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Radiation Protection and
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University School of Medicine

## Radiation Studies and Concepts I



#### Radiation Epidemiology & Dosimetry Course

**National Cancer Institute** 

www.dceg.cancer.gov/RadEpiCourse





#### Disclaimer

The opinions expressed during this presentation are entirely my own and not those of NCRP, ICRP, UNSCEAR, Vanderbilt or the Social Security Administration (which supports my health care).

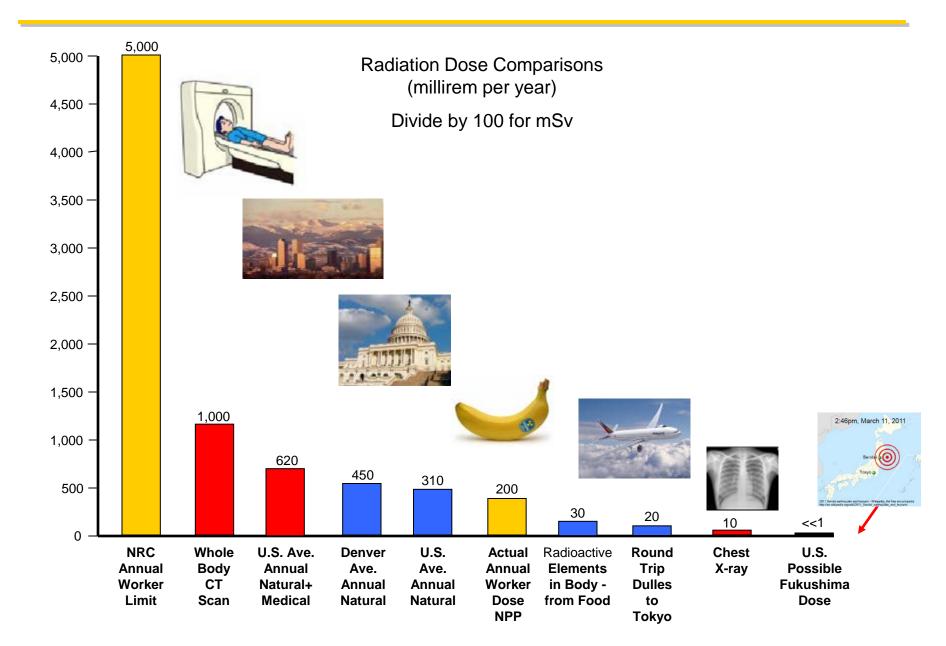
Opinions may be biased, confounded and based on unshared uncertainties.

## Topics Classic Studies and Basic Concepts



- Is Epidemiology and Dosimetry necessary?
- Classic Studies Personal view
- Basic Concepts Epidemiology is observational and the bane is bias and confounding

#### We live in a radioactive world



#### The Need for Radiation Scientists

Public exposures to radiation and radioactive material are increasing – along with public awareness – while radiation professionals are decreasing. Issues to deal with include:

- Medicine, e.g., CT exams
- Nuclear Power Generation
- Hydraulic Fracturing (TeNORM)
- Environmental Circumstances
- Nuclear Reactor Accidents, e.g., Fukushima
- Potential Terrorist Attacks





## The Need for Epidemiology (& Dosimetry)

#### H.R.35 - Low-Dose Radiation Research Act of 2015

114th Congress (2015-2016)

Passed in House (01/06/2015)

"... the rapid increase in medically-based radiation exposures, cleanup of radioactively contaminated sites, as well as the need for science-based policies regarding the possible expansion of nuclear power, require a level of research and scientific expertise that the US is rapidly losing – in universities, in national labs, and in industry."

## Radiation Epidemiology is more than Statistics!

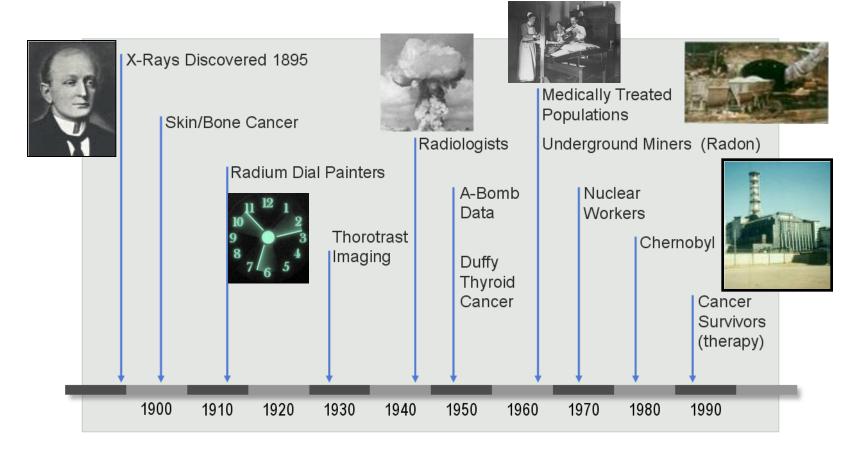


FRANK & ERNEST, Bob Thaves

- Science of Public Health (Observational)
- Relies on a working knowledge of probability and statistics
- A method of causal reasoning, that considers biological plausibility, consistency and sound research methods
- The bane of epidemiology is bias and confounding

