52nd Annual Meeting
July 18-22, 2010
Pennsylvania Convention Center
Philadelphia, Pennsylvania

Brian D. Kavanagh, MD, MPH
Department of Radiation Oncology
University of Colorado School of Medicine

PRACTICAL MEDICAL PHYSICS TU-D-202-3

Establishing an SBRT Program

Part III: Clinical and Radiobiological Considerations

3 of the AAPM SBRT sessions

- HOW do we and some others do SBRT?
  - Tuesday 730 am, “Physics and Dosimetry of SBRT”, moderator M Miften, Educational Session
- WHY did we reach this place?
  - Tuesday 130 pm, “Establishing an SBRT Program”, moderator S Benedict, Practical Medical Physics
- WHAT have we accomplished so far?
  - Wednesday 130 pm, “Stereotactic Body Radiotherapy (SBRT): Technical and Clinical Considerations”, moderator I Chetty, Therapy Symposium

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Revised title

100 years of Radiotherapy: Why did we arrive at SBRT?

100 years of Radiotherapy: *So much Magical Realism*

First edition of One Hundred Years of Solitude: Editorial Sudamericana, Buenos Aires, 1967

- Fantastical events mixed with everyday life
  - Has anyone ever seen a megavoltage x-ray?
- Non-linear time
  - You'll see: we return to past ideas again and again…
- Sense of mystery
  - Tumors come and go…How? Why?

Timeline of Radiotherapy Philosophical Debate about how many treatments should be given

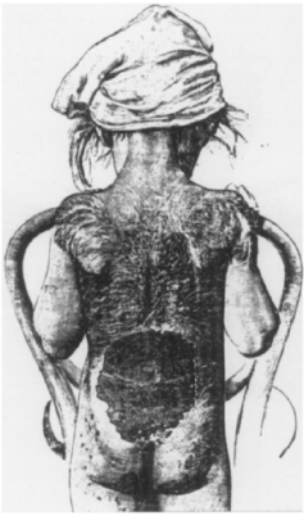
Give many treatments!

Arguments to go slowly will be up here

Use only a few treatments!

Arguments to go quickly will be down here

Leopold Freund (1868-1943): *first radiotherapy scientist*



Wiener
Medizinische Wochenschrift.

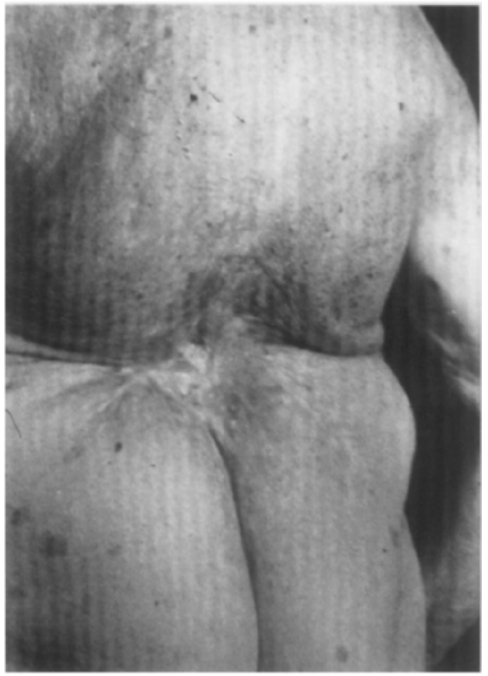
Aus der dermatologischen Abtheilung des Herrn Doz. Dr. Ed. Schiff am I. öffentl. Kinderkrankeninstitute in Wien.

Ein mit Röntgen-Strahlen behandelter Fall von Naevus pigmentosus piliferus.*)

Von Dr. LEOPOLD FREUND.

Meine im Folgenden mitgetheilten Versuche wurden im Juni 1896 durch eine Zeitungsnotiz angeregt, deren Pro-

