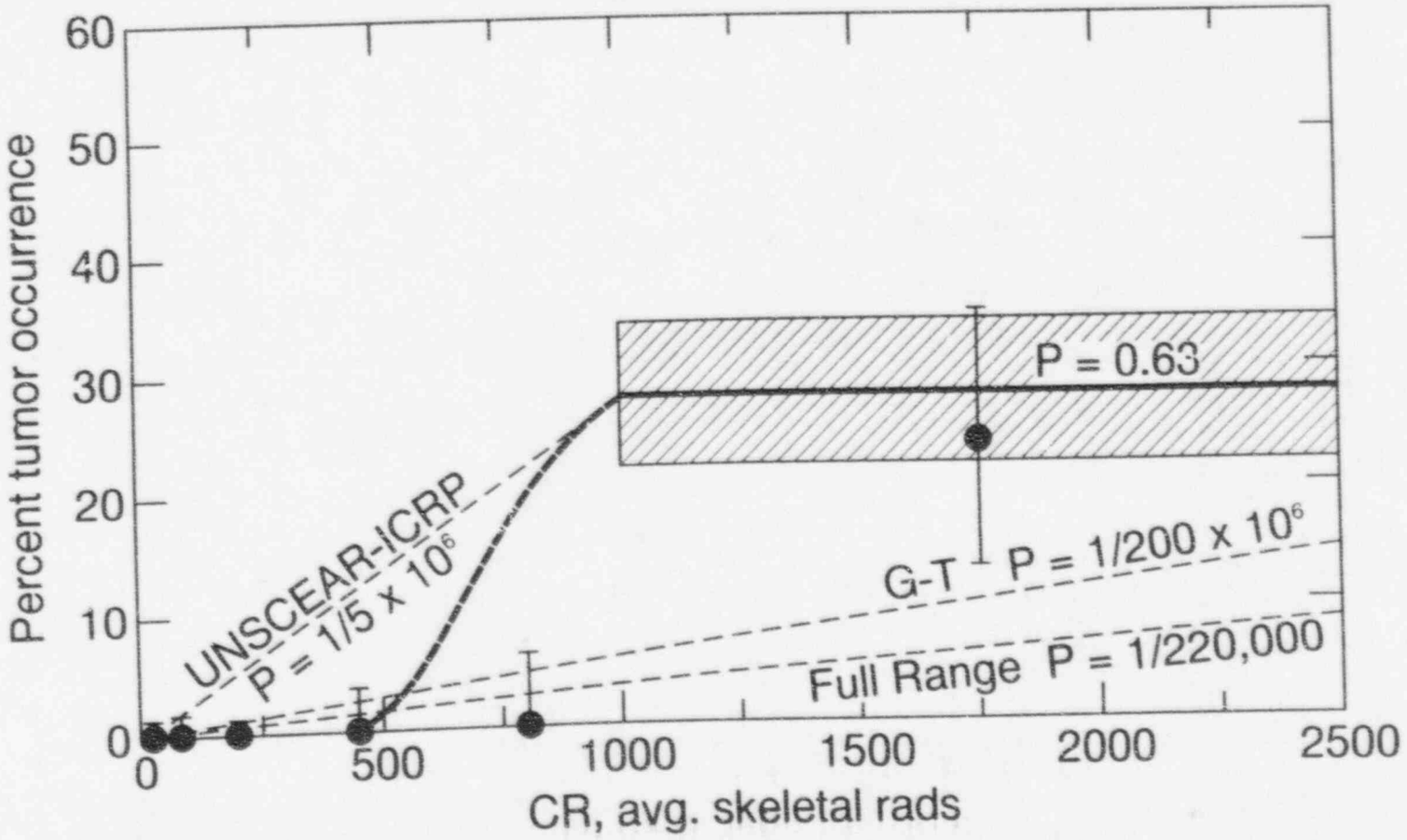


Table 1. Summary of Mortality, Standard Mortality Rate and 95% Confidence Interval for $NW_{>5}$, $NW_{<5}$ and NNW Shipyard Workers

Cause of Death	$NW_{>5}$	$NW_{<5}$	NNW
All Causes SMR (95% C.I.)	2,797 0.76 (0.73, 0.79)	1,168 0.81 (0.76, 0.86)	4,453 1.00 (0.97, 1.03)
Leukemia SMR (95% C.I.)	21 0.91 (0.56, 1.39)	4 0.42 (0.11, 1.07)	29 0.97 (0.65, 1.39)
LHC* SMR (95% C.I.)	50 0.82 (0.61, 1.08)	13 0.53 (0.28, 0.91)	84 1.1 (0.88, 1.37)
Mesothelioma SMR (95% C.I.)	18 5.49 (3.03, 8.08)	8 6.14 (2.48, 11.33)	10 2.54 (1.16, 4.43)
Lung Cancer SMR (95% C.I.)	237 1.07 (0.94, 1.21)	98 1.11 0.90, 1.35)	306 1.15 (1.02, 1.29)