## Epidemiology is the study of the distribution and causes of disease in

Radiation Epidemiology Dates Back 100 Years



#### Epidemiologic Studies of Exposed Human Populations



#### JAPANESE ATOMIC BOMB SURVIVORS

RADIOTHERAPY - CANCER

Cervical

**Endometrial** 

Childhood

**Breast** 

Hodgkin Lymphoma

DIAGNOSTIC

TB - Fluoroscopy

Pelvimetry

Scoliosis

General

P - 32

Ra - 224

Plutonium

**RADIONUCLIDES** 

Thorotrast

I - 131

Uranium

RADIOTHERAPY - NON-MALIGNANT

Spondylitis

Thymus

Tonsils -

Menstrual Disorders

Scalp Ringworm

Mastitis

Infertility

Otitis Media

Ulcer

Hemangioma

ENVIRONMENT

Chernobyl

Weapons Fallout Natl Background

Techa River

**Nuclear Facilities** 

OCCUPATION

Ra Dial Painters

Miners (Radon)

Radiologists

Technologists

**Nuclear Workers** 

**Atomic Veterans** 



#### Oldies but Goodies (Before 1950)

- Radium Dial Painters
- Thorotrast Patients
- Radiologists

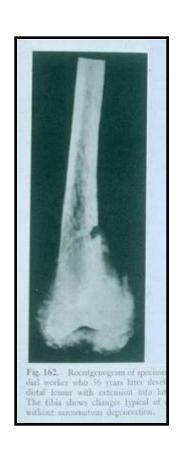
Ala DoReMi, MELODI, OPERRA

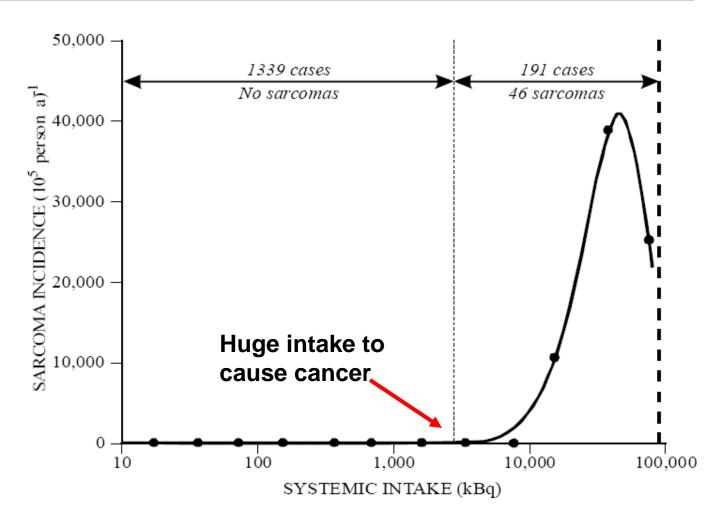
#### Radium Dial Painters





## Bone Cancer in Radium Dial Painters (UNSCEAR 2000; Rowland Rad Res 1978)





10 Gy suggested as a "practical threshold" for bone cancer

Bone Cancer, not leukemia

#### Radium Girls and Radon Breath

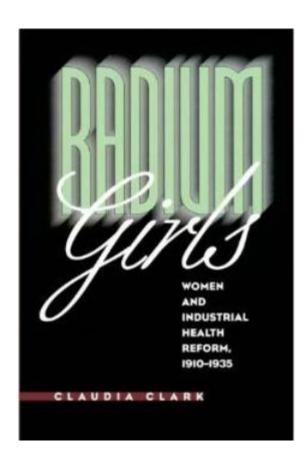


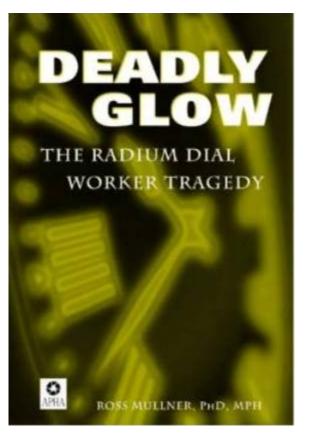
Women painting numbers using radioactive paint. Dozens died of radium poisoning. Recently a Radium Girl (Mae Keane) died in 2014 at 107 (she quit after a week – didn't like the gritty taste of the paint). Radium intakes estimated from breath analyses.