70 years later

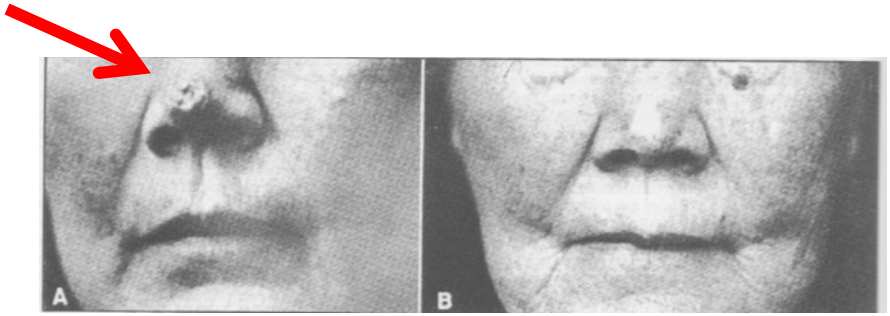


1896, pre- and post-RT

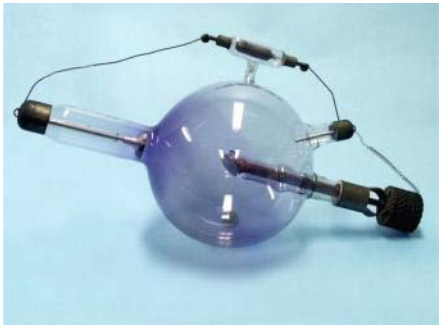
10 treatments to upper, 21 to lower

Kogelnick HD. Radiother Oncol 42: 203, 1997

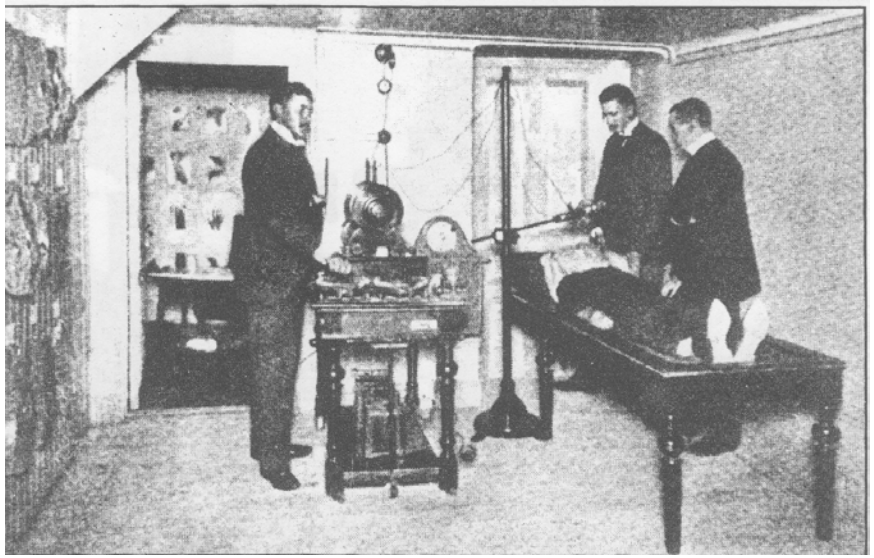
First successful treatment of cancer with radiotherapy, 1899



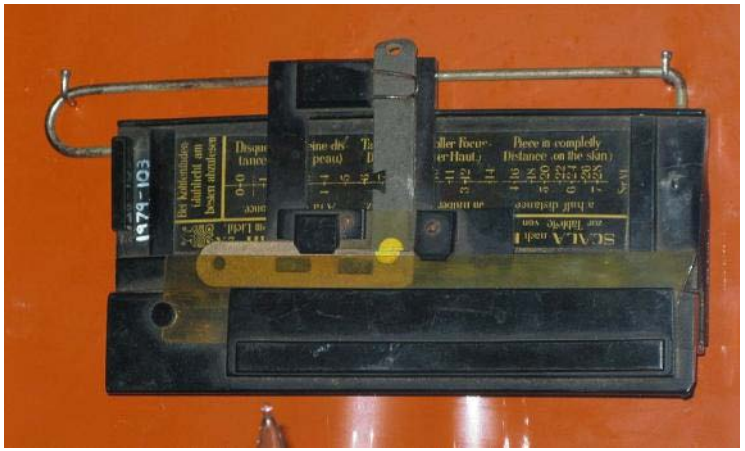
Before and 30 years later



Tor Stenbeck (left)
Roentgen Institute, Stockholm
Gas tube device
For pt above, 99 treatments given



Austrian proponents of “expeditive”radiotherapy: Holznecht, Kienock



chromoradiometer

ARCHIVES

— OF —

THE ROENTGEN RAY

AND ALLIED PHENOMENA

(*Formerly* ARCHIVES OF SKIAGRAPHY).

VOLUME XII.

JUNE, 1907, TO *MAY*, 1908.

