International Behavioural Neurology
Videoconference Rounds
Toronto, Ontario, Canada, May 26, 2021

Low Doses of Ionizing Radiation as a Treatment for Alzheimer's Disease

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INTERNATIONAL BEHAVIOURAL NEUROLOGY VIDEOCONFERENCE ROUNDS

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Canadian Neurological Sciences Federation
Canadian Neurological Society
Peter A. Silverman Global eHealth Program (PASGeP)
Canada-International Scientific Exchange Program (CISEPO)

Coordinated by the Division of Neurology, University of Toronto, Canada

Low Doses of Ionizing Radiation as a Treatment for Alzheimer's Disease

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UNIVERSITY OF TORONTO

Technion
Israel Institute of Technology

Wednesday, May 26, 2021

8:00 a.m. – 9:00 a.m. Eastern Daylight Time (Toronto, Canada)

Educational Objectives

1. History of medical treatments using low doses of ionizing radiation (LDIR)
2. Biological basis of stimulating patient's protection systems against oxidative damage with LDIR
3. Review treatment of a patient with advanced AD using CT brain scans over a 3-year period
4. Summary of Toronto pilot study and overview of upcoming clinical trials

Journal of Alzheimer's Disease

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IOS Press

https://doi.org/10.3233/JAD-200620

Low Doses of Ionizing Radiation as a Treatment for Alzheimer's Disease: A Pilot Study

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Handling Associate Editor: Amos Korczyn

Disclosure

Patents/Royalties

J. M. Cuttler had an agreement regarding a patent, to receive annual royalties on the subject matter in this paper. Patent Pub. No.: US 2016/0367837 A1

Outline

1. Early treatments with ionizing radiation
2. What is the mechanism for LDIR beneficial effects?
3. Treatment of patient with Alzheimer's in 2015
4. Pilot study in Toronto, 2017 to 2020
5. Conclusions

Low-dose radiotherapy for 120 years

Long ago: 1896-1970, physicians used X-rays and radium to

- **treat cancer, slow the progression, eliminate metastases**
- **stop infections: gas gangrene, carbuncles and boils, sinus, inner ear, whooping cough, pneumonia, etc.**
- **relieve arthritis and other inflammatory conditions, lymph glands, adenoids in children**
- **treat asthma, autoimmune diseases, type-I diabetes**
- **There were no reports of increased cancer incidence**

Review of diseases treated by X-rays

	Number of subjects	Successful treatment (%)	Studies (*N*)	References
Arthritis	>5000	~85	Cumulative experience	Kahlmeter[14] and Kuhns and Morrison[15]
Bronchial asthma	~4000	75–80	57	Calabrese et al.[12]
Carbuncles	187	60–90	5	Calabrese[6]
Cervical adenitis	893	75–90	11	Calabrese and Dhawan[10]
Deafness	15,000	>95%; performed prior to age 15	Cumulative experience	Crowe and Baylor[22]
Furuncles	420	75–95	5	Calabrese[6]
Gas gangrene	365	Mortality rate decreased from 40% to 10%	13	Calabrese and Dhawan[7]
Otitis media/ mastoides	564	~90	16	Calabrese and Dhawan[10]
Pertussis	~2400	~80	22	Calabrese et al.[13]
Pneumonia	863	80–85	18	Calabrese and Dhawan[8]
Sinus infection	4492	75–90	16	Calabrese and Dhawan[9]
Tendonitis/bursitis	3333	70–90	31	Calabrese and Dhawan[10]
	37,517			

Nasopharyngeal radium irradiation

The standard 50 mg monel metal radium applicator is passed into the nasopharynx after cocaine anesthesia and left in place for twelve minutes on each side. The treatment is given three times with intervals of two weeks between applications. Beneficial results may be expected within six to twelve weeks. It is probably unwise to submit the child to more than two series of such treatments[11,12] (Figure 7).

US CDC estimates up to 2,500,000 children received NRI from 1940-1970 as a standard medical practice to shrink adenoids. **Contact** gamma dose = 2000 rad (20 Gy); **1 cm depth** dose = 206 rad (2 Gy). Beta dose = 68 rad (0.7 Gy) from each applicator.

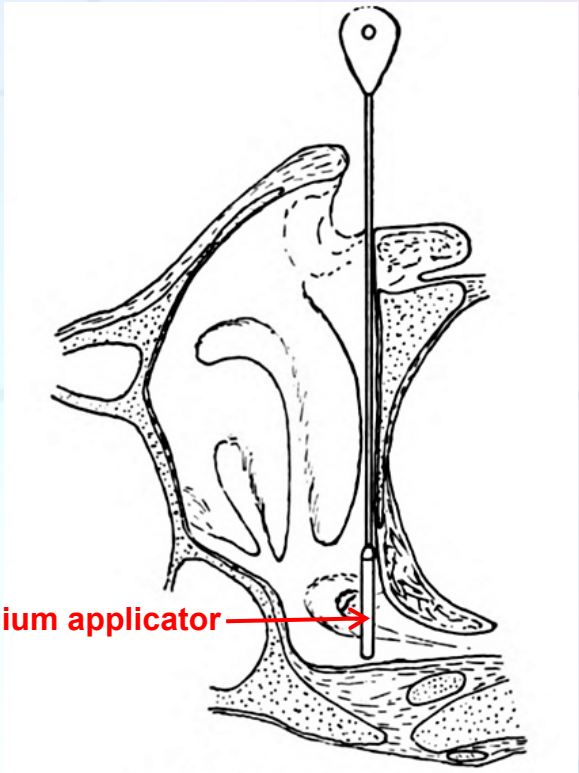


Fig. 7. Irradiation of the nasopharynx.
A. Diagram showing the radium capsule lying over the tubal orifice.

