Radiation Hormesis in Medicine
Low Dose Irradiation Therapy

J.M. Cuttler
Cuttler & Associates Inc.
The graph illustrates a linear dose-response model for excess cancer fatalities in relation to radiation dose. The model is based on Hiroshima/Nagasaki data and shows the percentage of the population affected as a function of radiation dose in both Gy and rad.

Key points:
- Linear dose-response model
- Excess cancer fatalities
  - $0.78 \times 10^{-6}$ per millirem whole body
  - $0.39$ per 500 rem

The graph shows an extension to "zero" dose, indicating the expected health effect in the absence of radiation exposure.
al 1000 times higher in boys. Some statisticians increase approximately 100,000 of the events (12), in a distinct progression to the progression of each occurring with year. Whether in a defined order or not is not made clear by the diagrams. Colon cancer is so compe other events are the optimal position of each event in the age. The possibility of an unusual exposure to the exposure of a cancer is not sufficient for the steps, greatly increasing the risk of developing cancer. The age-dependent cancer is any other adult tumor. Carcinogenesis is the nature of the malignancy. To learn the biology of cancer, one needs to understand the behavior of cancer cells. Can the multiple steps be described in consecutive steps on the development of the malignancy? Are there any steps that are not fully normal?
Figure 1. A Mind/Body Model of Cancer Development.
Studies of the Mortality of Atomic Bomb Survivors
Report 12, Part 1
by Donald Pierce et al, Radiation Research 146, 1-27 (1996)

Table II, Observed and expected deaths for solid cancers, 1950-90

<table>
<thead>
<tr>
<th>Dose</th>
<th>Subjects</th>
<th>Observed deaths</th>
<th>Expected background</th>
<th>Excess deaths</th>
<th>Standard deviation</th>
</tr>
</thead>
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<tr>
<td>0</td>
<td>0</td>
<td>36,459</td>
<td>3013</td>
<td>3055</td>
<td>-42</td>
</tr>
<tr>
<td>0.005 - 0.1</td>
<td>0.5 - 10</td>
<td>32,849</td>
<td>2795</td>
<td>2710</td>
<td>85</td>
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<tr>
<td>0.1 - 0.2</td>
<td>10 - 20</td>
<td>5,467</td>
<td>504</td>
<td>486</td>
<td>18</td>
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<tr>
<td>0.2 - 0.5</td>
<td>20 - 50</td>
<td>6,308</td>
<td>632</td>
<td>555</td>
<td>77</td>
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<tr>
<td>0.5 - 1.0</td>
<td>50 - 100</td>
<td>3,202</td>
<td>336</td>
<td>263</td>
<td>73</td>
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<tr>
<td>1.0 - 2.0</td>
<td>100 - 200</td>
<td>1,608</td>
<td>215</td>
<td>131</td>
<td>84</td>
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<tr>
<td>&gt; 2.0</td>
<td>&gt; 200</td>
<td>679</td>
<td>83</td>
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<td>39</td>
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<tr>
<td>Totals:</td>
<td>86,572</td>
<td>7578</td>
<td>7244</td>
<td>334</td>
<td></td>
</tr>
</tbody>
</table>
Linear no-threshold (LNT) hypothesis

- LNT hypothesis assumes all radiation doses are harmful in linear proportion to dose, down to zero dose
- The LNT theory is employed to calculate the number of “excess” cancer deaths from minute fractions of background radiation
- There is no human data to support this use
- There are many data that contradict LNT hypothesis, i.e., less cancer mortality after low radiation dose
Recent discoveries

- An enormous rate of oxidative damage is occurring naturally to our cells

- Our survival until old age depends on our very capable damage control biosystem that prevents, repairs or removes almost all of the DNA alterations

- Those DNA alterations which are not eliminated by our biosystem are residual mutations

- A very small fraction of these residual mutations eventually becomes cancers as a result of creation of special genes that enable cancers to grow and spread
Radiation’s direct effect on cells is negligible

• The rate of DNA mutations caused directly by background radiation is ~10 million times less than the rate caused by the natural oxidative damage
• Our common exposure to chemicals has a far greater adverse effect on cells than low-level radiation
Indirect effect is very important

- Radiation has a very significant effect on our damage-control biosystem.
- High doses of radiation decrease biosystem activity, causing higher than normal cancer mortality.
- Low doses of radiation stimulate biosystem activity, causing lower than normal cancer mortality.
- The predictions of this hormesis model have been confirmed by many observations.
The antimitogenic DNA damage-control biosystem.