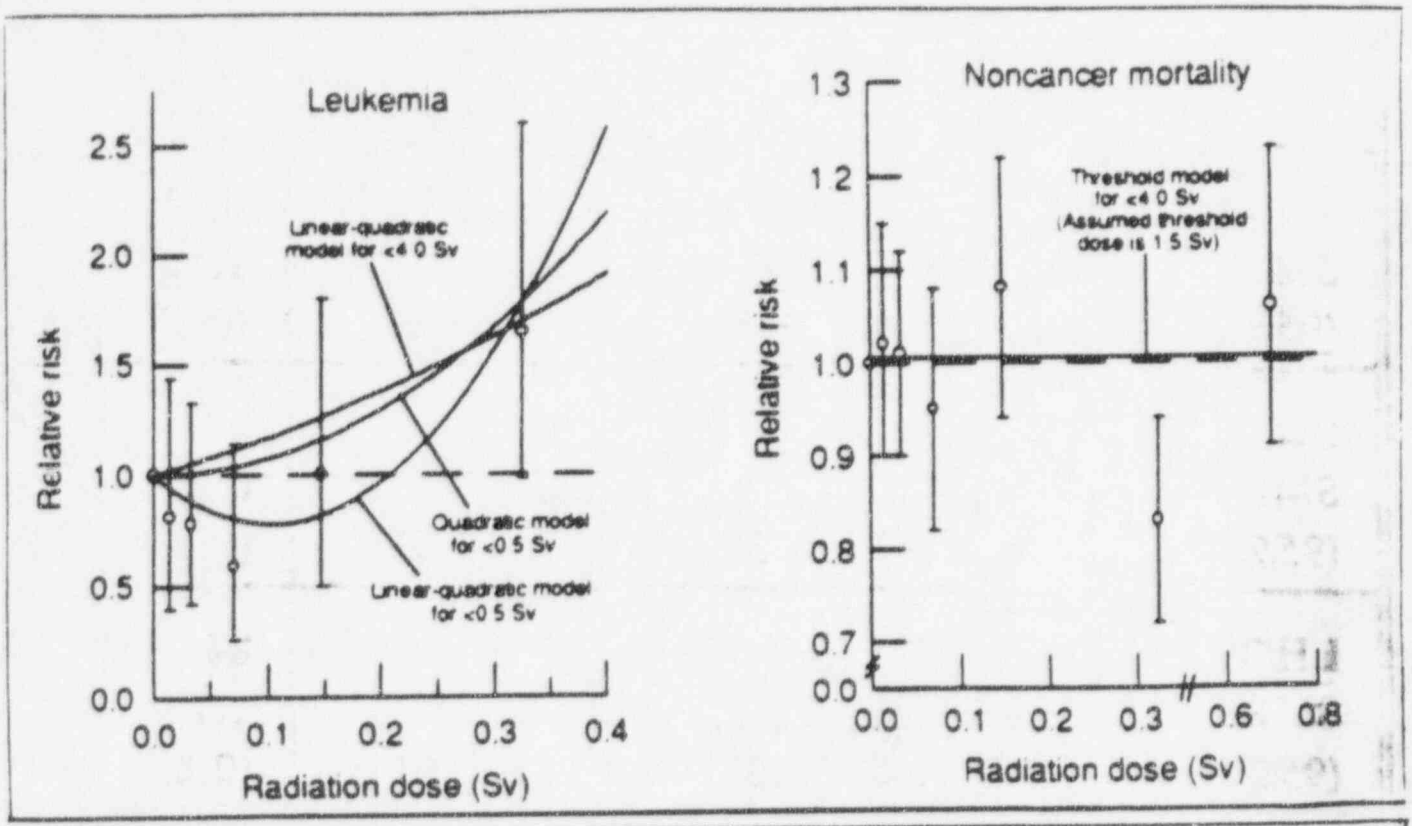
*Lymphatic and Hematopoietic Cancers

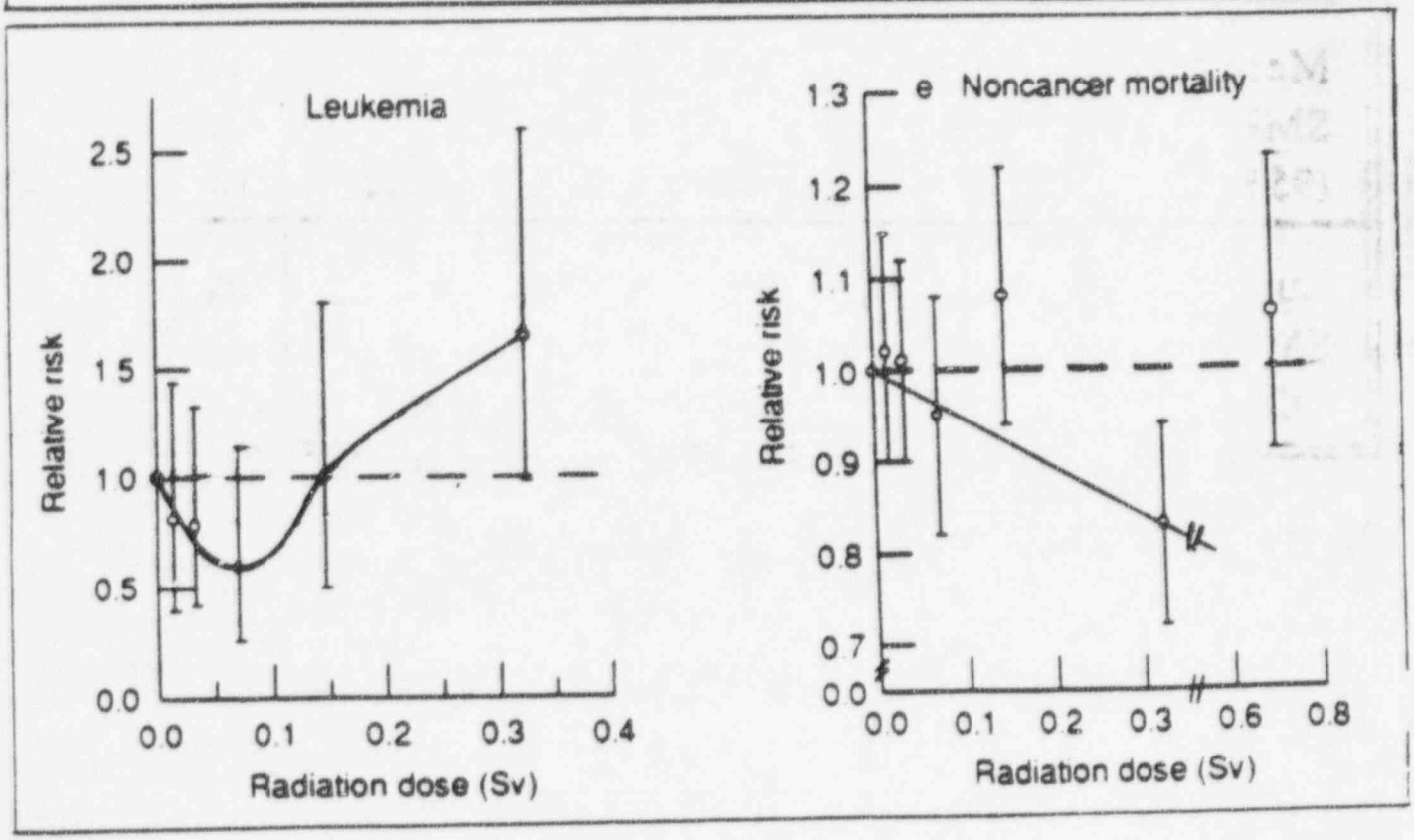
Dose-response Analysis of Atomic Bomb Survivors Exposed to Low-level Radiation