London:

REBMAN LIMITED,

129 SHAFTESBURY AVENUE

1908

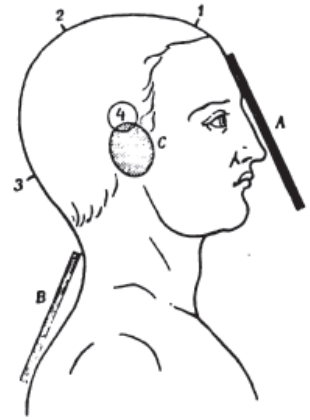


Fig. 2.

1, 2, 3, 4, Position of the normal ray in the various positions of the focus-tube; *A*, *B*, *C*, position of the leaden shield for irradiations 1, 3, and 4.

ON THE RADIO-THERAPEUTIC TREATMENT OF DISEASES OF THE HAIR.

*By Professor Dr. ROBERT KIENBÖCK, Vienna.**

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 4.

FIG. 5.

FIG. 6.

TO ILLUSTRATE PROFESSOR DR. KIENBÖCK'S ARTICLE ON PAGE 12.

PLATE CCLXVII.

("*Archives of the Roentgen Ray and Allied Phenomena.*"—Copyright.)

Interpretation of Some Results of Radiotherapy and an Attempt at Determining a Logical Technique of Treatment[1]

De Quelques Resultats de la Radiotherapie et Essai de Fixation d'une Technique Rationnelle

J. BERGONIÉ AND L. TRIBONDEAU

Comptes-Rendus des Séances de l'Académie des Sciences 143, 983-985, 1906.
Translated by Gilbert Fletcher. Radiat Res. 1959

- The "Law of Bergonie and Tribondeau":
  - "X-rays are more effective on cells which have a greater reproductive activity; the effectiveness is greater on those cells which have a longer dividing future ahead, on those cells the morphology and the function of which are least fixed. From this law it is easy to understand that roentgen radiation destroys tumors without destroying healthy tissues."

The other thing Bergonie and Tribondeau said:

From the standpoint of the practice of radiotherapy, one must learn from these facts that one must avoid the production of atypical mitoses by radiotherapeutic treatments. It seems pretty clear that the practice of delivering small and repeated doses, in contradistinction to the technique of few and heavy doses, is more apt to produce these nondestructive irritations with resulting monster cells. **Therefore, one should prefer the method of massive doses.**

The ideal technique…would be to make this complex tissue absorb in one sitting the maximal dose of radiation compatible with the preservation of the other elements one wishes to preserve.

Timeline of Radiotherapy Philosophical Debate about how many treatments should be given

Go slow to monitor effect

More is better!

1900 1910 1920 1930 1940 1950 1960 1970 1980 1990 2000 2010 2020

Hurry up!

Don’t cause cancer!

Do “expeditive” RT: and measure dose!