#### Radium Dial Painters





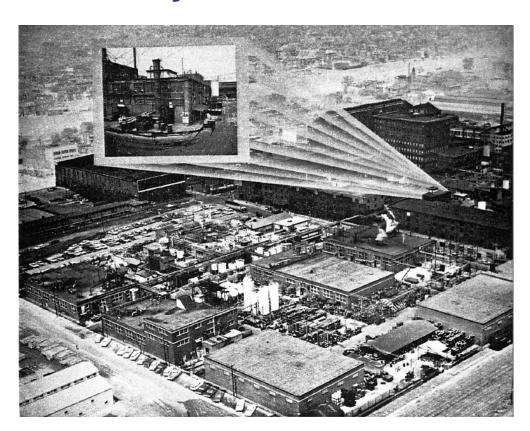


Am. J. Epidemiol. (2002) 155 (3): 290-291.

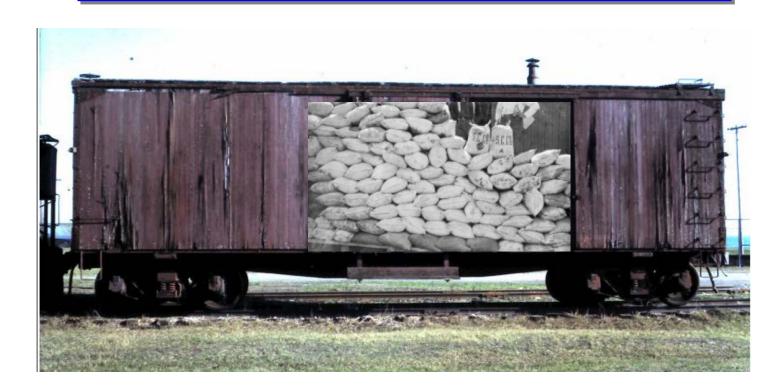
#### Fast Forward – Today's Research

#### Mallinckrodt Chemical Works (St Louis)

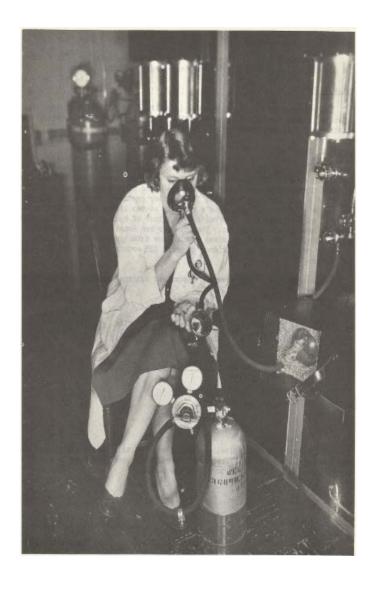
How many tons of uranium oxide was processed for Manhattan Project between July and Dec 1942 and why?



## Box Cars Filled with Pitchblende from Belgium Congo, had to remain open for 12-24 hrs because of radon levels



Radon
breath
analyzer
tests – to
determine
radium
intakes



 Uranium/radium dust and radon breath measurements done frequently to estimate radium content in body (HASL/EML in NYC)



### Radon in Breath for Mallinckrodt Worker over Time

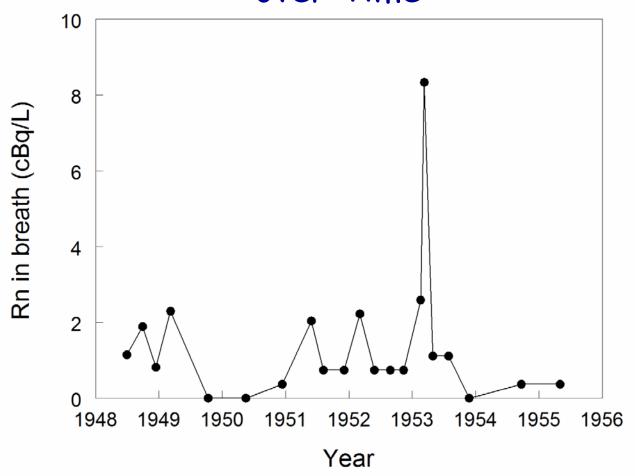


Figure B. Illustration of breath radon data for a Mallinckrodt radium worker. The tick mark above year 1952, for example, is positioned at January 1, 1952.