Pollycove M and Feinendegen LE.
Figure 7. Immune system response to radiation. Mouse splenic cells primed with antigenic sheep red blood cells. Makinodan T, James SJ, 1990.
Figure 10. The antmutagenic DNA damage-control biosystem response to high background radiation = 120% Estimates based on data in literature. Pollycove M and Feinendegen LE.
Hormesis:

adaptive response of biological organisms to low levels of stress or damage, leading to a modest overcompensation to the disruption, and resulting in improved fitness
RADIATION HORMESIS: Origins, History, Scientific Foundations

- Radiation Hormesis: Its Historical Foundations as a Biological Hypothesis
  Edward J. Calabrese and Linda A. Baldwin
- Radiation Hormesis: The Demise of a Legitimate Hypothesis
  Edward J. Calabrese and Linda A. Baldwin
- Tales of Two Similar Hypotheses: The Rise and Fall of Chemical and Radiation Hormesis
  Edward J. Calabrese and Linda A. Baldwin

Dose-response curve depicting characteristics of the chemical hormetic zone

Abbreviations:
NOAEL = no observed adverse effect level
LOAEL = lowest observed adverse effect level
ZEP = zero equivalent point
Dose and Risk in Diagnostic Radiology: How Big? How Little?

by Edward W. Webster
Figure 1 Exposure to patients and personnel from a non-protective fluoroscope in use circa. 1930. [Based on C. B. Braestrup in Radiation Hazard Symposium, Am. J. Roentgenol. 78 (1957) (3)].

with dose and between 0.7 and 7 per million per year per rad, with a best value of 2 per million. That estimate remains almost unchanged today. 35 years later! In 1958 A. M. Brues
Figure 12. Dose responses in Canadian study of breast cancer mortality in women following multiple fluoroscopic chest exposures during treatment for tuberculosis. The significantly different dose response curves for women in Nova Scotia and those in the other provinces are plotted from data in Miller et al (1989) (42). The error bars show the standard deviation of the mortality rates in each dose group. [Data points for Nova Scotia are shown on a wider dose scale in the upper right insert.]

The dose responses were largely based on the linear dose responses and the similarity of relative risk for the A-bomb survivors with single acute dose and the Massachusetts patients (e.g. 1.9/Gy in Japan with RBE = 20, and 1.7/Gy in Massachusetts, both for mortality studies) (41,43). It is however of considerable interest...
Canadian breast cancer fluoroscopy study

The authors predicted lifetime excess risk of death from breast cancer after a single exposure at age 30

- 60 per million women for 1 cGy (1 rad)
- 900 per million women for 15 cGy

But their data show that 15 cGy would prevent 7000 deaths per million women
Radiation treatment for hyperthyroidism

- University of Birmingham study of 7414 adult patients treated in Birmingham UK between 1950 and 1991
- Published in The Lancet, Vol. 353, June 19, 1999, pg 2111
- Mean cumulative dose 308 MBq of Iodine-131
- Corresponds to 50,000 rem to thyroid, 28 rem to whole body
- 638 cancers diagnosed vs 761 expected (age/sex/period)
- Standardized incidence ratio: 0.83 (95% CI: 0.77 to 0.90)
- 448 cancer deaths vs 499 expected
- Standard mortality ratio: 0.90 (95% CI: 0.92 to 0.98)
- “Decrease in overall cancer and mortality rates is reassuring”
Science vs the LNT hypothesis

“The great tragedy of science is the slaying of a beautiful hypothesis by an ugly fact.”
T.H. Huxley (1825-1895)
Collected Essays 1893-1894
Biogenesis and Abiogenesis

The linear no-threshold (LNT) hypothesis of radiation carcinogenesis seems to be an important exception to this fundamental requirement of science. Why?
Intense disagreement continues among scientists and analysts regarding:

- validity of the LNT model
- reality of beneficial health effects of radiation

Controversy due to political, social, economic issues

- cloud objective research and thinking
- increase resistance to change of established paradigms

Extensive research already done over past century

- disagreement not resolved by more scientific data
- scientists often do not look for beneficial effects
- do not design experiments to find beneficial effects
Scientific societies now challenge LNT scare

- 1995  French Academy of Sciences
- 1996  Health Physics Society
- 1997  Council of Scientific Societies
- 1998  International Nuclear Societies Council
- 1998  U.S. Dept of Energy funds new research on health effects of low dose radiation
- 1999  American Nuclear Society
Low dose irradiation therapy – what is it?