1920's

THE SPRINGFIELD SUNDAY UNION AND REPUBLICAN, SPRINGFIELD, MASS. NOVEMBER 23, 1926

Dr. William D. Coolidge *and his NEW*

MAGIC RAY

Producing as Many ELECTRONS Every SECOND as a TON of RADIUM

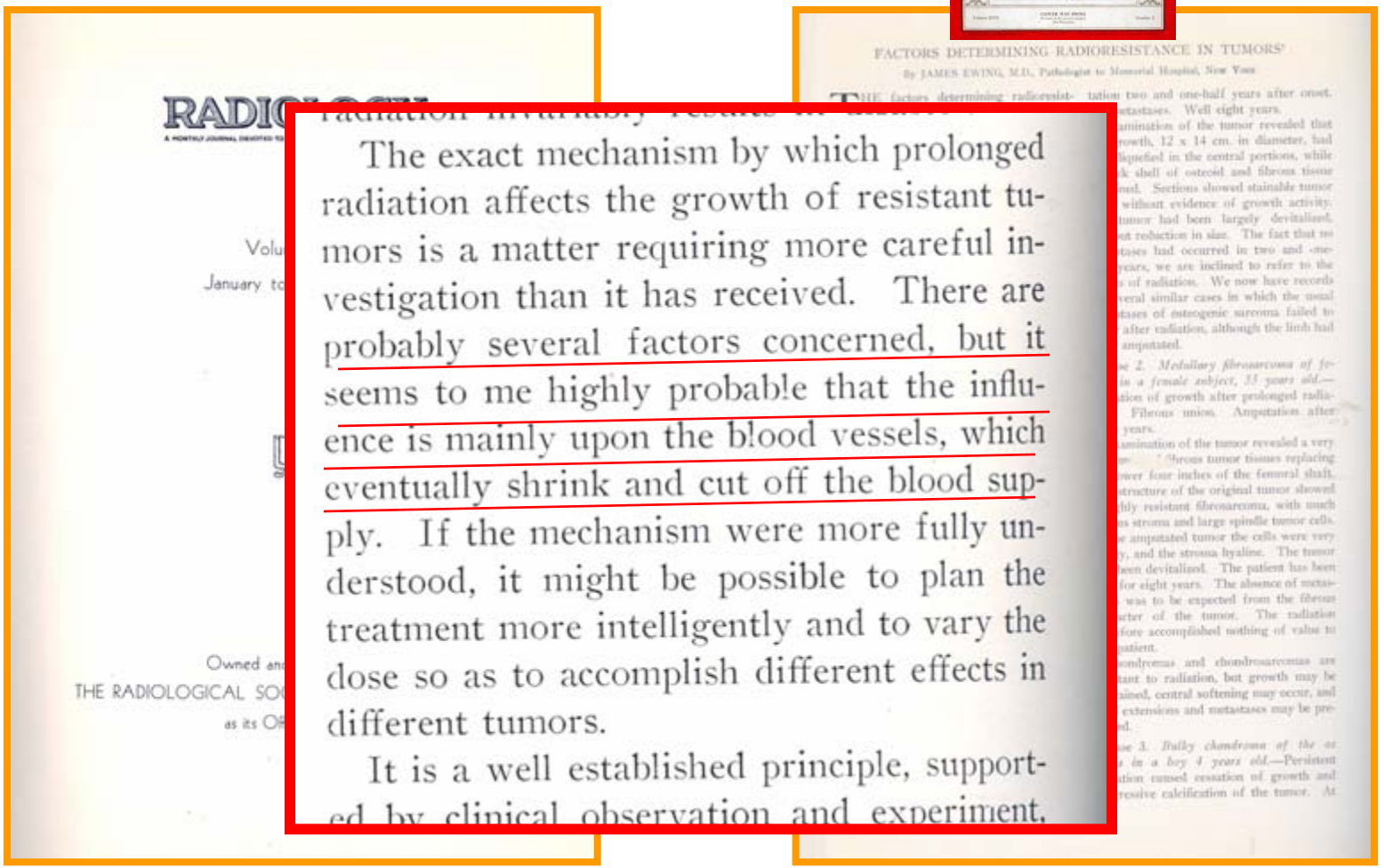
WHAT will it do for Humanity ?

By Robert Merrill

Dr. Coolidge, assistant director of the Research Laboratories of the General Electric Company, Schenectady, recently startled scientists by his cathode tube

In the picture is shown the new type of vacuum tube, perfected by Dr. Coolidge, which projects the magic cathode ray, the modern alchemist that changes solids into liquids and liquids into solids. [illegible] capabilities in the animal world have not been definitely determined, but it is known to produce marvelous changes in living tissues

Notable science, ca. 1930: James Ewing



The exact mechanism by which prolonged radiation affects the growth of resistant tumors is a matter requiring more careful investigation than it has received. There are probably several factors concerned, but it seems to me highly probable that the influence is mainly upon the blood vessels, which eventually shrink and cut off the blood supply. If the mechanism were more fully understood, it might be possible to plan the treatment more intelligently and to vary the dose so as to accomplish different effects in different tumors.

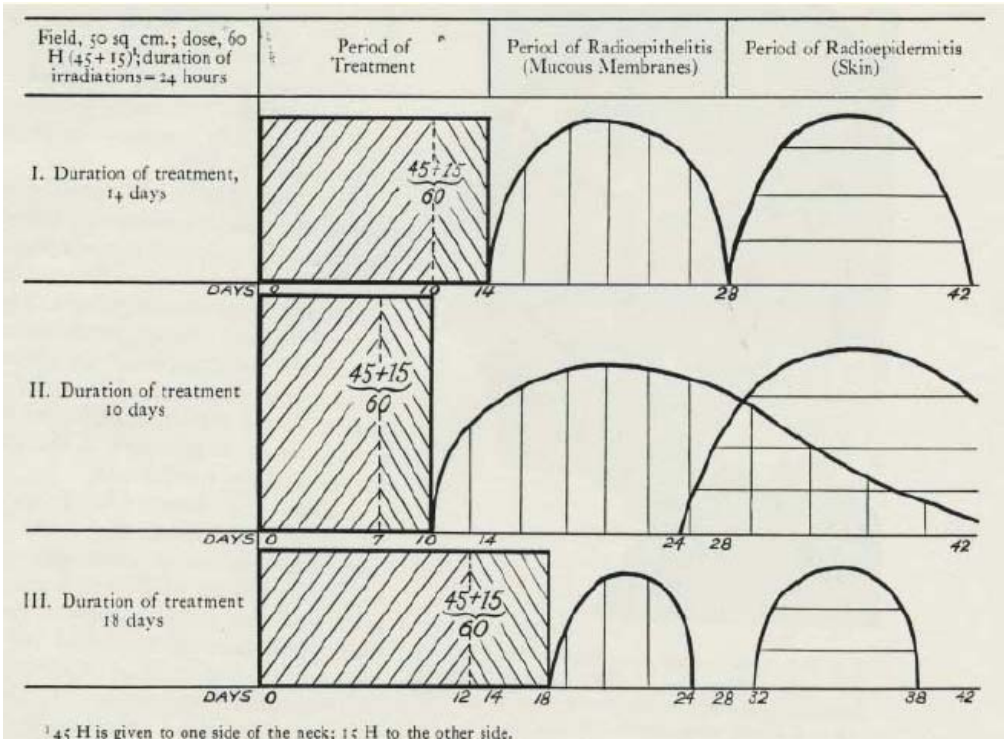
It is a well established principle, support-