http://www.cancer.gov/cancertopics/factsheet/Risk/nasopharyngeal-radium

National Cancer Institute
at the National Institutes of Health

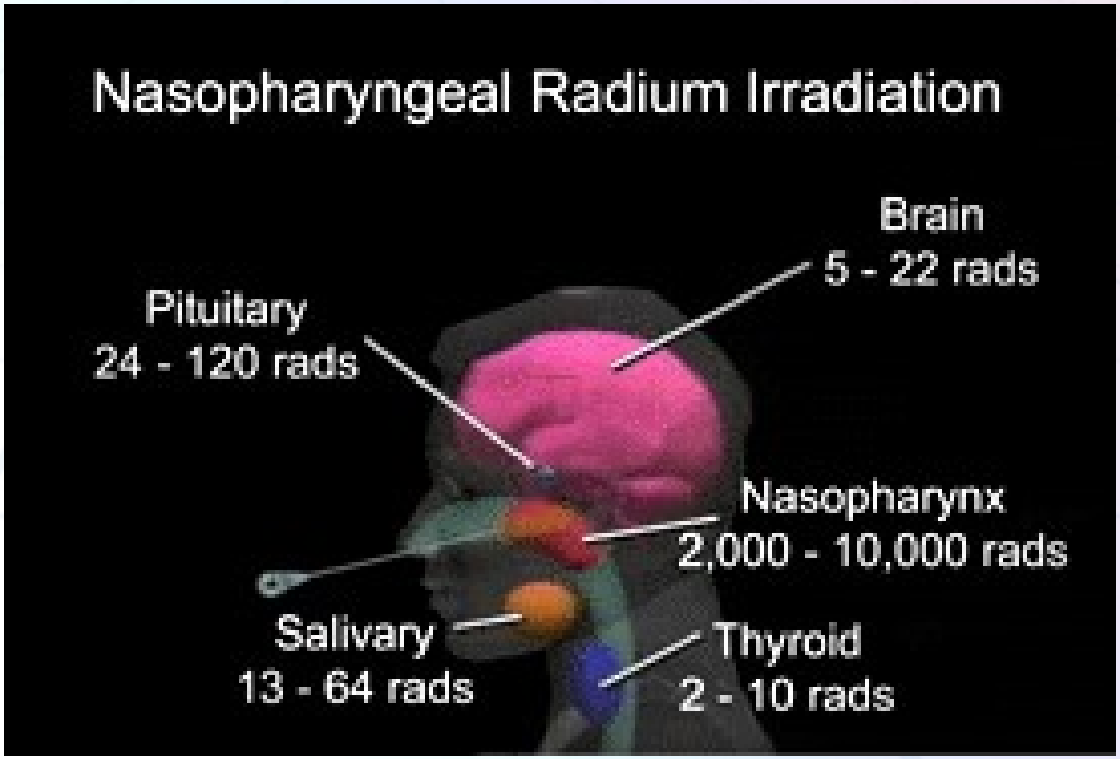
No link to any disease

Reviewed: January 10, 2003

Nasopharyngeal Radium Irradiation (NRI) and Cancer: Fact Sheet

Key Points

- Nasopharyngeal radium irradiation, (NRI) was widely used from 1940 through 1970 to treat ear dysfunctions in children and military personnel. Use of NRI was stopped when concern arose about possible adverse effects, including cancer.
- The purpose of NRI was to shrink swollen tissue in the nasopharyngeal cavity—the opening behind the nose and mouth. The treatment involved inserting a radioactive compound through the nostril into the nasopharyngeal opening for short periods of time. Some radiation exposure to the salivary, thyroid, and pituitary glands, and to brain tissue also occurred during this process.
- NRI was used in several European countries, Canada, and the United States. In the United States, it is estimated that between 0.5 million and 2.5 million children and at least 8,000 military personnel were treated with NRI.
- Children are considered to be the most vulnerable to radiation-related cancers.
- At this time, worldwide studies have not confirmed a definite link between NRI exposure and any disease.



20 – 100 Gy mucosal lining of nasopharynx
0.24 – 1.20 Gy pituitary gland
0.13 – 0.64 Gy salivary gland
0.05 – 0.22 Gy brain
0.02 – 0.10 Gy thyroid

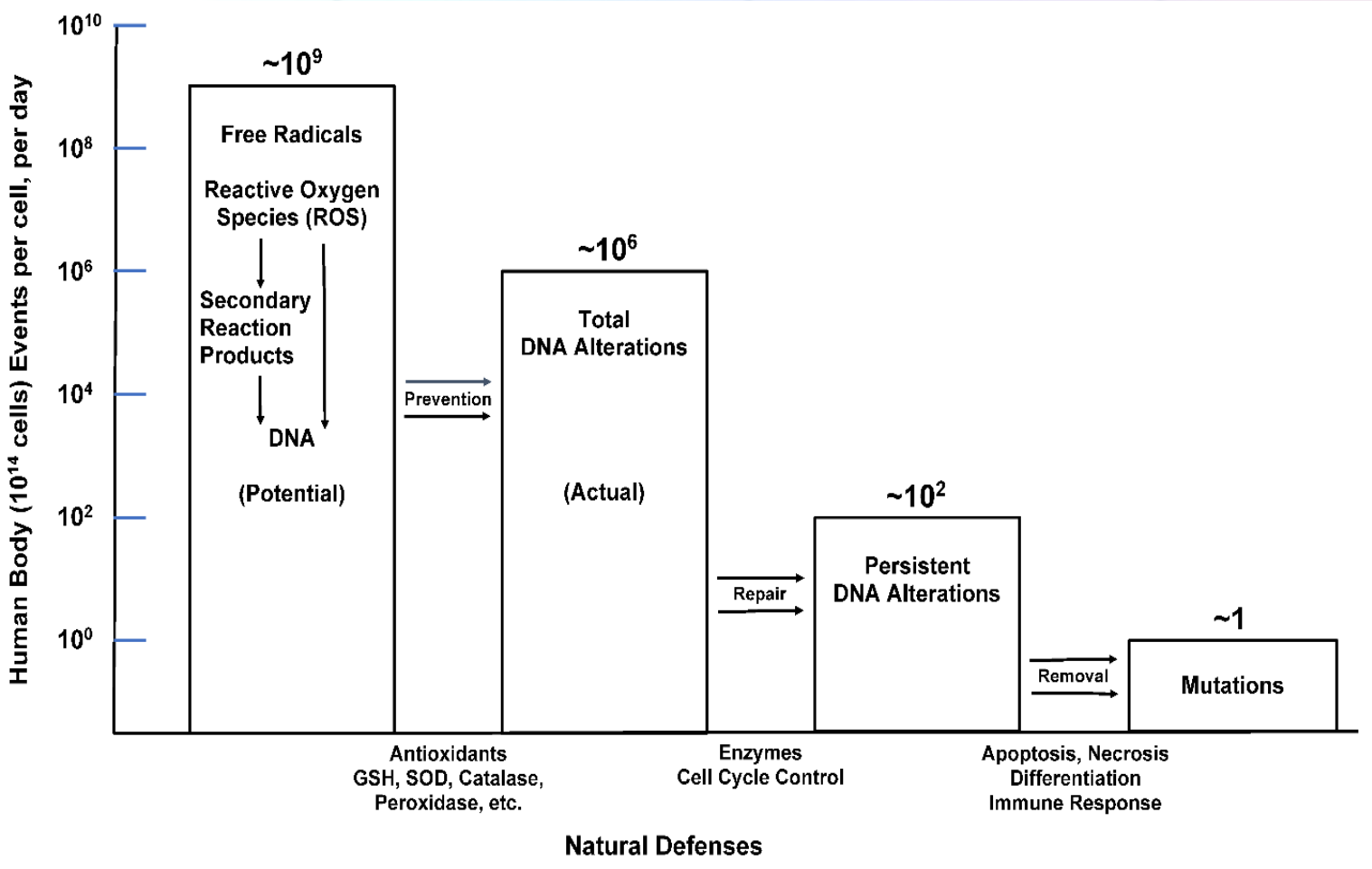
https://www.cdc.gov/nceh/radiation/nri/default.htm