- total or half-body irradiation (TBI or HBI) with X-rays to stimulate the patients natural defense mechanisms against diseases
- TBI or HBI increases cancer fighting activity
- 10 or 15 cGy doses @ 5 cGy/minute
- 30 cGy/week for 5 weeks = 150 cGy total
- booster therapy after 6 months, if needed
Figure 18. Treatment of patients with Non-Hodgkins Lymphoma with half (HBI) or total (TBI) body irradiation. Adapted from Sakamoto, et. al. J Jpn Soc Ther Radiol Oncol 9:161-175, 1997
Were clinical trials done on cancer?

- 1970s Harvard University for non-Hodgkins lymphoma (NHL)
- 1986-94 Institute Bergonie, France for NHL
- 1990s Tohuku University (Sakamoto) NHL
- have >20 abstracts for trials in Europe, Japan
- thousands of papers on human treatments for curing many other diseases
EORTC Lymphoma Cooperative Group

A phase III randomized study on low-dose total body irradiation and involved field radiotherapy in patients with localized, stages I and II, low grade non-Hodgkin's lymphoma

Protocol Chairman
J.H. MEERWALDT
MEDISCH SPECTRUM TWENTE
Haksbergerstraat 55 - Postbus 50800
NL-7500 KA ENSCHEDE
The Netherlands
Tel +31 53 4872750
Fax +31 53 4873072
rath_mst@euroint.nl

Group Chairman
Patrice CARDE
Institut Gustave Roussy
Dept of Medicine C
39, rue Camille Desmoulins
94805 VILLEJUIF CEDEX
France
Tel +33 142114321
Fax +33 142114270
carde@igz.fr

EORTC Data Center
David WILING
Medical Advisor
I. Teodorovic
phone + 32 2 774 16 09
fax: +32 2 772 3545
dwu@eortc.be

Statistician
A. Anagnostopoulou
phone + 32 2 774 16 64
fax: +32 2 772 3545
anis@eortc.be

Dates:
Outline approved: January 26, 1999
Current draft: 13 September, 1999
Final version, PRC-NTC approval
Figure 15. CT (computerized tomographic) scan of upper nasal cavity before and after half body irradiation (HBI). Nasal tumor, though outside HBI field, disappeared after low-dose HBI.

COMPARISON OF LOW-DOSE IRRADIATION OF HALF BODY (HBI) OR TOTAL BODY (TBI) OF PATIENTS WITH NON-HODGKIN’S LYMPHOMA

4 year survival: TBI-HBI 84%  Chemotherapy 66%  (79% of TBI-HBI Survival)
9 year survival: TBI-HBI 84%  Chemotherapy 50%  (60% of TBI-HBI Survival)

Patients in both groups received chemotherapy and localized tumor high-dose radiation.
Figure 20. Adapted from Sakamoto, et. al. J Jpn Soc Ther Radiol Oncol 9:161-175, 1997
Following the Canadian participation in the June conference of the World Council of Nuclear Workers (see Contact, August), the original 1965 estimate of the H-N dose included the effect of neutrons. In 1985, the dose was restimated and the effect of neutrons was adjusted. Since then, the dose has been refined further, with the latest estimate incorporating more recent data and improved understanding of the neutron dose effect. The current estimate is based on a comprehensive analysis of available data, including information from historical events and recent studies. The final result reflects a consensus among experts in the field, taking into account the latest scientific developments.
Mr. Jerry M. Cuttler
Cuttler & Associates Inc.
1781 Medallion Court
Mississauga, Ontario
L5J 2L6 Canada

May 7, 2001

Dear Mr. Cuttler,

Thank you very much for your e-mail. I read with much interest your article. When will it be published? Is it possible to quote it?

Please find enclosed an article published in January 2000 in the journal *Radiation Environ Biophys*. I hope that it will interest you. I have another article in preparation for the WONUC conference in June 2001 in Dublin.

It was good to hear from you. I remember with much pleasure my visit to Toronto and Ottawa.

With best wishes.