Ewing J. Factors determing radioresistance in tumors. Radiology 14: 186-191, 1930

1930s:
The normal tissue argument for multiple fractions

Claudius Regaud
1870-1940

Henri Coutard
1876-1950



Short duration treatment
More acute toxicity

Long duration treatment
Less acute toxicity

Coutard, H. Roentgen Therapy of epitheliomas of the tonsillar region, hypopharynx, and larynx from 1920 to1926. *Am. J. Radiol.* ***3, 313–331 (1932).***

The Coutard Technique in the US, 1930s

CALIFORNIA
AND
WESTERN MEDICINE

Owned and Published Monthly by the California Medical Association
Four Fifty Sutter, Room 2004, San Francisco
Accredited Representative of the California and Nevada Medical Associations

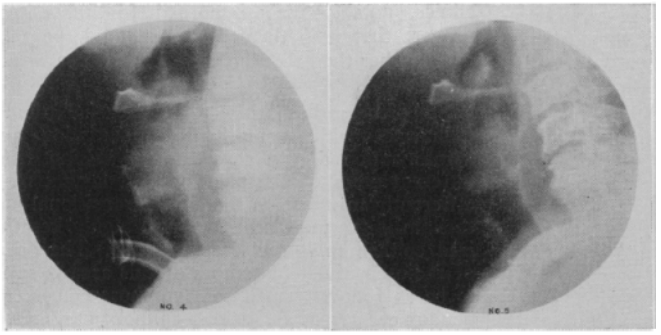
Vol. 41 NOVEMBER, 1934 No. 5

CARCINOMA OF THE LARYNX*

OBSERVATIONS ON CASES TREATED BY PROTRACTED (COUTARD) ROENTGEN THERAPY

By L. H. Garland, M. D.
San Francisco

Coutard believes it is always necessary to treat patients until a marked radio-epithelitis has developed. If the tumor has entirely disappeared by that time, and if its histological appearance suggests that it is of a very anaplastic type, treatment is discontinued. If, on the other hand, it is of a highly differentiated type, treatment may be continued; the duration of further treatment and the extent of further dosage depends upon personal judgment and experience.



Typical dose: 6000 r, 6d/wk, 200 kV
Alternate single fields, tumor+3cm
3600 to more affected side, 2400 to other