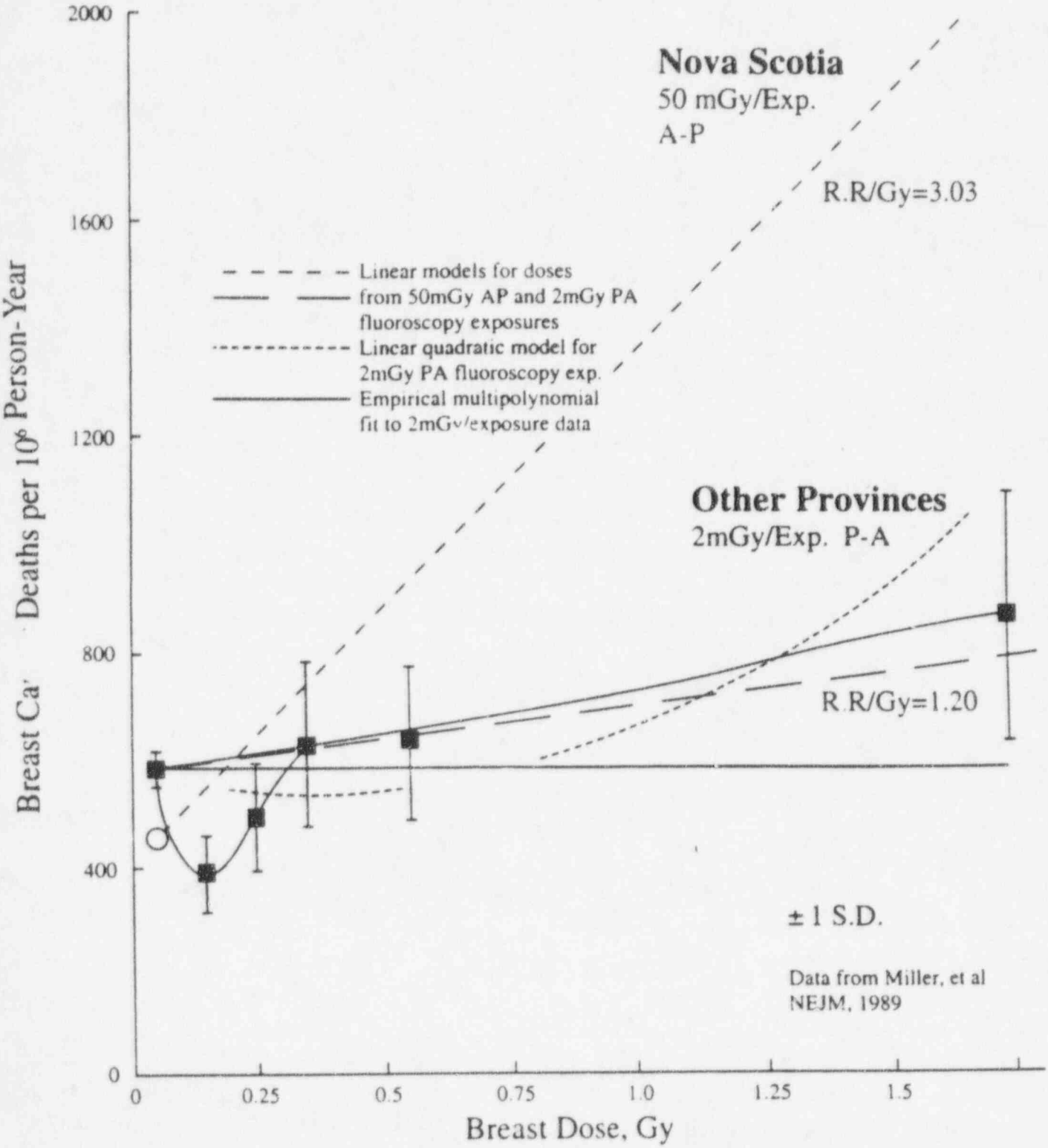
A comparison of dose-effect relationships among various dose levels in the less-than-0.5-Sv region fails to indicate the presence of hormesis.

by Yukiko Shimizu,[1] Hiroo Kato,[2] William J. Schull,[3] and Kiyohiko Mabuchi[1]

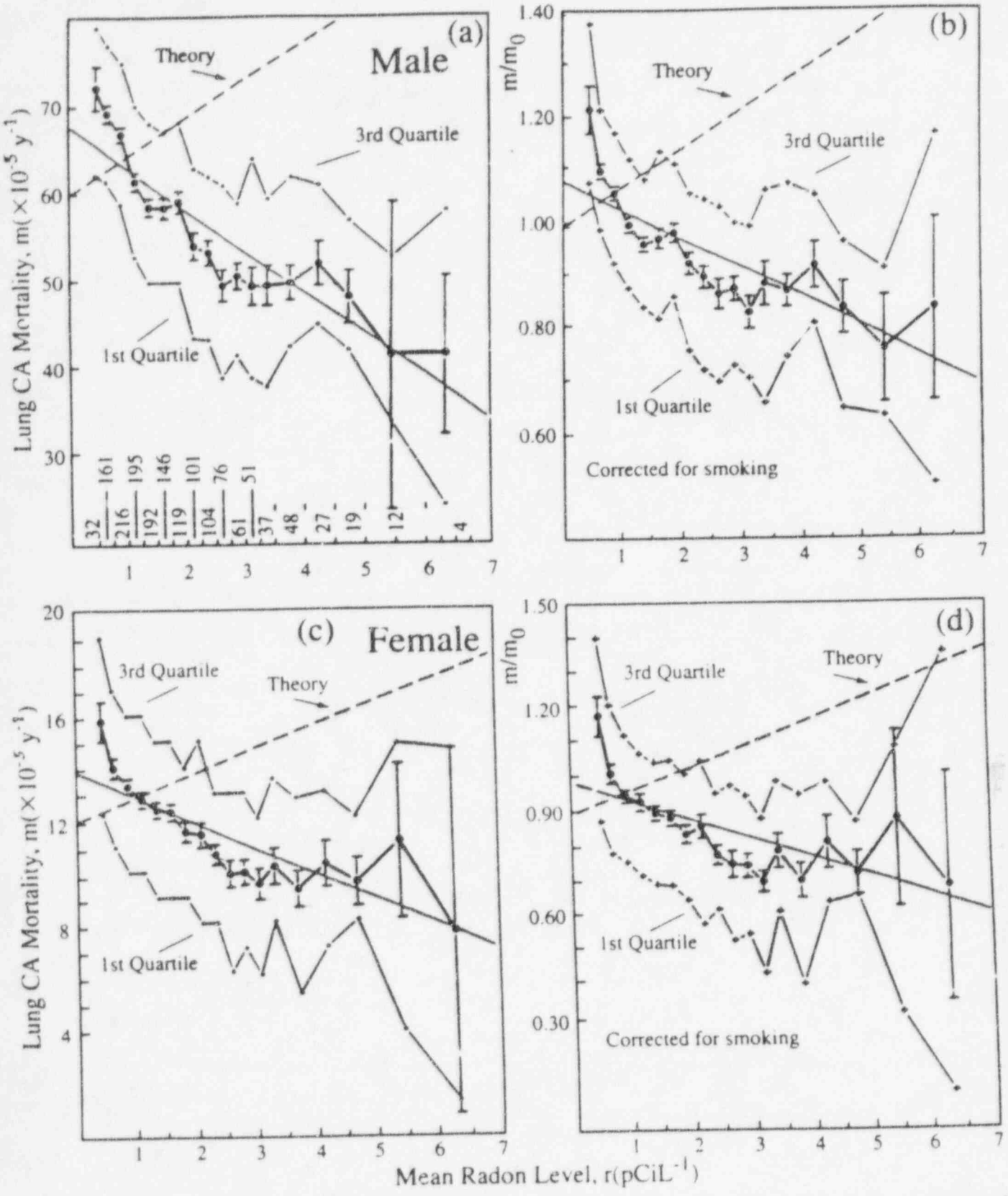
RERF Update Autumn 1992







A graphic plot of the Miller et al. tabular data showing their "best-fit" linear model and linear-quadratic model relationships, and the best-fit empirical polynomial function for the data.



Lung cancer mortality rates compared with mean home radon levels by U.S. county, and comparison with presumed linear model by BEIR IV.