#### Dust, An Example of Confounding

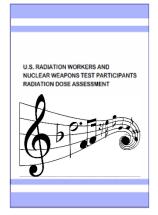


Kidney cancer	No.	Cases	RR
<10 (mSv)	988	4	1.00
10 – 49 50+	784 601	5 4	1.87 3.55 p = 0.002

- Based on 40,000 urine assays, 2,500 radon samples and 1000s of uranium dust measurements, we were able to evaluate uranium intake and silica potential
- - Likely cause of kidney disease was not external gamma but heavy metal properties of uranium and confounding effects of silica

## Dosimetry is Key to Good Epidemiology

SC 6-9: U.S. Radiation Workers and Nuclear Weapons Test Participants Radiation Dose Assessment















R Toohey Co-Chairman

H Beck

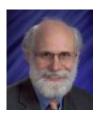
**T Brock** 

L Dauer















**K Eckerman** 

**D** Hagemeyer

R Leggett

**B** Napier

**K** Pryor

M Rosenstein S Balter

















**J Thompson** 

**D** Schauer

S Sherbini

**D** Miller

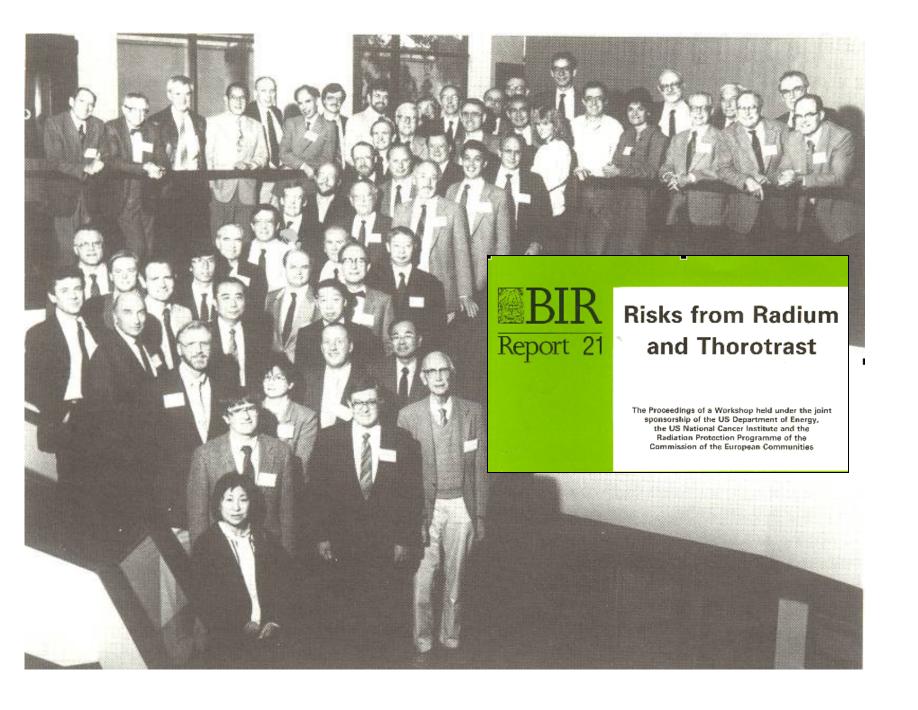
**D** Stram

J Till

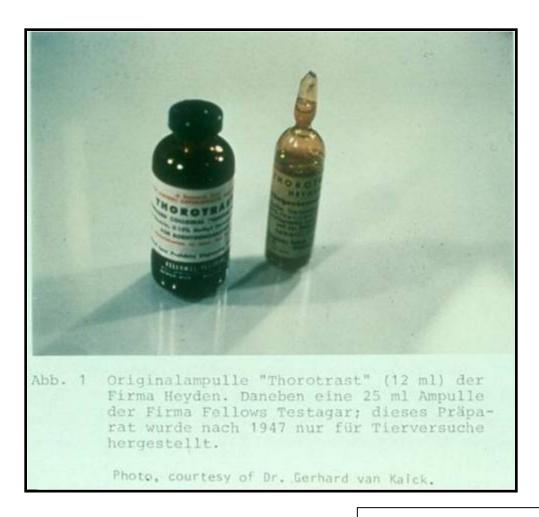
**C** Yoder

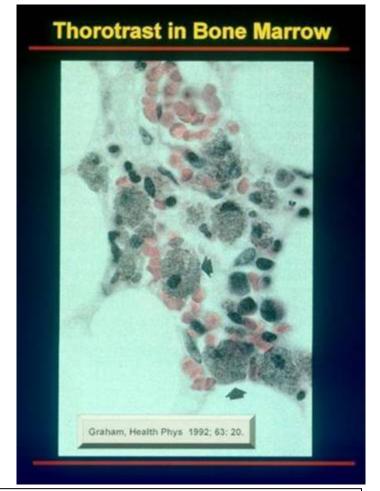