What is the mechanism for beneficial effects?

- Organisms require redox cell-signaling agents, superoxide (O_2^-), peroxide (H_2O_2) and other oxidants. These are reactive oxygen species (ROS). They are produced in cell mitochondria, enzymes and multiple other sources and processes
- However, as a side effect, ROS cause oxidative damage at an enormous rate to all biomolecules, including DNA
- Powerful innate *adaptive protection systems* prevent, repair and remove damage due to all internal and external causes, including the oxidative damage caused by ROS
- These defences become weaker with age.

http://het.sagepub.com/content/22/6/290

Protection systems act against very high DNA oxidative damage rate due to ROS



Burst of ionizing radiation kicks the protection systems (natural defences)

- A burst of radiation (DNA hits and radiolysis of H_2O) kicks the protection systems to respond faster and harder
- *High* dose *inhibits or damages* these systems
- *Low* dose *stimulates* the systems to over-respond and remediate not only the radiation damage, but also heal diseases due to
  - internal causes: ROS damage*, immune disorders, etc.
  - external causes: infections, toxins, injuries, etc.

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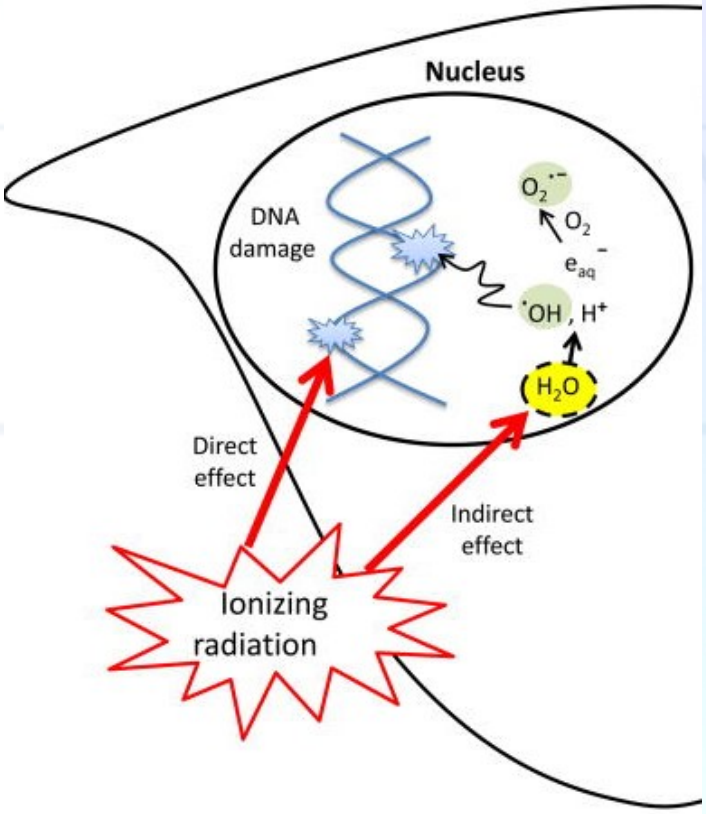
*Neurodegenerative diseases