Estimated Spontaneous DNA Degradation Events (Cell/h)[a]

Reaction	Single-strand DNA	Double-strand DNA
Depurination	4000	1000
Depyrimidination	200	50
Deamination of cytosine	4000	15
Chain break resulting from depurination	—	1000
Direct chain break	—	4000

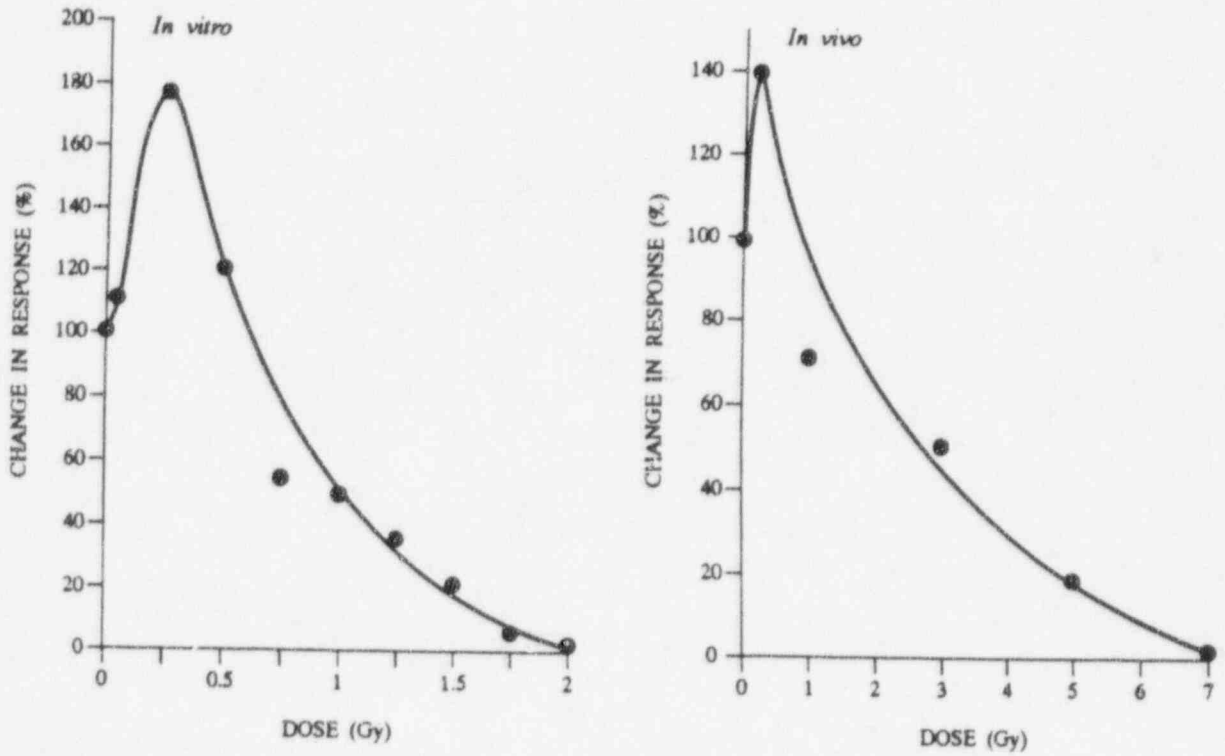
[a] Calculated from Shapiro (14).

DNA Damage Events per Mammalian Cell

Character of Event	Spontaneous DNA Damage Events			DNA Damage/cGy[a]
	Per Second	Per Hour	Per Year	
Single-strand breaks	1.4	~5 x 10^3	~4.4 x 10^7	10
Double-strand breaks				0.4
Depurination and/or base lesions	0.8	~1.5 x 10^3 ~1.25 x 10^3	~1.4 x 10^7 ~1.1 x 10^7	9.5
Total events	2.2	~8.0 x 10^3	~7 x 10^7	~20
cGy equivalents (1cGy = 100 events)[b]	0.022	8.0 x 10^1	7 x 10^5	

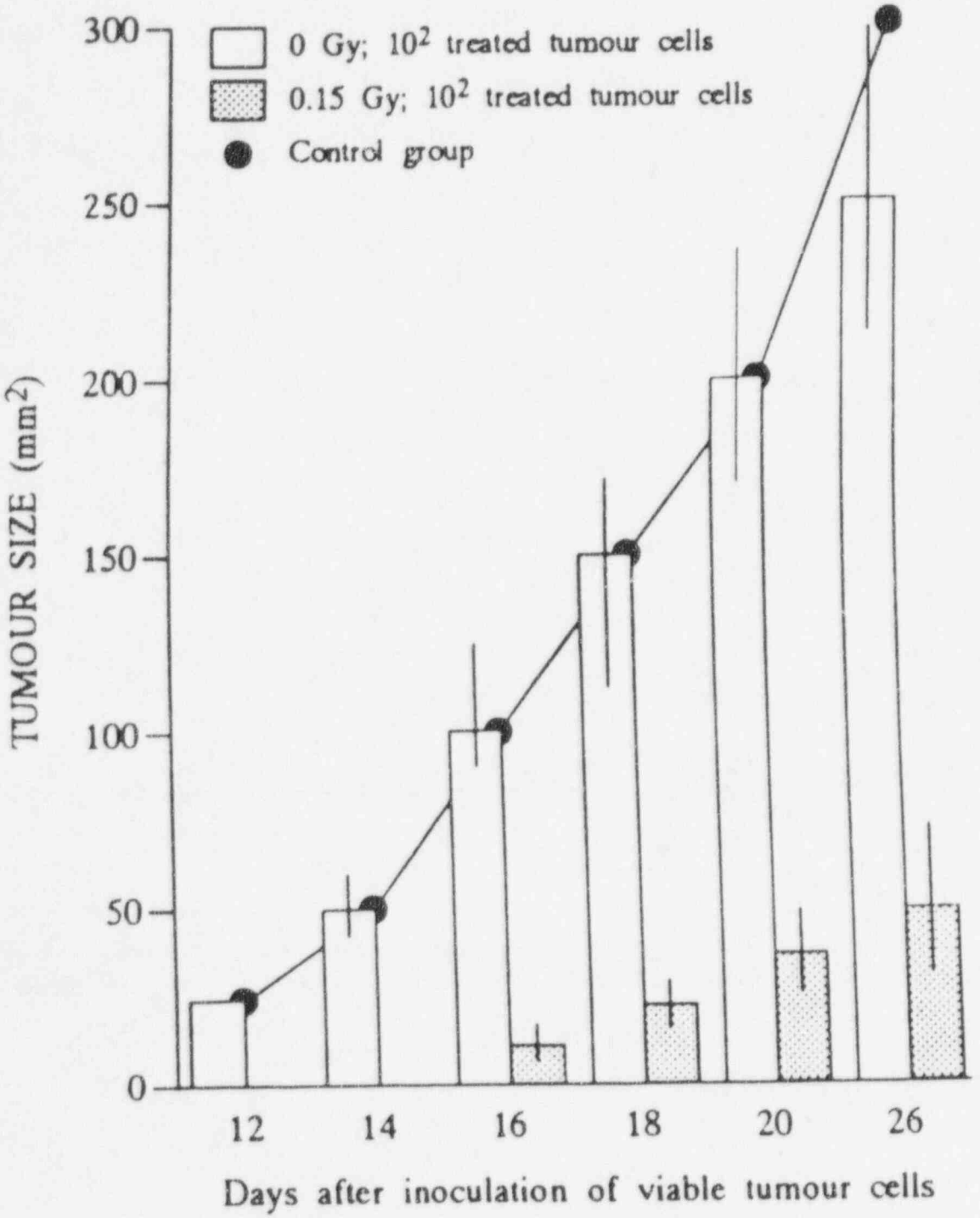
[a] From Ward (20).

[b] Since other radiation-induced DNA damage such as DNA-protein crosslinking and base modifications (18) occur, 100 events/cGy is used as a "ballpark" value for ease of comparison with spontaneous events.