C Zeitlin





#### Thorotrast - Thorium Dioxide Solution Contrast Agent for Cerebral Angiography





Leukemia, not Bone Cancer – Chemistry Matters



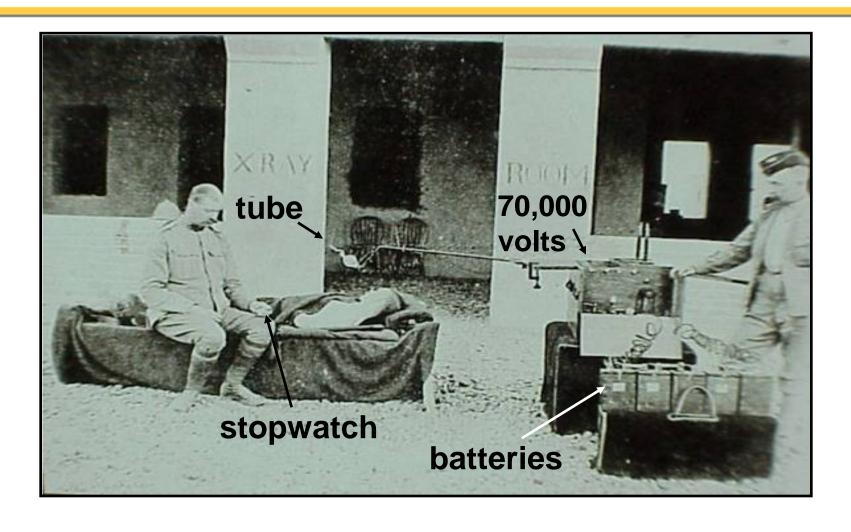
## Thorotrast – Brain Cancer Example of Confounding by Indication

#### Site-Specific Cancer Mortality Among Thorotrast-Exposed & Nonexposed Patients in the United States

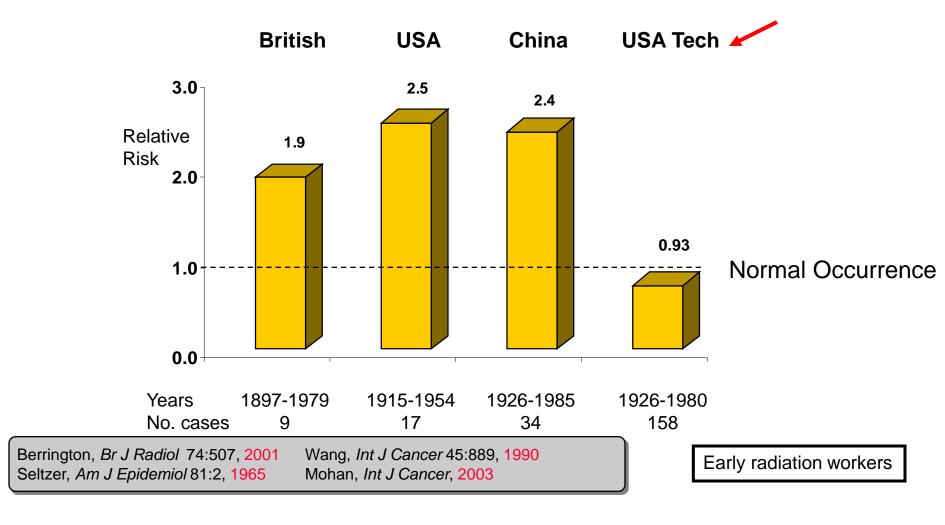
Cancer	Thorotrast-Exposed		Comparison Group		Rela	tive Risk
Cancer	OBS	SMR	OBS	SMR	RR	95 % CI
Brain & other CNS	21	33.6	6	15.6	1.3	0.6 - 3.7

Patients who have examinations because of a suspicion of tumor usually are more likely to develop the tumor regardless to whether the exam included radiation or not. Travis *et al.* (2004) Confounding by indication.

#### Early Radiologists and Technicians 1898 - Sudan



#### Leukemia Among Early Radiologists / Technologists



#### Radiation Exposure to Radiologists

1930: 100 rad / yr est.

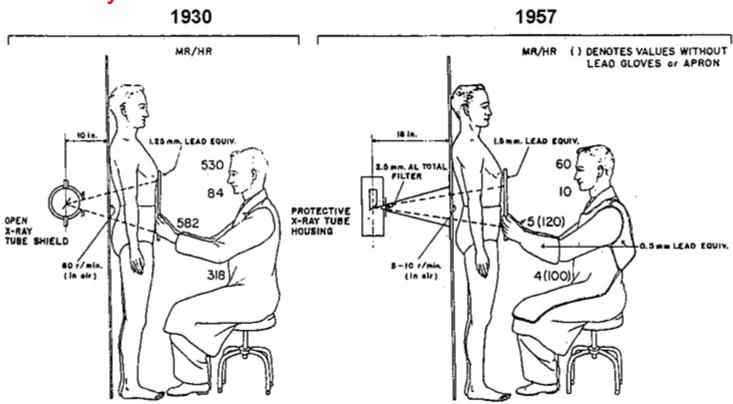


Fig 1. Comparison of stray radiation from vertical fluoroscopes.