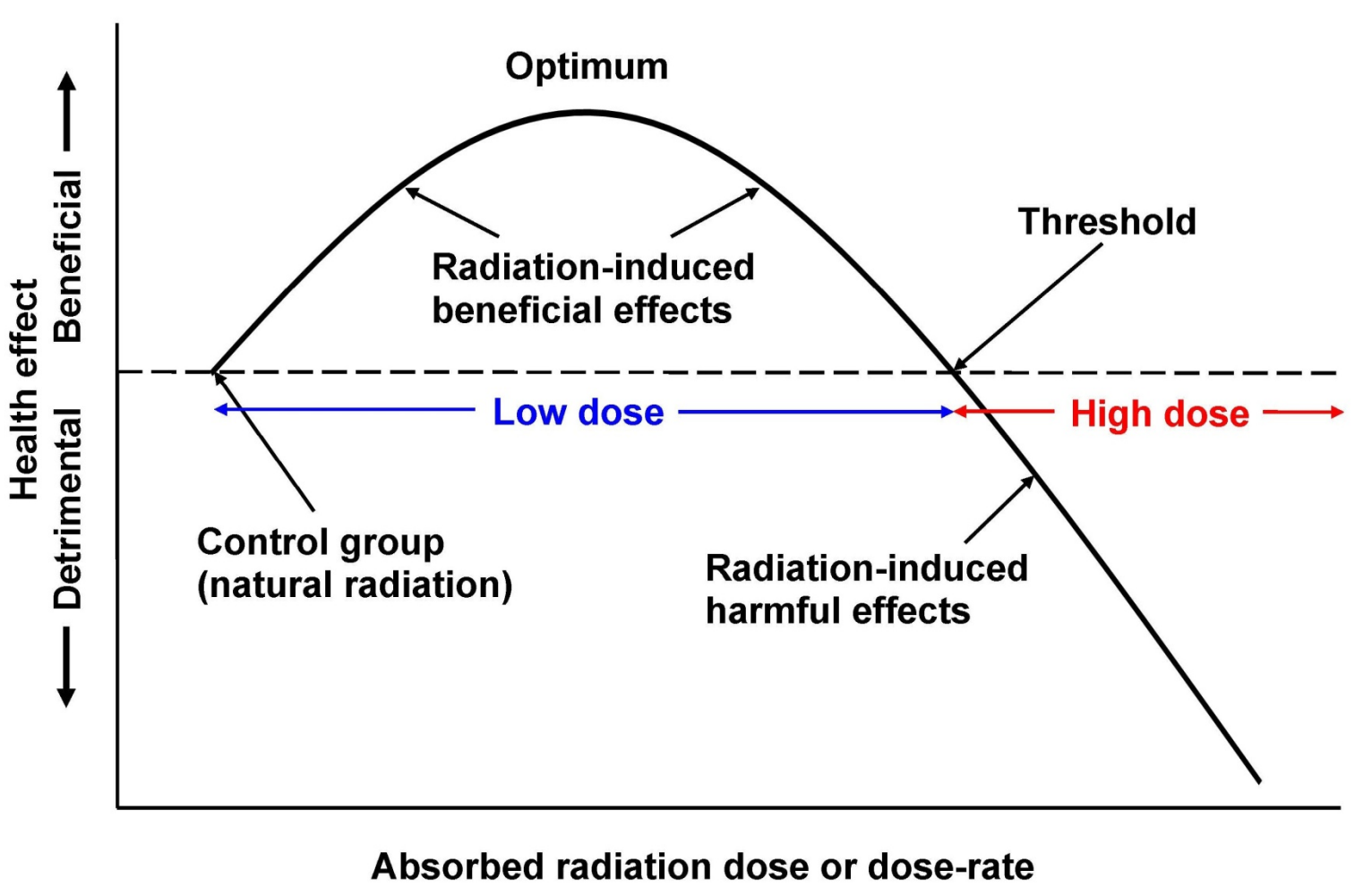
Burst of ionizing radiation damages DNA

Hits damage DNA
Radiolysis of water makes ROS, damages DNA



Definition of “low dose”

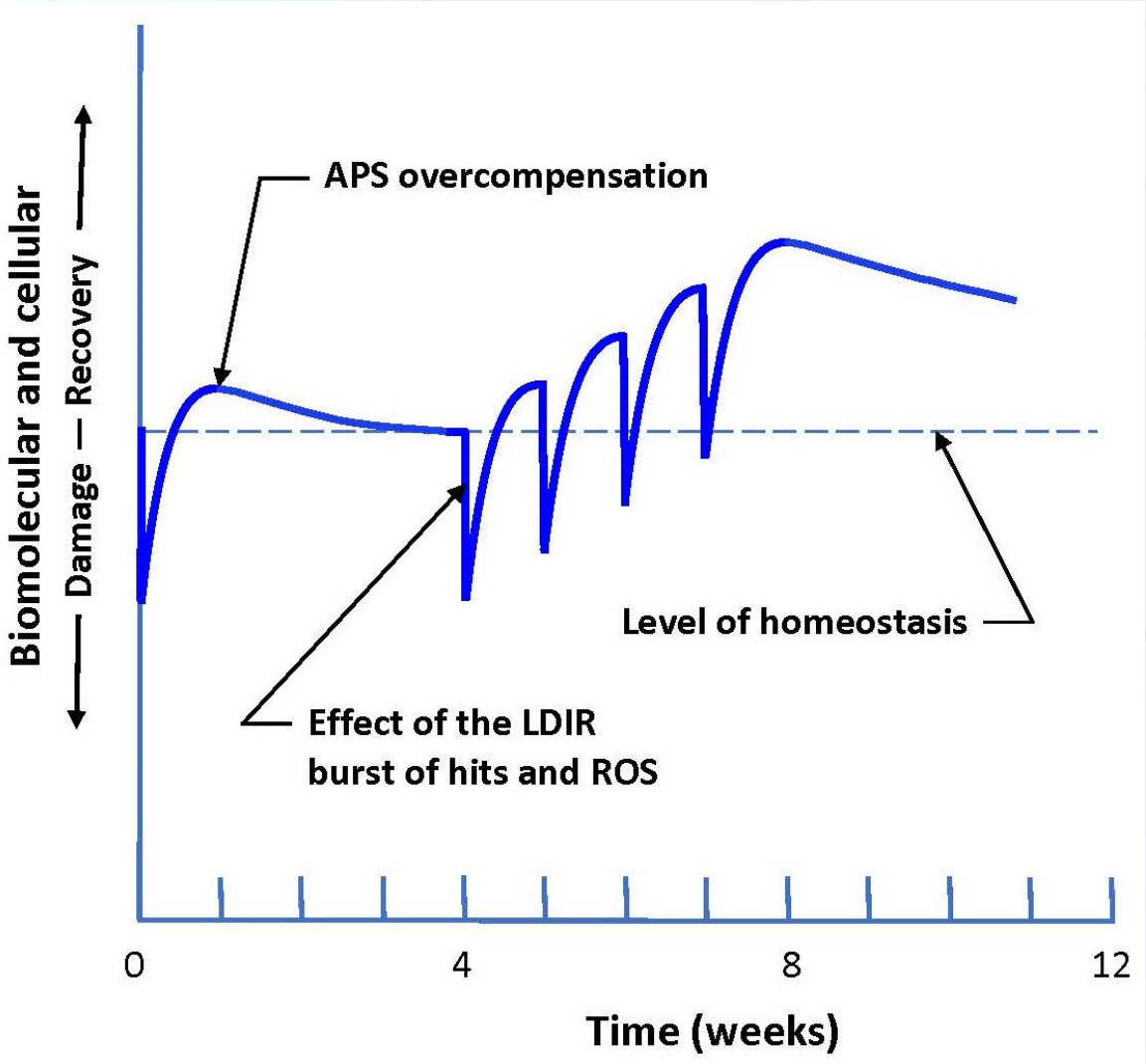
Biphasic dose-response model



Single and repeat X-ray treatments

Over-response to an acute dose.