Yours sincerely,

[Signature]

Professor M. Tubiana

Encl.
Application of Low Doses of Radiation for Curing Cancer

Jerry M. Cuttler  DSc
Cuttler & Associates Inc.
1781 Medallion Court
Mississauga ON L5J2L6 Canada
jerrycuttler@home.com

Myron Pollycove  MD
U.S. Nuclear Regulatory Commission
Rockville, MD 20852
mxp@nrc.gov

James S. Welsh  MD
Johns Hopkins Medical Institute
Baltimore, MD
welshja@jhmi.edu

Abstract

Successful clinical trials of low dose irradiation therapy for curing cancer were carried out in the USA in the 1970s and, more recently, in Japan and France. A cure of colon cancer and a case study of the successful control of a cancer of the blood following this low-dose therapy are reported. The prompt, beneficial response of the patient’s blood data to the radiation exposures supports the notion of radiation hormesis in humans. Widespread application of low dose therapy would help many cancer patients and could help to correct misconceptions and resolve the controversy about the biological effects of low doses of ionizing radiation.
LDI therapy - Johns Hopkins Medical Institute

- US Navy Captain Edward J. Bauser, age 81
- Waldenstrom’s Macroglobulinemia in 1992
- Jan-Jun 98 chemo, IgM 4000 to 1600 mg/dL
- Sep-Oct 99 LDI, IgM 4000 to 1600 mg/dL
- no symptomatic adverse effects from LDI
- Mar 2000, IgM returned to 2800 mg/dL
- Apr-May received booster LDI therapy
Table 1. Diagnostic data regarding treatment of Edward J. Bauer for Waldenstrom’s Macroglobulinemia

| Date     | IgM mg/dL | PVIS Plasma viscosity | PLTS Platelet count x1000/mL | Hgb Hemoglobin g/dL | T Help cells/mm³ | TH/T S Ratio of helper to suppressor | CD4 cells/mm³ | NK Natural killer cells per mm³ | WBC White blood cells per mm³ | RBC Red blood cells x10⁶ per mm³ | PCV Packed cell volume | Spleen volume cm³ |
|----------|-----------|---------------------|-----------------------------|---------------------|------------------|----------------|----------------|-----------------|----------------|----------------|----------------|----------------|-------------------|
| Normal   | 40-300    | 1                   | 100-400                     | 14-17               | variable         | changes in life | changes in life |                 |                 |                 |                 |                   |                  |
| Chemo    |           |                     |                             |                     |                  |                |                |                 |                 |                 |                 |                   |                  |
| 1998 Jan | 4080      | 3.3                 | 300                         | 9.9                 |                  |                |                |                 |                 |                 |                 |                   |                  |
| 1998 Jun | 1605      | 1.8                 | 100                         | 12.4                |                  |                |                |                 |                 |                 |                 |                   |                  |
| TBI      |           |                     |                             |                     |                  |                |                |                 |                 |                 |                 |                   |                  |
| 1999 Aug 31 | 4170    | 2.9                 | 335                         | 11.1                | 43.1             | 1.32           | 637            | 43.0            | 7680           | 3.75           | 34.1             | 100.4             |                  |
| 1999 Sep 07 | 3870    |                     |                             |                     |                  |                |                |                 |                 |                 |                 |                   |                  |
| 1999 Sep 16 | 301     | 10.8                |                             |                     |                  |                |                |                 |                 |                 |                 |                   |                  |
| 1999 Sep 23 | 4040    | 11.2                |                             |                     |                  |                |                |                 |                 |                 |                 |                   |                  |
| 1999 Sep 30 | 199     | 10.8                |                             |                     |                  |                |                |                 |                 |                 |                 |                   |                  |
| 1999 Oct 07 | 95      | 10.8                |                             |                     |                  |                |                |                 |                 |                 |                 |                   |                  |
| 1999 Oct 11 | 2530    | 2.2                 |                             |                     |                  |                |                |                 |                 |                 |                 |                   |                  |
| 1999 Oct 19 | 1770    | 1.9                 |                             |                     |                  |                |                |                 |                 |                 |                 |                   |                  |
| 1999 Oct 27 | 69       | 10.9                |                             |                     |                  |                |                |                 |                 |                 |                 |                   |                  |
| 1999 Nov 03 | 1630    | 1.8                 |                             |                     |                  |                |                |                 |                 |                 |                 |                   |                  |
| 1999 Nov 10 | 174     | 10.6                |                             |                     |                  |                |                |                 |                 |                 |                 |                   |                  |
| 1999 Nov 17 | 171     | 10.9                |                             |                     |                  |                |                |                 |                 |                 |                 |                   |                  |
| 1999 Nov 18 | 178     | 11.4                |                             |                     |                  |                |                |                 |                 |                 |                 |                   |                  |
| 1999 Dec 01 | 1794    | 12.1                |                             |                     |                  |                |                |                 |                 |                 |                 |                   |                  |
| 1999 Dec 31 | 2420    | 12.9                |                             |                     |                  |                |                |                 |                 |                 |                 |                   |                  |
| 2000 Jan 28 | 2540    | 1.7                 |                             |                     |                  |                |                |                 |                 |                 |                 |                   |                  |
| 2000 Mar 06 | 2760    | 1.9                 |                             |                     |                  |                |                |                 |                 |                 |                 |                   |                  |
Apr 5, 2000, L to R: Cuttler JM, AECL; Bauser EJ, US Navy (ret); Pollycove M, US NRC; Hattori S, CRIEPI
Japanese research – health effects of LDI