Braestrup, Am J Roentgenol 78:988, 1957

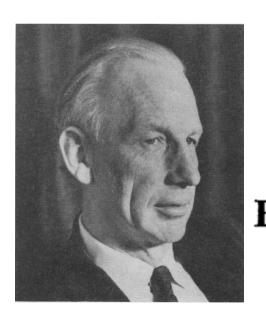


#### Legendary Hits (1950-1970s)

- Ankylosing Spondylitis
- Cervical Cancer
- Prenatal X-ray
- Underground Miners

#### PRIVY COUNCIL

#### MEDICAL RESEARCH COUNCIL SPECIAL REPORT SERIES No. 295



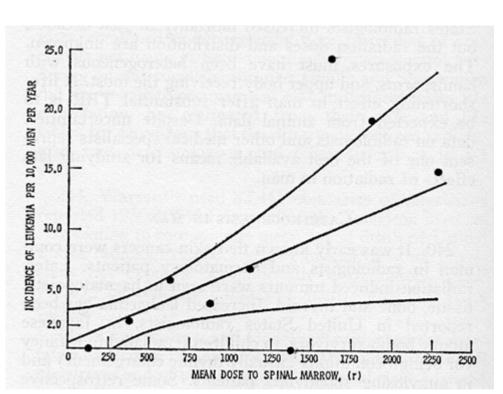
# LEUKAEMIA AND APLASTIC ANAEMIA IN PATIENTS IRRADIATED FOR ANKYLOSING SPONDYLITIS

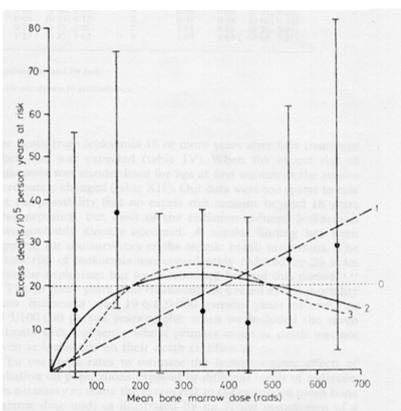
W. M. COURT-BROWN, O.B.E., M.B., B.Sc., F.F.R. and R. DOLL, O.B.E., M.D., F.R.C.P.

1957

Second study designed to evaluate leukemia dose response

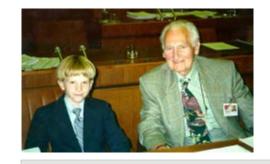
#### Leukemia - Ankylosing Spondylitis, UK





Court Brown & Doll, UK, 1957 UNSCEAR, 1962 Smith & Doll, *BMJ*, 284:449, 1982 Weiss et al, *Radiat Res* 142:1, 1995

Smith PG. The 1957 MRC report on leukaemia and aplastic anaemia in patients irradiated for ankylosing spondylitis. J Radiol Prot. 2007



#### Sir Richard Doll on Ankylosing Spondylitis Study

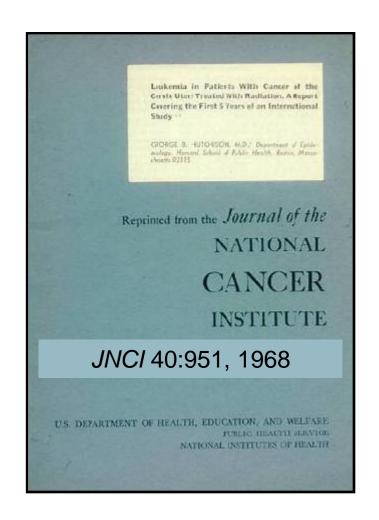
"My favourite paper is the one with Michael Court-Brown deriving the dose—response relationship between radiation and leukaemia. . . . But this work is not often remembered nowadays. I doubt if many epidemiologists would pick the dose—response relationship between radiation and leukaemia if they were asked to associate particular observations with my work. Yet, it is certainly the second most important piece of work that I have done, after the effects of smoking, and it provided the first suggestive evidence of a linear relationship for the carcinogenic effect of ionising radiation down to quite small doses. In fact, the estimate of the risk of leukaemia per unit dose that it provided is not very different from the value that is accepted now.

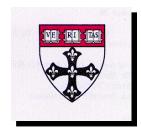
"It was quite a difficult study to organise. We had to collect information on 14 000 patients treated throughout the country by radiotherapy for the benign condition of ankylosing spondylitis, and we had to measure the dose of radiation received in the marrow by doing experiments on a model man. In many ways it was the best-designed study I have ever participated in and possibly my best work."