Repeat doses give increased, longer lasting recovery



Two patients were treated in Michigan in 2015

A call for help

- In April 2015, Dr. Eugene Moore* called me:
- He: "I put my wife in hospice; she has Alzheimer's"

  "Can we do anything to save her life?"
- Me: "I reviewed this article in 2014"

  "Low Dose Radiation Adaptive Protection to Control Neurodegenerative Diseases"

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* Chemical engineer (83) retired from Dow Chemical, in Midland, Michigan

Dose-Response, 12:277–287, 2014
Formerly Nonlinearity in Biology, Toxicology, and Medicine

ISSN: 1559-3258
DOI: 10.2203/dose-response.13-030.Doss

International Dose-Response Society

LOW DOSE RADIATION ADAPTIVE PROTECTION TO CONTROL NEURODEGENERATIVE DISEASES

Mohan Doss □ Fox Chase Cancer Center

□ Concerns have been expressed recently regarding the observed increased DNA damage from activities such as thinking and exercise. Such concerns have arisen from an incomplete accounting of the full effects of the increased oxidative damage. When the effects of the induced adaptive protective responses such as increased antioxidants and DNA repair enzymes are taken into consideration, there would be less endogenous DNA damage during the subsequent period of enhanced defenses, resulting in improved health from the thinking and exercise activities. Low dose radiation (LDR), which causes oxidative stress and increased DNA damage, upregulates adaptive protection systems that may decrease diseases in an analogous manner. Though there are ongoing debates regarding LDR's carcinogenicity, with two recent advisory committee reports coming to opposite conclusions, data published since the time of the reports have overwhelmingly ruled out its carcinogenicity, paving the way for consideration of its potential use for disease reduction. LDR adaptive protection is a promising approach to control neurodegenerative diseases, for which there are no methods of prevention or cure. Preparation of a compelling ethics case would pave the way for LDR clinical studies and progress in dealing with neurodegenerative diseases.

Condition of Alzheimer's patient in 2015

- Age 81, diagnosed 10 years prior with Alzheimer's
- Examined May 15: "completely nonresponsive"
- Now at final stages
- Refused medication
- Almost totally non-communicative
- Almost immobile; no attempt to rise from wheel-chair in months

Low dose radiotherapy

- Suggested whole-body LD radiotherapy---not acceptable
- Her MD agreed to prescribe one CT scan of her brain
- Radiologist quoted $4000, including image analysis
- CT scan with no image analysis (cost $75) was accepted
- Patient moved during scan; operator repeated the scan, $CTDI_{vol}$ dose = 2 x 40 mGy = 80 mGy
- Next morning, her caregiver observed improved:

  Cognition, Memory, Speech, Movement and Appetite
- Husband and her friends were surprised and delighted
- She recognized her husband and friends, but not her son

“Barbara, look at the camera!”

Appetite

Responsive

Photos in: Cuttler JM, Moore ER, Hosfeld VD, Nadolski DL. Letter to the Editor. Update on a patient with Alzheimer disease treated with CT scans. Dose Response. 2017; 15(1):1-2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5347268/

Ongoing treatments

- I expected improvements to be short lived
- I suggested 2 scans every week (cancer)
- Her physician agreed to 1 scan every 2 weeks
- Improvement seen after 2 more treatments
- Setback after 4th but patient soon recovered
- Patient was moved on Nov 20th from hospice to seniors' home with a stimulating day program
- Four CT scans during 2016, at different intervals

Dates and doses

Date	Interval (days)	Dose (mGy)
07/23/2015		82**
08/06/2015	14	39
08/20/2015	14	47
10/01/2015	42	39
02/24/2016	146	40
06/22/2016	119	40
10/27/2016	127	40
12/13/2016	47	40
01/24/2017	41	80**

** two CT scans

"she was able to give simple verbal responses to direct simple questions. Not all of her responses were related to the direct questions, but she seemed to be reacting appropriately to the prosody and nonverbal cues of those around her."

Progress Note

PATIENT NAME: Barbara A. Moore
DATE OF BIRTH: October 28, 1934

PATIENT NUMBER: 5646
DATE SEEN: April 15, 2016

I met with Mr. and Mrs. Moore and their son, David. Unlike our last visit, Mrs. Moore was able to give simple verbal responses to direct, simple questions. Not all of her responses were related to the direct questions, but she seemed to be reacting appropriately to the prosody and nonverbal cues of those around her. This represents some improvement from October 12, 2015 when I last saw her.

Mr. Moore has been living at Bicksford Home in Midland since March 1, 2011. Mr. Moore reported that his wife is no longer receiving services through hospice at this time because of her lack of decline. He indicated that she was able to get out of the car by herself with some standby assist. However, she has not resumed walking independently. Mr. Moore reported that his wife occasionally feeds herself, but she still requires cueing.

Mr. Moore feels the low-dose x-ray treatment for tremor and the immune system is helping with his wife's cognitive difficulties. He is presenting a paper on the initial results at the 15th Annual International Conference on Dose-Response at the University of Massachusetts next week.

DIAGNOSTIC IMPRESSION: Senile dementia-probable Alzheimer's disease.

William D. MacInnes, Ph.D., A.B.N.
Diplomate in Clinical Neuropsychology
American Board of Professional Neuropsychology

Cc: David Nadolski, M.D.