Central Research Institute Electric Power Industry

• organized hormesis research steering committee
• involved 14 universities, 2 research institutes
• found extraordinary biopositive effects:
  - cell rejuvenation
  - psychological stress moderation by enzyme stimulation
  - suppression/therapy of adult diseases: diabetes, hypertension …
  - cancer suppression by immune system enhancement
  - cancer suppression by activation of DNA repair, cell killing
• difficulty communicating discoveries to world
Cooperation between Japan and Canada?

- Central Research Institute of Electric Power Institute of Japan urged University of Ottawa to review, duplicate and extend the Japanese studies in Canada.
- International Centre for Low Dose Radiation Research at University of Ottawa tried to organize:
  - attachment of Japanese scientists in Canada
  - participation of Chalk River Laboratories
  - hospitals in Ottawa
  - hospitals in Toronto
- Japanese were keen, but there is no interest in Canada.
Nuclear Shipyard Worker Study (NSWS)

- Best epidemiological study of radiation workers
- $10 M study funded by US Department of Energy
- Excellent peer review during 1980-88 study
- Technical Advisory Panel of 8 scientists, expert in:
  radiation biology, radiation physics, medicine, genetics,
  industrial hygiene, epidemiology, biostatistics
- Beneficial results of NSWS were intentionally ignored
- 28,000 workers received Co-60 gamma ray exposure
- 32,500 other workers received no or negligible exposure
- Study compared workers in both groups: same jobs, ages
- Average exposure of nuclear workers ~5x background
- Nuclear worker death rate from all causes 24% lower
- This is 16 standard deviations ($p < 10^{-16}$) lower
- This statistical power, no doubt low dose is beneficial
- Surprising result was not mentioned in report narrative
- Cancer mortality 4 standard deviations lower ($p < 10^{-3}$)
- There are no other studies that contradict this study
- Reference is: Matanoski G, *Health effects of low-level radiation in shipyard workers, final report*. 471 pages,
  Baltimore MD, DOE DE-AC02-79 EV 10095 (1991) – and it was never published in a scientific journal
Twelve-Year Review of X-Ray Therapy of Gas Gangrene

JAMES F. KELLY, M.D., F.A.C.R., and D. ARNOLD DOWELL, M.D.
Omaha, Nebraska

The first report on the x-ray treatment of gas gangrene was made in December 1931, before the Radiological Society of North America at the Seventeenth Annual Meeting in St. Louis (1). The mortality rate for gas gangrene up to that time had been 50 per cent or higher and that figure was attained only by the sacrifice of many arms and legs. The mortality rate in the group of 8 cases then reported was 25 per cent, and no additional tissue was removed in any case after x-ray therapy was begun.

The technic used in the 6 cases involving the extremities was described and was considered adequate, but the 2 patients with involvement of the trunk died, and for the a disease as gas gangrene with its former high mortality and morbidity. The x-ray, however, has definitely removed gas gangrene from that group of diseases in which experimental therapy is any longer justifiable.

Chemotherapy has failed in our vicinity and also in other places, as was to be expected, since in a well developed case of gas gangrene there is definite interference in the circulation to the infected area and consequently in the most serious cases the chemical fails to reach the diseased tissues. The x-ray, however, has no difficulty in effectively reaching all cells and fluids in any infected area. Other ways of treating gas gangrene may be developed but there
lected from the literature. It is a satisfaction to realize that we have not been misleading in our claims and that the method has in most instances been successful in other hands. It is noteworthy, also, that those cases which have been included in our statistics on clinical evidence only show a much higher mortality rate (twice as great) than cases in which Cl. welchii was demonstrated in the laboratory. In that in the group analyzed the error in diagnosis should not exceed 2 per cent, and we hope that it is even less. The cases reported in the literature we have accepted as given.