## Study of Leukemia Radiotherapy for Cervical Cancer

Third study in 1960s designed to quantify risk of leukemia







#### Cervical Cancer and Leukemia Blood Studies and Clinical Follow-up 30 Radiotherapy Centers in 9 Countries



Number 30,000 women

Dose 5-15 Gy (marrow)

Leukemia

Observed 13

Expected 15.5

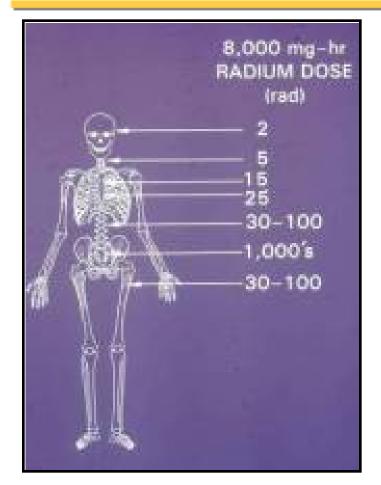
Risk No excess

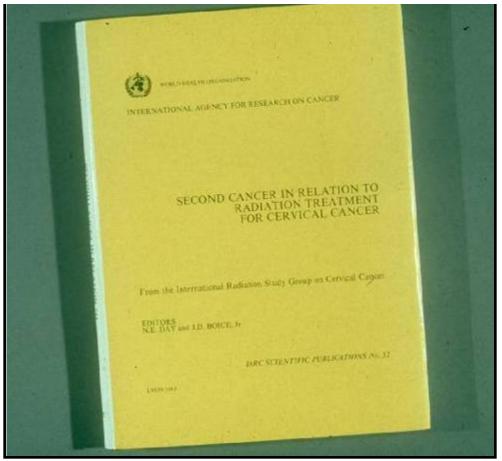
Huge dose but no risk

Boice & Hutchison, *JNCI* 65:115, 1980

## International Cervical Cancer Study Expansion – 16 Radiotherapy Centers and 17 Cancer Registries in 14 Countries



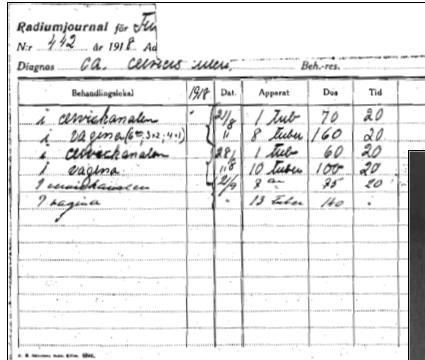




200,000 women

#### Elis Berven (1885-1966) på Radiumhemmet

Filter- Sek.