Eugene Moore
mooreer@aol.com

Alzheimer's worsened in 2017---death in 2018

- Quality of life was good in 2016
- Last treatment on Jan 24, 2017; condition deteriorated
- She was moved back to hospice on Mar 6th, 2017
- She lost reflex to swallow; her weight decreased from 185 to 160 pounds
- Celebrated 83rd birthday party on Oct 28th
- Died on May 18th, 2018

Treatment of Parkinson disease

- Husband (age 83) has Parkinson's
- He requested a CT scan (Oct 6, 2015)
- First night in bed, the constant tremors stopped
- Slept well and awoke refreshed
- Carbidopa/Levodopa pills; cut from 6 to 2-3 per day

CT scans for Parkinson patient

4 to 6 weeks was suitable interval

Date	Interval (days)	Dose (mGy)
10/06/2015		40
06/16/2016	253	40
07/13/2016	28	40
09/29/2016	51	40
11/21/2016	80	40
12/21/2016	30	40

Effects on Parkinson's patient

- Received 5 CT scans during 2017
- Almost no tremors, so medication was stopped, perceives tremor decrease after each CT scan
- Vision improved: can read at 18" without glasses, decreased Fuchs' dystrophy (corneal edema)
- Hearing improved: 5 dB at 4000 Hz and 18 dB at 6000 Hz
- Neuropsychological evaluation: "notable improvements and relatively mild declines"
- He still receives LDIR treatments every 4-6 weeks, in 2021

Papers on AD and PD patients

Original Article

Treatment of Alzheimer Disease With CT Scans: A Case Report

2016

Dose-Response:
An International Journal
April-June 2016: 1–7
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DOI: 10.1177/1559325816640073
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Jerry M. Cuttler[1], Eugene R. Moore[2], Victor D. Hosfeld[3], and David L. Nadolski[4]

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4826954/ http://dos.sagepub.com/content/14/2/1559325816640073.full

Abstract

Alzheimer disease (AD) primarily affects older adults. This neurodegenerative disorder is the most common cause of dementia and is a leading source of their morbidity and mortality. Patient care costs in the United States are about 200 billion dollars and will more than double by 2040. This case report describes the remarkable improvement in a patient with advanced AD in hospice who received 5 computed tomography scans of the brain, about 40 mGy each, over a period of 3 months. The mechanism appears to be radiation-induced upregulation of the patient's adaptive protection systems against AD, which partially restored cognition, memory, speech, movement, and appetite.

Keywords

Alzheimer disease, CT scan, adaptive protection systems, ionizing radiation

Letter to the Editor

Update on a Patient With Alzheimer Disease Treated With CT Scans

2017

Dose-Response:
An International Journal
January-March 2017:1-2
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DOI: 10.1177/1559325817693167
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Jerry M. Cuttler[1], Eugene R. Moore[2], Victor D. Hosfeld[3], and David L. Nadolski[4]

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5347268/

Letter to the Editor

Second Update on a Patient With Alzheimer Disease Treated by CT Scans

2018

Dose-Response:
An International Journal
January-March 2018:1-2
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Jerry M. Cuttler[1], Eugene R. Moore[2], Victor D. Hosfeld[3], and David L. Nadolski[4]

Pilot study in Toronto

- Physicians do not believe the Michigan evidence
- I urged Baycrest to repeat the treatments on 3 patients with severe Alzheimer's
- Sunnybrook has 5 CT scanners, so a joint Baycrest-Sunnybrook pilot study was started in July 2017
- Protocol, TAHSN and Consent Form were prepared
- Health Canada accepted use of CT scans for therapy
- 2 Research Ethics Boards approved study in July 2018
- No funding for the study
- Clinical trial registered at www.ClinicalTrials.gov

Hypothesis

- **Oxidative stress is a major factor in the development of Alzheimer's disease***
- **Stimulation of the adaptive protection systems in the brain by the low radiation dose of a CT scan will reverse or delay progression of this disease**

*** The brain is highly vulnerable to oxidative damage due to its high metabolic demand.**

Baycrest-Sunnybrook study, 2017-2020

- 4 participants (Apotex Hospital residents at Baycrest)
- 3 treatments for each (in 2019)
- Subjective, qualitative data:
  - Observations of patient responses and behaviours by relatives, caregivers and study investigators
  - Written and verbal reports, photos, and videos
- Objective, quantitative measures:
  - Severe impairment battery (SIB)
  - Cohen-Mansfield Agitation Index (CMAI)
  - Alzheimer Disease Functional Assessment and Change Scale (ADFACS)

Treatment in 2019; $CTDI_{vol}$ doses (mGy)

	1st Treatment	2nd Treatment	3rd Treatment
Case 1 (88 yrs)	Feb 8	Feb 22	Mar 8
Dose	81.0	41.0	43.0
Case 2 (90 yrs)	Jul 16	Jul 30	Aug 13
Dose	89.0	46.0	40.0
Case 3 (84 yrs)	Sep 10	Sep 24	Oct 8
Dose	79.0	40.0	43.0
Case 4 (82 yrs)	Dec 17	Dec 31	Jan 14
Dose	80.0	40.3	40.4

Results

- **1 case:**
  - very severe case of Alzheimer's showed no improvements
- **3 cases:**
  - subjective response to relatives, friends and caregivers revealed remarkable improvements in cognition and behaviour
  - objective measures showed only minor improvements

Note that a mouse study gives evidence that strongly supports the hypothesis of the mechanism of X-ray therapy

Case 4, female, age 82, MMSE 0/30

Five days after the first treatment, at Chanukah concert, she spoke in short sentences with two of her sons and daughter, in response to their remarks and questions. She listened and nodded as relatives, friends, and many events were mentioned. They reminisced about how she met her husband, their life in Toronto, the births of her six children, and their family inn at a summer resort.

While listening to the reminiscing, she said jokingly, “Don’t give away all the family secrets.”

She cried a few times. When asked whether she was in pain or upset, she replied, “No, I’m very happy.”

She laughed when asked whether she was ready to dance, as her legs moved to the rhythm of the music.

She expressed gratitude for her recovery.

Primary goal of therapy for old adults?