Anyone with clinical experience in the management of gas gangrene appreciates that the diagnosis depends on several factors, no one of which may be considered as final in the early or doubtful stages of the disease.

From Hippocrates’ time (400-370 B.C.) to 1900 A.D. the mortality rate of gas gangrene was high, but was not always due to the disease. Between 1900 and 1920 the mortality rate was markedly reduced, but in the last 20 years no further improvement has been noted. X-ray therapy will prevent or cure the disease. The broken perpendicular lines separate the three periods.


In other words, the inclusion of cases with questionable diagnoses has raised rather than lowered our mortality rate.

We have included no case in our statistics which did not have evidence of toxemia, nor have we excluded any in which death occurred because there was a plausible pretense by which it might be rejected. Errors through rejection of true gas bacteria infections which showed no evidence of toxemia because of early x-ray treatment may have occurred, but we believe the diagnosis, which is the most important time for the diagnosis to be made.

The consistency of the mortality figures in the foregoing analysis is maintained in figures relative to other important data, and the present study will serve to verify the general trend of our previous reports.

**REPORTS IN THE LITERATURE**

All reports on the roentgen treatment of gas gangrene that have appeared thus far in the literature have been favorable.
Figs. 7–8. Case 1: Severe hand injury, with multiple compound fractures and some gas in tissues (left). Fig. 8 (right) shows same hand a few days after prophylactic x-ray irradiation: no gas in the tissues, no infection, hand on way to complete recovery.

TABLE V: CASES WHICH RECEIVED PROPHYLACTIC IRRADIATION AND HAVE BEEN REPORTED IN THE LITERATURE

Those which do not appear until three or four days have elapsed. It is evident from Figure 6 that the second, third, and
Is there a need for LDI therapy?

• > 25% of Canadians die of cancer - all types
• This dreaded disease is not well understood
• Intensive research underway to determine the causes and to find better cures/therapies
• The currently “accepted” therapies:
  - surgery (local)
  - high-dose irradiation (local)
  - chemotherapy (distributed, harsh side-effects)
Cancer patients and other terminal patients

- should have a life-or-death interest in this controversy over beneficial effects.
- Low-dose radiation therapy to stimulate defense mechanisms would:
  - cure certain types of cancer (e.g. NHL)
  - extend lifespan without symptomatic side-effects
  - treat diabetes and other adult diseases.
- Such patients would insist on this therapy, if physicians would only agree to provide it.
Concerns?

• LDI therapy is not widely accepted because
  - physicians lack knowledge about LDI therapy
  - anti-nuclear political activity
  - myth that any amount of radiation causes cancer

• But cancer patients already have cancer!
• They have little to lose from LDI therapy.
• High dose radiation (200 cGy) is permitted!
GLOBAL AVERAGE INDIVIDUAL WHOLE BODY RADIATION DOSE (Each Year)

- Medical Diagnostics
- Nuclear Explosions
- Chernobyl
- Nuclear Power

Lower End of Natural Background Radiation

To More Than 700 mSv

Dose Per Year mSv Rem

- Guaraí beach, Brazil: up to 700 mSv
- Ramsar, Iran: up to 700 mSv
- Southwest France: up to 88 mSv

Kerala beach, India: up to 35 mSv

Araxá, Brazil: up to 25 mSv

Sweden: up to 18 mSv

US Rocky mountain states: 6-12 mSv
Evacuated land near Chernobyl: 6 mSv
US Capitol & Grand Central Station, NYC: 5 mSv

World average: 2.4 mSv
San Francisco, US Gulf states: 0.8-1.2 mSv

Adapted from Z. Jaworowski's paper at the "International Conference on Radiation," Tehran, Iran, Oct 18-20, 2000, based on UNSCEAR figures.
Recognize public fear of nuclear radiation

- One in four die of cancer
- People want cures for cancer
- People want to know the causes
- People know almost nothing about nuclear radiation
- People believe radiation in any amount causes cancer
- Result of our continued use of LNT model
Gunnar Walinder:

• The LNT hypothesis is a primitive, unscientific idea that cannot be justified by current scientific understanding.

• As practiced by the modern radiation protection community, the LNT hypothesis is one of the greatest scientific scandals of our time.