Figure

Effect of radiation on mouse splenic cells primed with antigenic sheep red blood cells.
Results are expressed as the mean per cent change in peak antigen response relative to the highest responder group.
[M18]



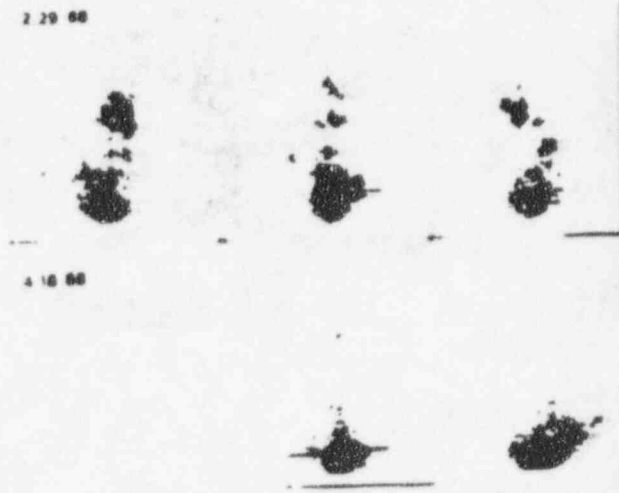
Effect of 0.15 Gy upon response of A/J mice to varying numbers of mitomycin-treated Sal cells. Groups of 60 mice were exposed to whole-body irradiation or sham-irradiated and inoculated subcutaneously with the indicated numbers of mitomycin-treated tumour cells. Twenty-one days later, all animals received 10^4 untreated Sal cells and were followed for tumour size. A control group did not receive mitomycin-treated cells.

[A4]

8.01.91
9. 24.91

Figure 1 shows Ga scintigrams for a 64-year-old man with stage III T cell lymphoma (diffuse large cell type) before and after TBI alone (case 1). He had multiple tumors in the right tonsil, bilateral cervical and inguinal regions, and received thrice-a-week TBI with 0.1Gy/fraction and a total dose of 1.5 Gy. It is found that the ^{67}Ga uptakes by the tumor in the cervical region almost disappeared.

Figure 2 shows CT scans for a 61-year-old woman with stage I lymphoma (diffuse large cell type) before and after HBI alone (case 2). She had a tumor in the nasal cavity and received twice-a-week HBI with 0.15Gy/fraction and a total dose of 1.5 Gy. Most of the tumor in the nasal cavity (white arrow) disappeared in the right picture. It is very interesting that this tumor was completely outside the HBI field.

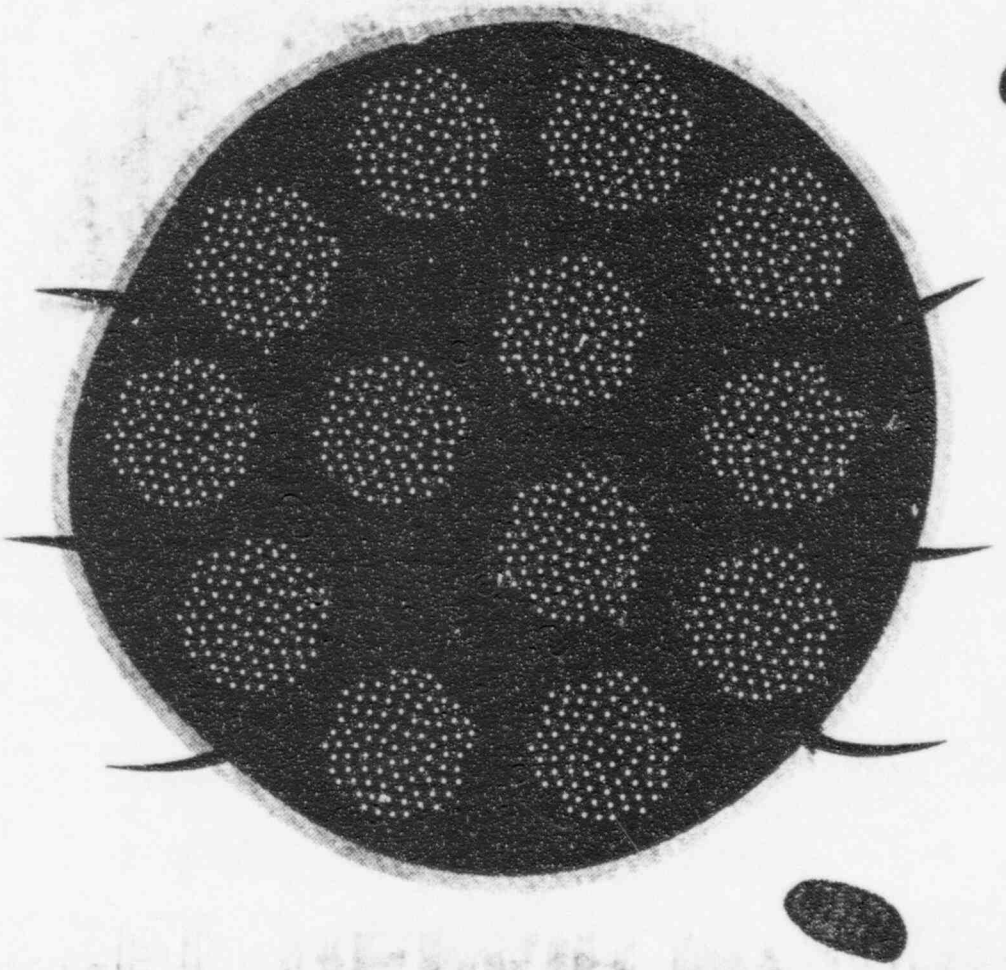


Case 1:Ga scintigrams of the head & neck before (top) and after (bottom) TBI.

Case 2:CT scans of the nasal cavity before (left) and after (right) HBI.