Improve the quality of life by:

- **Optimizing their well-being**
- **Staying their brain health**
- **Restoring communication with family and friends to avoid social isolation, loneliness, under stimulation**

Old adults to recognize their spouse, children, and grandchildren

Limitations of this study

- Small sample size, only 4 cases
- Only subjective evidence of the improvements
- Quantitative, objective measures were insensitive
- No biological markers of oxidative damage
- No placebo group
- Open-label design; potential for bias (patient and investigators were aware of treatments)

Future Research:

- Do double-blind, placebo-controlled trials of the X-ray therapy to determine its efficacy
- Biological markers, to quantify oxidative damage
- Include patients with milder disease

Objective, quantitative evidence supports hypothesis that X-rays restore cognition

Neurotox Res (2018) 33:824–836
https://doi.org/10.1007/s12640-017-9833-7

ORIGINAL ARTICLE

Restoration of Cognitive Performance in Mice Carrying a Deficient Allele of 8-Oxoguanine DNA Glycosylase by X-ray Irradiation

Tim Hofer[1,2] · Nur Duale[2,3] · Martine Muusse[1] · Dag Marcus Eide[1,2] · Hildegunn Dahl[2,3] · Fernando Boix[4] · Jannike M. Andersen[4] · Ann Karin Olsen[2,3] · Oddvar Myhre[1,2]

Received: 30 June 2017 / Revised: 13 October 2017 / Accepted: 18 October 2017 / Published online: 3 November 2017

Abstract Environmental stressors inducing oxidative stress such as ionizing radiation may influence cognitive function and neuronal plasticity. Recent studies have shown that transgenic mice deficient of DNA glycosylases display unexpected cognitive deficiencies related to changes in gene expression in the hippocampus. The main objectives of the present study

Keywords adrenergic receptor · behavior · brain · interleukin · knockout · peroxiredoxin

Introduction

An X-ray restored cognition in transgenic mice

- Oxidative stress leads to accumulation of damage in brain; linked to neurodegenerative diseases
- Base excision repair is the major way to remove oxidative damage in DNA
- DNA glycosylases gene recognizes and excises damaged bases
- Mice lacking DNA glycosylases, heterozygous in the $Ogg1^{+/-}$ gene, poorly repair oxidative damage; deficiencies in early-phase learning and memory
- Just one 0.5 Gy full-body X-ray upregulated repair, which improved cognition; same as normal mice
- This mouse evidence supports my hypothesis that a dose of X-rays restores cognition in Alzheimer's

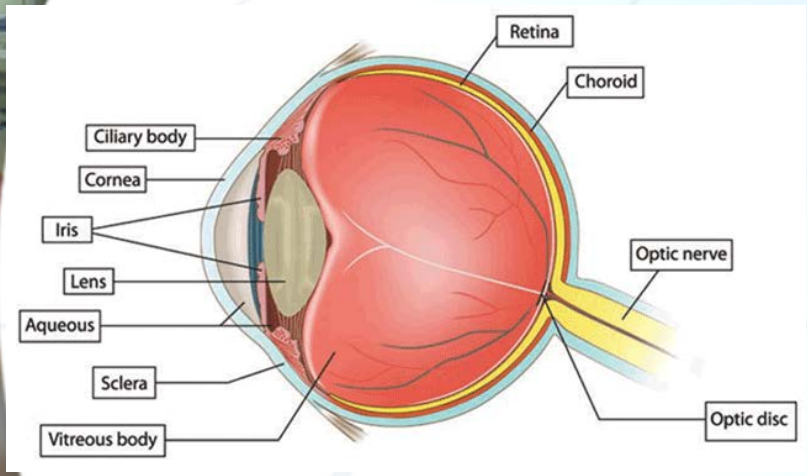
How to improve LDIR therapy?

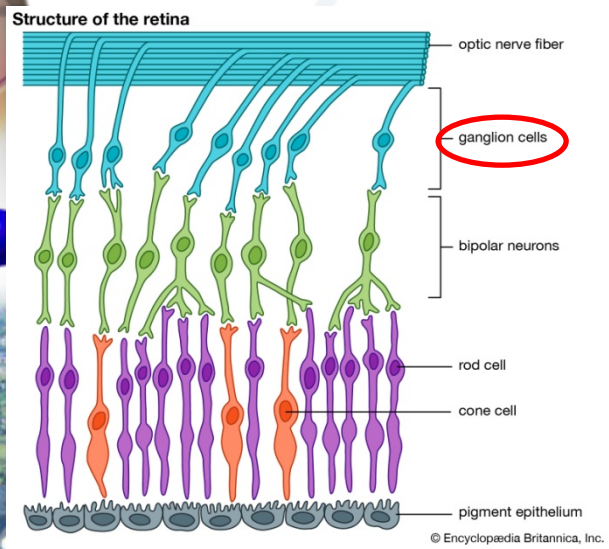
- Determine optimal X-ray dose (200 mGy?)
- Determine optimal time between treatments
- Measure biological markers* to quantify the improvement and its duration
- Use low-cost, portable X-ray device instead of CT scanner
- Develop specific protocol for each AD patient

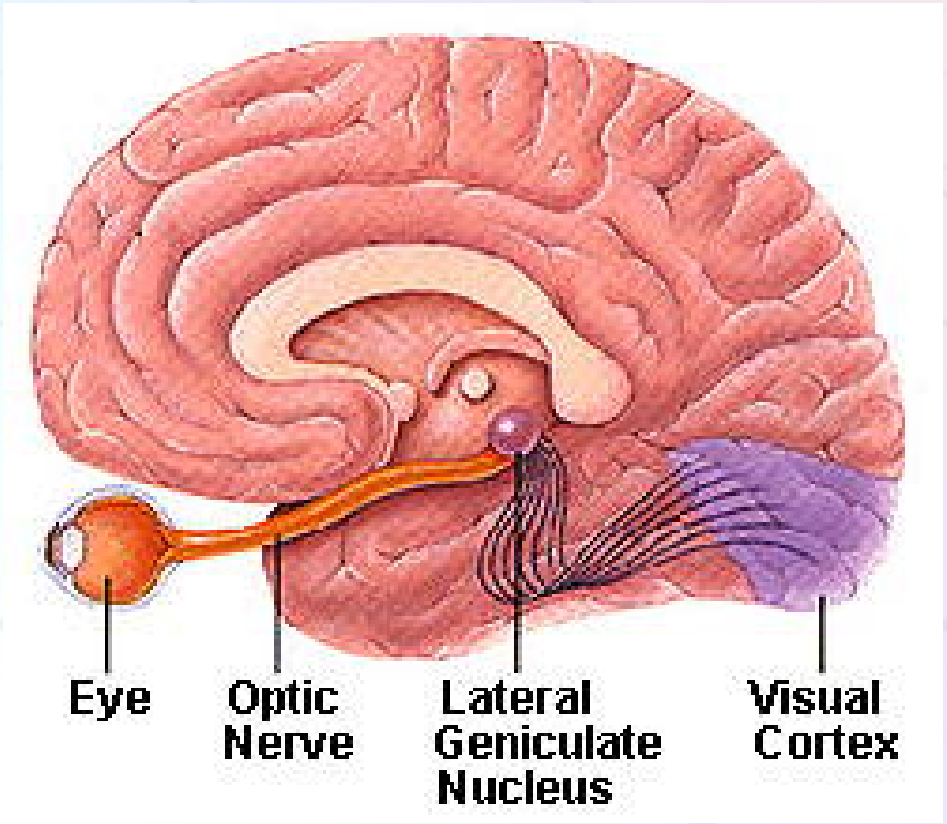
* F2 isoprostanes in cerebrospinal fluid have been found to be a good marker of oxidative stress that is associated with Alzheimer's