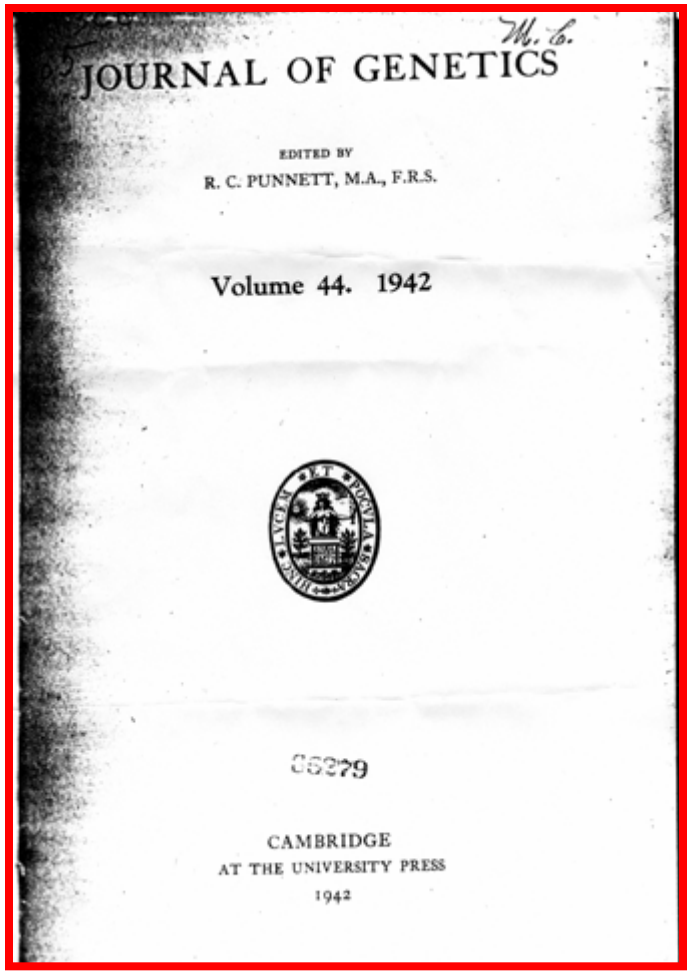
Table 3.—*Summary of Roentgen Therapy Results*

Total number of cases treated	9
Clinically well (arrested?)	4
Improved (but died of subsequent bronchopneumonia)	3
Unchanged (no extension) of lesion for some months	1
No improvement (died)	1
Total number living	5
Total number dead	4

Table 6.—*Summary of Surgical Results*

Total number of cases operated	8
Clinically well (untraced but ? arrested)	2
Improved but developed recurrence	3
No improvement (died postoperative)	3
Total number living unknown, but possibly	3
Total number dead	5

Lea DE, Catcheside DG.
J Genetics 1942; 44:216-245, cf. p227



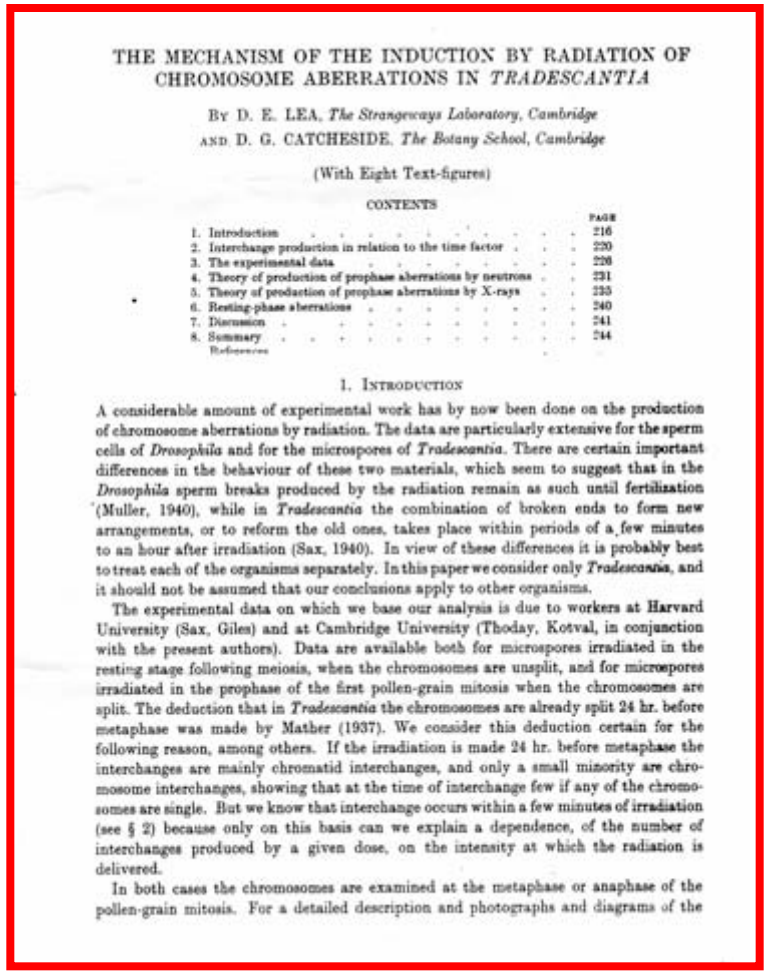
M. C.

JOURNAL OF GENETICS

EDITED BY
R. C. PUNNETT, M.A., F.R.S.