NORMAL REPAIR MECHANISMS

Background Radiation



Up-Regulation of Genes and Their Influence on Cell Cycle Kinetics

Activation of Genes and Their Enzyme Products that Repair DNA Defects

Proliferation of Immune System Spleen and Thymus Cells

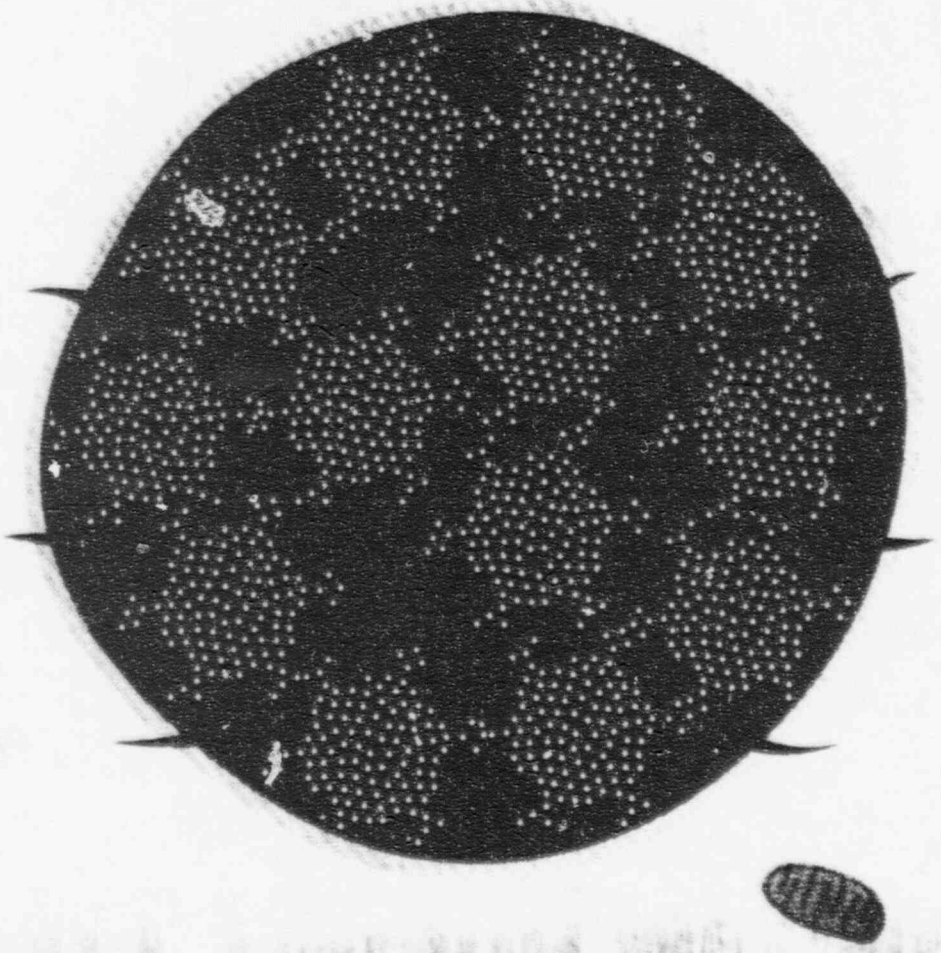
Cross-Activation of Genes and Stress Response Proteins by Low-Dose Radiation, UV, Chemicals, and Heat Shock

Activation of Membrane Receptors and Release of Growth Factors

Removal of Toxic Radicals

DECREASED REPAIR MECHANISMS

High Dose Rad[illegible]n



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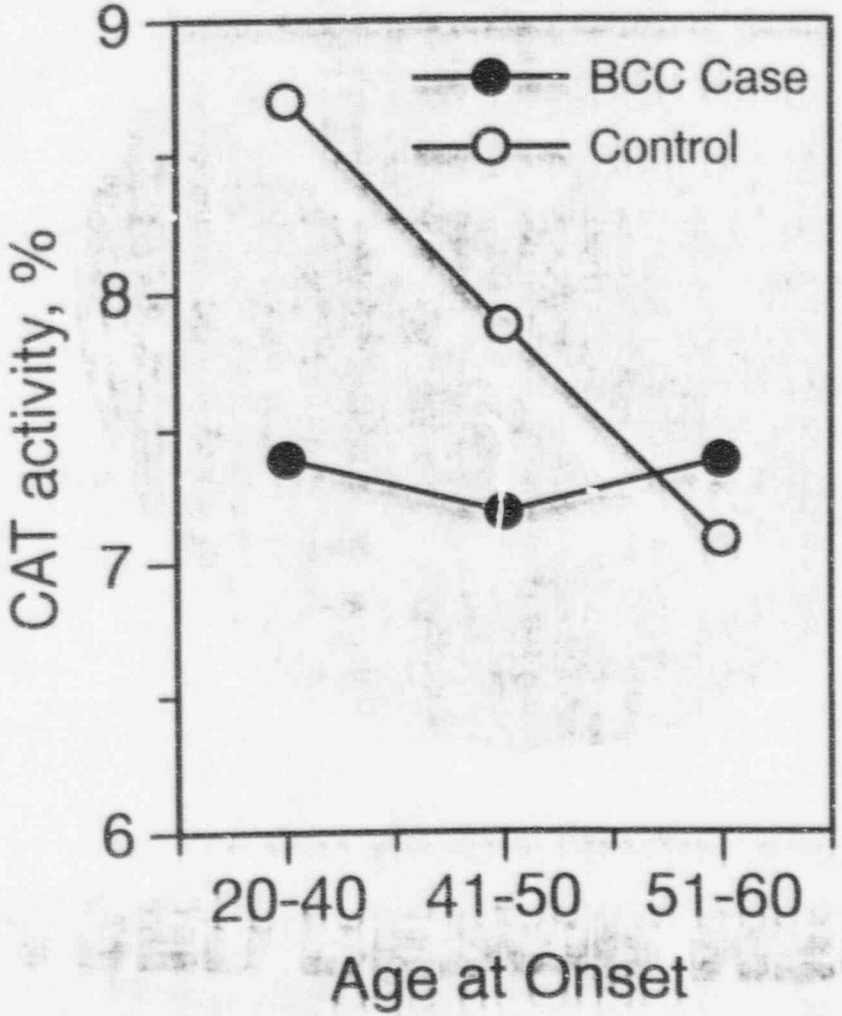
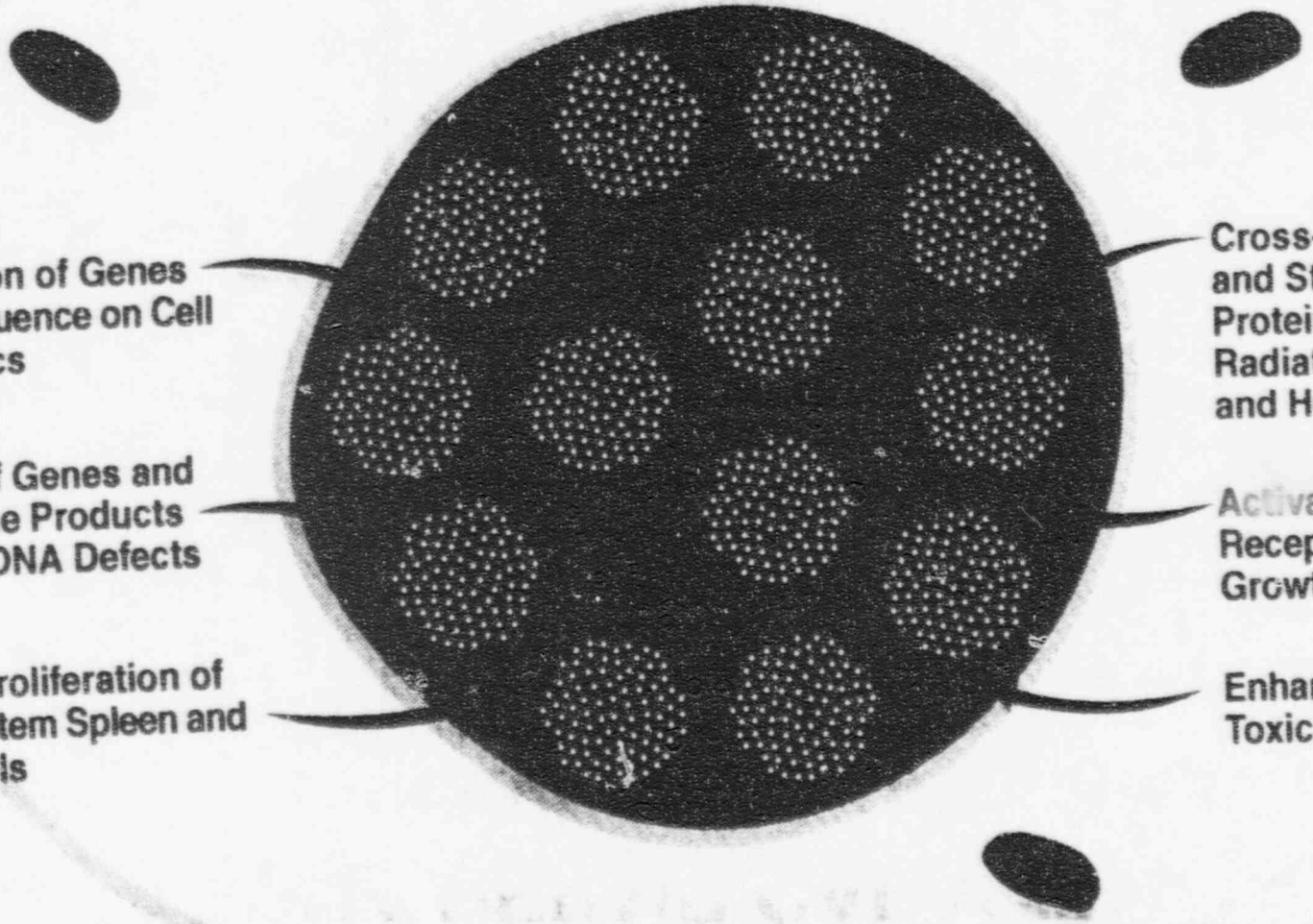
DNA REPAIR CAPACITY
Age and Basal Cell Carcinoma