Potential LDIR treatment for glaucoma

Caused by neurodegeneration of retinal ganglion cells







Weinreb RN, Aung T, Mederiros FA. The pathophysiology and treatment of glaucoma: A review. *JAMA*. 2014;311(18):1901-1911. https://jamanetwork.com/journals/jama/fullarticle/1869215

Goldberg JL. Glaucoma and the brain. Glaucoma Research Foundation. 2017. https://www.glaucoma.org/glaucoma/glaucoma-and-the-brain.php

Mouse study on X-ray repair of retinal nerves

The American Journal of Pathology, Vol. 180, No. 1, January 2012

DOI: 10.1016/j.ajpath.2011.09.025

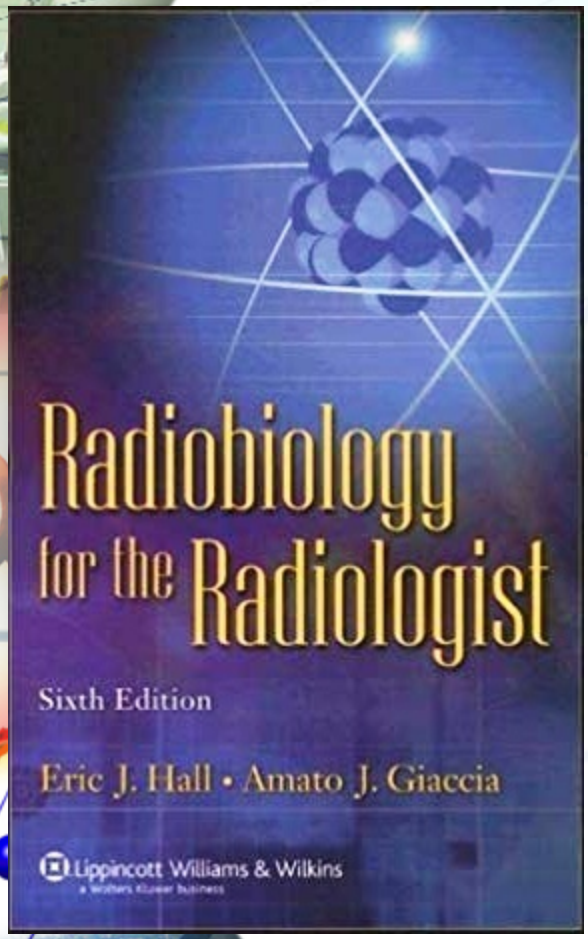
Neurobiology

Low-Dose-Rate, Low-Dose Irradiation Delays Neurodegeneration in a Model of Retinitis Pigmentosa

Atsushi Otani, Hiroshi Kojima, Congrong Guo, Akio Oishi, and Nagahisa Yoshimura

From the Department of Ophthalmology, Kyoto University Graduate School of Medicine, Kyoto, Japan

has been widely used in the field of toxicology, where it is defined as "an adaptive response characterized by biphasic dose responses of generally similar quantitative features with respect to amplitude and range of the stimulatory response that are either directly induced or the result of compensatory biological processes following an initial disruption in homeostasis."[1] Some researchers



Physicians are carefully taught that

radiation-induced mutations and cancer can be predicted by the LNT dose-response model

This book fails to mention:

- **that organisms produce essential redox cell-signaling agents that cause oxidative damage to DNA and other molecules at very high rate**
- **that organisms have powerful protection systems to remediate all internal and external causes of damage**
- **that low radiation stimulates these protection systems, including immune system, to induce beneficial health effects**
- **the dose and dose-rate thresholds for onset of detrimental effects**

Physicians are wrongly urged to minimize exposures:
https://doi.org/10.1177/1559325821995653

Conclusions

1. Low doses of radiation have been used for ~ 120 years to treat cancer, infections, inflammations, autoimmune diseases, others
2. Organisms produce reactive oxygen species (ROS), which are essential redox cell-signaling agents, but they cause oxidative damage at a very high rate.
3. Organisms have powerful protection systems against ROS and all other internal and external causes of damage and disease
4. A *low dose* of radiation stimulates the protection systems, which include the immune system
5. In 1956, the world was misled by recommendation to use linear no threshold (LNT) dose-response model for radiation-induced genetic mutation and cancer risk assessment

6. In 1960, *precautionary principle* and ALARA were adopted
7. Physicians stopped employing these X-ray therapies, and they disregard all information about their remarkable efficacy
8. Medical textbooks follow LNT—omit information on radiation stimulation of protection systems against diseases
9. Clinical trials on X-ray therapies encounter difficulty obtaining medical endorsement and funding
10. X-ray therapy is promising for neurodegenerative diseases
11. Further research is needed to demonstrate efficacy

Note: Baycrest Communication issued this news release May 20:
https://www.baycrest.org/Baycrest-Pages/News-Media/News/Research/Low-doses-of-radiation-may-improve-quality-of-life