Volume 44. 1942

CAMBRIDGE
AT THE UNIVERSITY PRESS
1942



THE MECHANISM OF THE INDUCTION BY RADIATION OF CHROMOSOME ABERRATIONS IN *TRADESCANTIA*

BY D. E. LEA, *The Strangeways Laboratory, Cambridge*
AND D. G. CATCHESIDE, *The Botany School, Cambridge*

(With Eight Text-figures)

CONTENTS

1. INTRODUCTION

A considerable amount of experimental work has by now been done on the production of chromosome aberrations by radiation. The data are particularly extensive for the sperm cells of *Drosophila* and for the microspores of *Tradescantia*. There are certain important differences in the behaviour of these two materials, which seem to suggest that in the *Drosophila* sperm breaks produced by the radiation remain as such until fertilization (Muller, 1940), while in *Tradescantia* the combination of broken ends to form new arrangements, or to reform the old ones, takes place within periods of a few minutes to an hour after irradiation (Sax, 1940). In view of these differences it is probably best to treat each of the organisms separately. In this paper we consider only *Tradescantia*, and it should not be assumed that our conclusions apply to other organisms.

The experimental data on which we base our analysis is due to workers at Harvard University (Sax, Giles) and at Cambridge University (Thoday, Kotval, in conjunction with the present authors). Data are available both for microspores irradiated in the resting stage following meiosis, when the chromosomes are unsplit, and for microspores irradiated in the prophase of the first pollen-grain mitosis when the chromosomes are split. The deduction that in *Tradescantia* the chromosomes are already split 24 hr. before metaphase was made by Mather (1937). We consider this deduction certain for the following reason, among others. If the irradiation is made 24 hr. before metaphase the interchanges are mainly chromatid interchanges, and only a small minority are chromosome interchanges, showing that at the time of interchange few if any of the chromosomes are single. But we know that interchange occurs within a few minutes of irradiation (see § 2) because only on this basis can we explain a dependence, of the number of interchanges produced by a given dose, on the intensity at which the radiation is delivered.

In both cases the chromosomes are examined at the metaphase or anaphase of the pollen-grain mitosis. For a detailed description and photographs and diagrams of the

The 1942 Lea-Catcheside paper

- Concerned with the rate of chromatid interchanges as function of radiation dose
- The "D^2" comes from the expectation of kinetics similar to a bimolecular reaction
- Here, the two components are essentially the same entity, namely a broken chromatid

$$[A]+[B]\rightarrow[AB]$$

$$\frac{d[AB]}{dt}=k[A][B]$$

$$\frac{d[chromatid\_exchanges]}{dt}=k[chromatidbreaks]^2$$

$$\frac{d[chromatid\_exchanges]}{dt}=k'[dose]^2$$

The 1942 Lea-Catcheside paper, continued

- There was also a factor proposed to modify the "D^2" term with the term *G*
- The *α* term counts double strand breaks as a function of dose
- Purpose of *G* was to account for exposures that took enough time for there to be decay of the chromatid breaks produced as the radiation exposure continues

$$\alpha D + \beta D^2 G$$

$$G = (2/D^2) \int_{-\infty}^{\infty} \dot{D}(t)dt \int_{-\infty}^{t} e^{-\lambda(t-t')} \dot{D}(t')dt'$$

1940s, 1950s….and continuing on for a while: A resurrection of an old trick to give large doses—”grid” or “sieve” radiotherapy

RADIOTHERAPY OF ACCESSIBLE MALIGNANT TUMOURS BY ALTERNATING CHESS-BOARD METHOD

BENJAMIN JOLLES
M.D. Florence, D.M.R.
CONSULTANT RADIOTHERAPIST I/C RADIOTHERAPY DEPARTMENT, GENERAL HOSPITAL, NORTHAMPTON

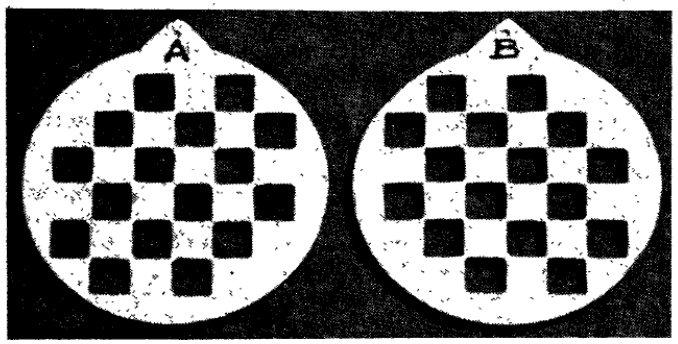


Fig. 1.—Lead chess-board panels. The order of transparent and opaque 1 cm. squares is reversed in the two panels.