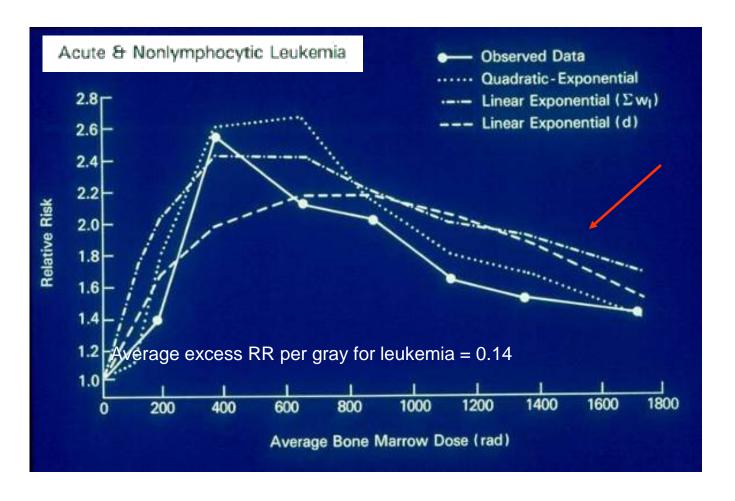


Radiumjournal År 1918

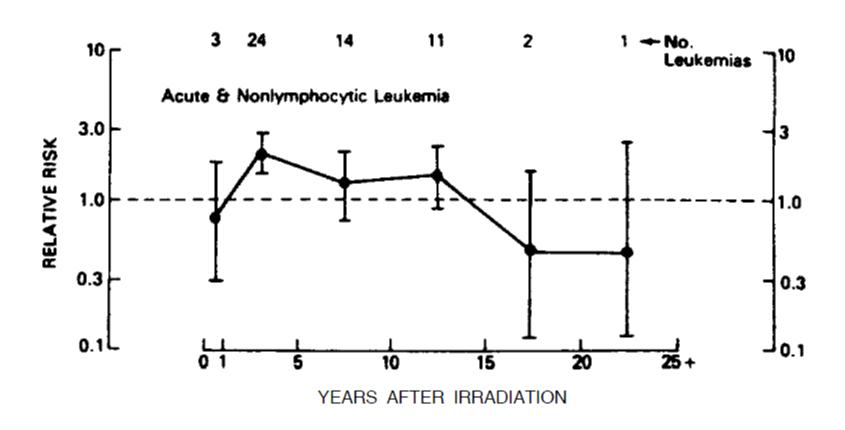


#### Bone Marrow Dosimetry Downturn at High Doses





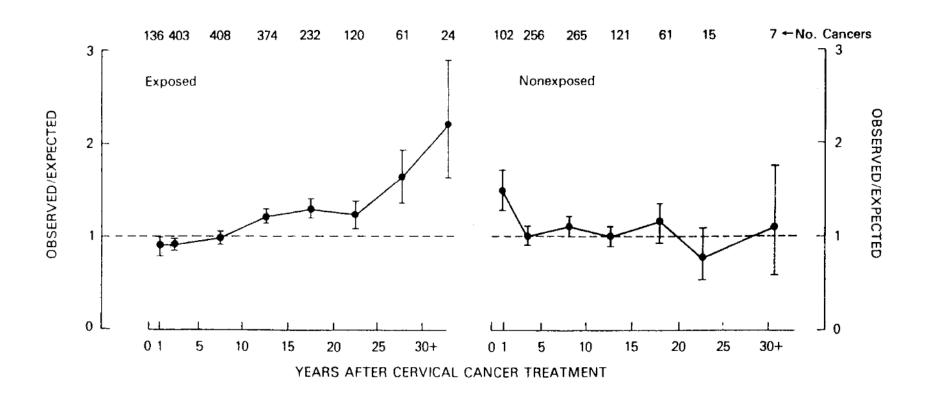
## Characteristic Wave-like Pattern for Radiation-Induced Leukemia



Boice, JNCI, 74:955, 1985

Comparison - CLL

#### Solid Cancers After Radiotherapy Long Minimum Latency





#### Oxford Prenatal X-ray Survey



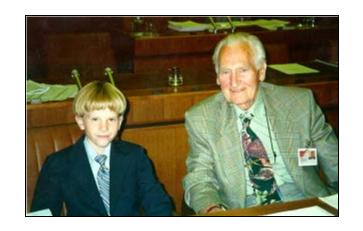
#### Is the low-dose association causal?

Childhood cancer	Cases	% X-ray	RR
Leukemia			
Lymphatic	2,007	14	1.5
Myeloid	866	14	1.5
Lymphoma	719	13	1.4
All leukemia/lymphoma	4,771	14	1.47
Wilms	590	15	1.6
CNS, Brain	1,332	13	1.4
Neuroblastoma	720	14	1.5
Bone	244	11	1.1
Other solid	856	15	1.6
All solid	3,742	14	1.47

Bithell, Stewart, Br J Cancer 31:271, 1975

Biologically plausible to have same RR?

## WM Court Brown, R Doll, A Bradford Hill – 1960 No Cohort Study is Positive



"Altogether information was obtained about **39,166 liveborn children whose mothers were known to have been subjected to abdominal or pelvic irradiation during their pregnancy.** Among their children, nine were discovered to have died of leukaemia before the end of 1958. The expected number was estimated to be 10.5...

It is concluded that an increase of leukaemia among children due to radiographic examination of their mother's abdomen during the relevant pregnancy is not established."

BMJ November 26, 1960



#### ICRP Publication 90 (2003) Biological Effects after Prenatal Irradiation (Embryo and Fetus)

"Although the arguments fall short of being definitive because of the combination of biological and statistical uncertainties involved, they raise a serious question of whether the great consistency in elevated RRs, including embryonal tumours and lymphomas, may be due to biases in the OSCC study rather than a causal association."

Christian Streffer, Chairman

NCRP REPORT No. 174

## PRECONCEPTION AND PRENATAL RADIATION EXPOSURE: HEALTH EFFECTS AND PROTECTIVE GUIDANCE





#### Arguments favoring causality (p 146-8):

- consistency of estimated risks for all forms of childhood leukemia
- decline in risks in more recent birth cohorts (reduced dose and reduced exposure)
- comparable childhood leukemia risks in the case-control twin studies

#### **Arguments opposing causality:**

- lack of confirmation in cohort studies, although statistical power is limited;
- decreased risk of childhood leukemia and other cancers in twin cohorts, which may reflect an intrinsic biologic difference between twins and singletons; and
- similarity of the RR estimates for almost all types of childhood cancers in the Oxford Survey.

#### Questions and Answers

U.S. Department of Health and Human Services
National Institutes of Health | National Cancer Institute
www.dceg.cancer.gov/RadEpiCourse

1-800-4-CANCER

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