INCREASED REPAIR MECHANISMS

Low Dose Radiation



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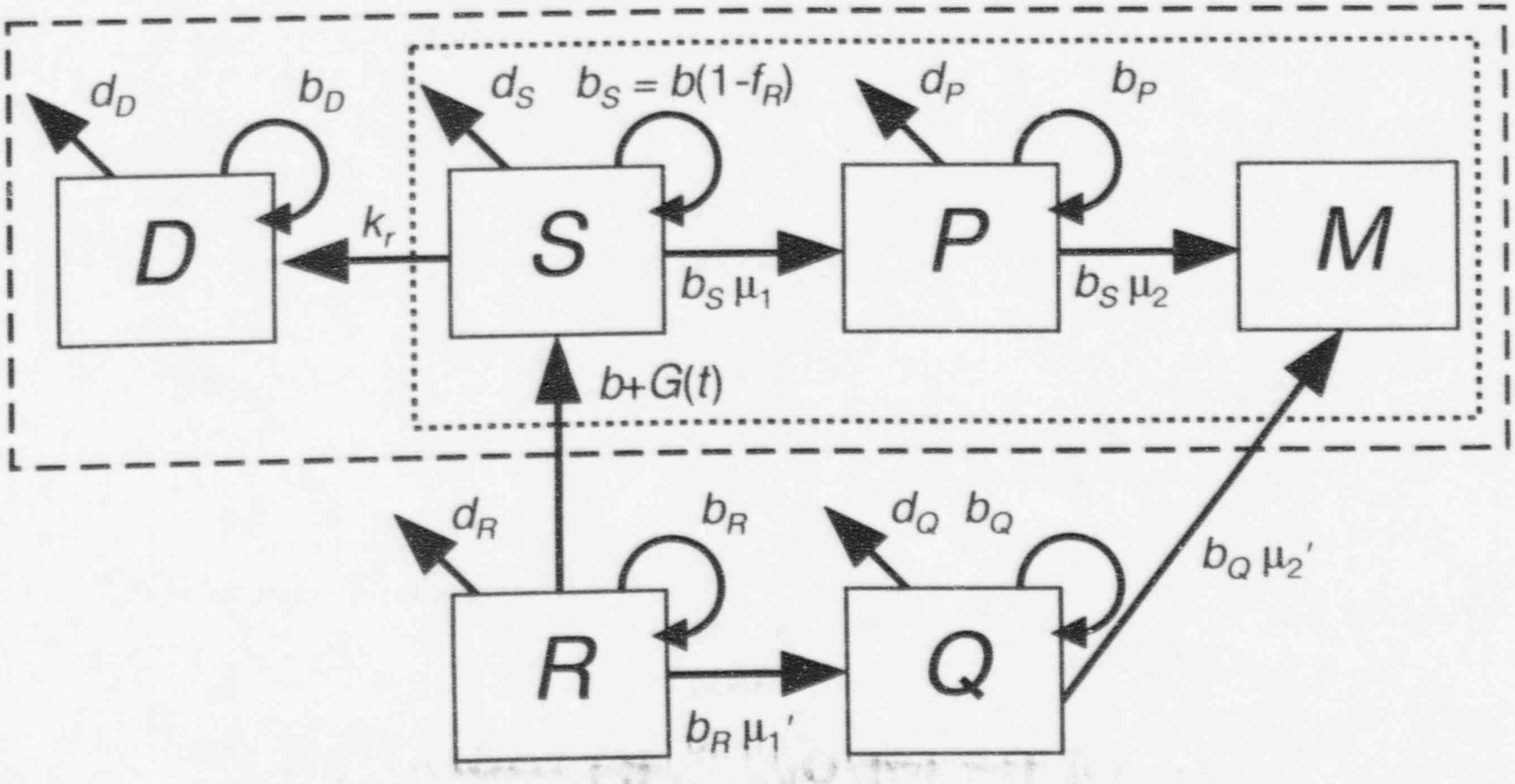
A SINGLE MUTATION IS NOT ENOUGH TO CAUSE CANCER

In a lifetime, every single gene is likely to have undergone mutation on about 10^{10} separate occasions in any individual human being. The problem of cancer seems to be not why it occurs, but why it occurs so infrequently.

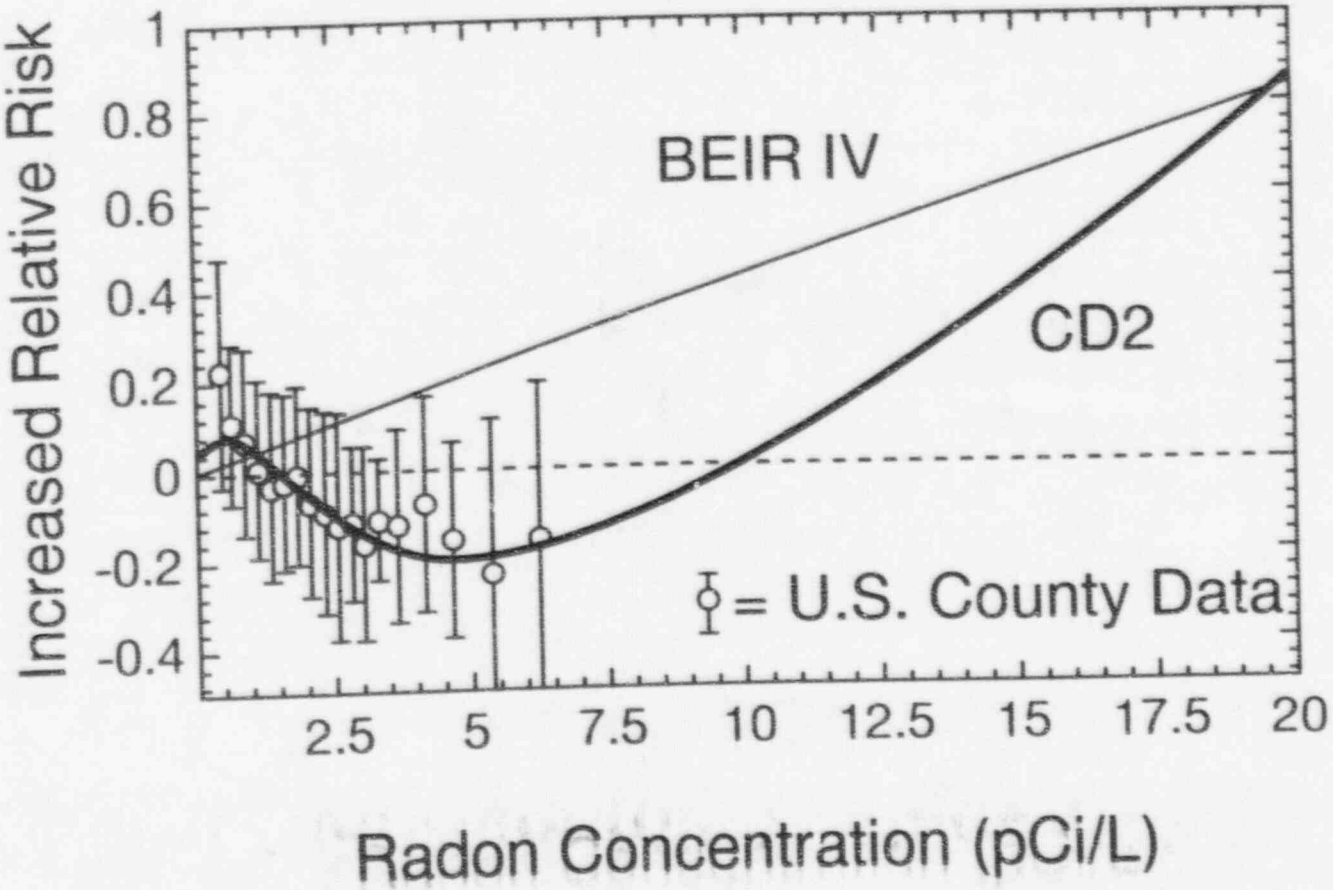
Evidently, the survival of mammals must depend on some form of double—or more than double—insurance in the mechanisms that protect us from being overrun by mutant clones of cells that have a selective advantage over our healthy normal cells: if a single mutation in some particular gene were enough to convert a typical healthy cell into a cancer cell, we would not be viable organisms.

Chapter 21 | Cancer
Molecular Biology of The Cell
Bruce Alberts, et. al. eds. 1989

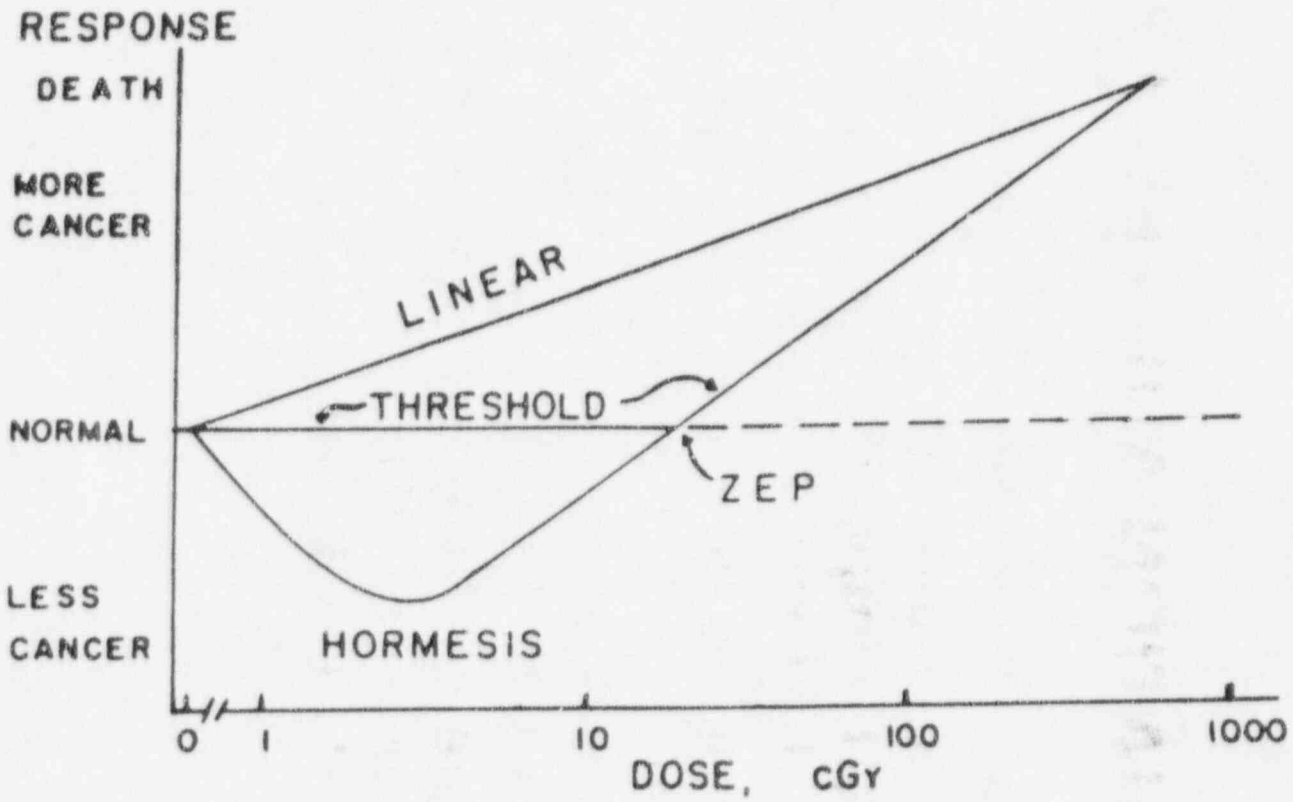
K.T. Bogen: Cytodynamic 2-Stage (CD2) Model of Lung Carcinogenesis by Inhaled Radon



K.T. Bogen: CD2 Model Fit to Both High Dose Data of Uranium Miners (Beir IV) Low Dose Data of US Residents (B. Cohen)



Radiation Hormesis



Three models for dose-response curves. The responses on the ordinate are the opposite from those in other chapters. This follows classic cancer presentations.

SCIENCE: IMAGINATION AND OBSERVATION

"In general we look for a new law by the following process:

First we guess it. Then we compute the consequences of the guess to see what would be implied if this law we guessed is right. Then we compare the result of the computation with nature, with experiment or experience, compare it directly with observation, to see if it works. If it disagrees with experiment it is wrong. In that simple statement is the key to science. It does not make any difference how beautiful your guess is . It does not make any difference how smart you are, who made the guess, or what his name is—if it disagrees with experiment it is wrong. That is all there is to it."

Richard P. Feynman
Professor of Theoretical Physics
California Institute of Technology
Nobel Prize for Physics in 1965

Feynman, R.P. The Character of Physical Law
(MIT Press, Cambridge MA, 1965)