The Lancet, 1949

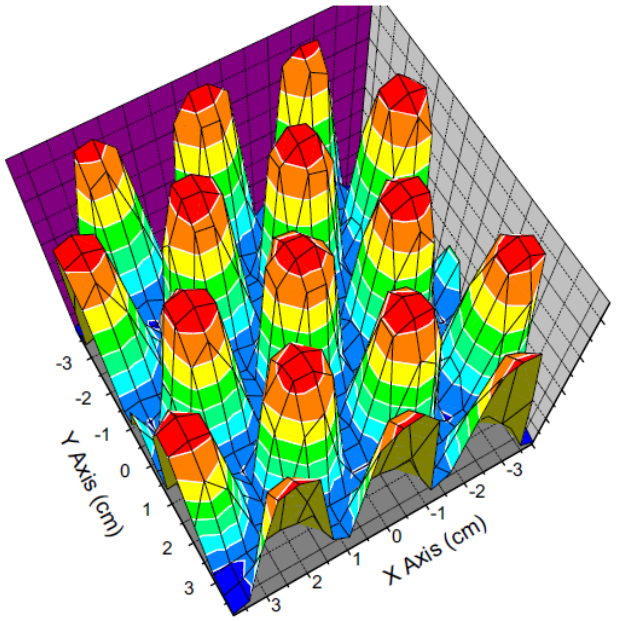
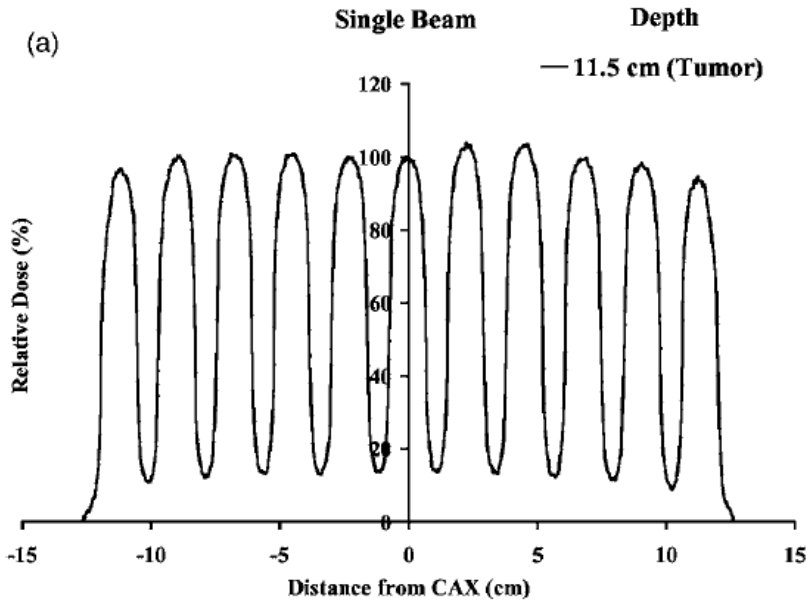


Fig. 7. Two-dimensional dose distribution at 1.5 cm depth from Monte Carlo simulation.

Zhang et al, DOSIMETRIC VALIDATION OF THE MCNPX MONTE CARLO SIMULATION FOR RADIOBIOLOGIC STUDIES OF MEGAVOLTAGE GRID RADIOTHERAPY, IJROBP 2006

Grid radiotherapy: theoretical advantages

- Some skin sparing achieved
- Mimics interstitial brachytherapy dose distribution to some extent
- Maybe even allow for normal tissue stem cell migration into high dose volumes



1990, *The British Journal of Radiology*, *63*, 871–874

Lack of late skin necrosis in man after high-dose irradiation using small field sizes: experiences of grid therapy

By *H. Shirato, MD, *N. K. Gupta, FRCR, †T. J. Jordan, PhD and ‡J. H. Hendry, PhD

*Department of Radiotherapy, †Department of Medical Physics and ‡Cancer Research Campaign Department of Radiobiology, Paterson Institute for Cancer Research, The Christie Hospital and Holt Radium Institute, Manchester M20 9BX, UK

- Patients treated with single dose of 45 Gy to surface for lung cancer
- No skin necrosis seen in long-term (2+ yr) survivors
- Proposed explanation:
  - volume effect, ie can do this with small grid holes that don't cause necrosis

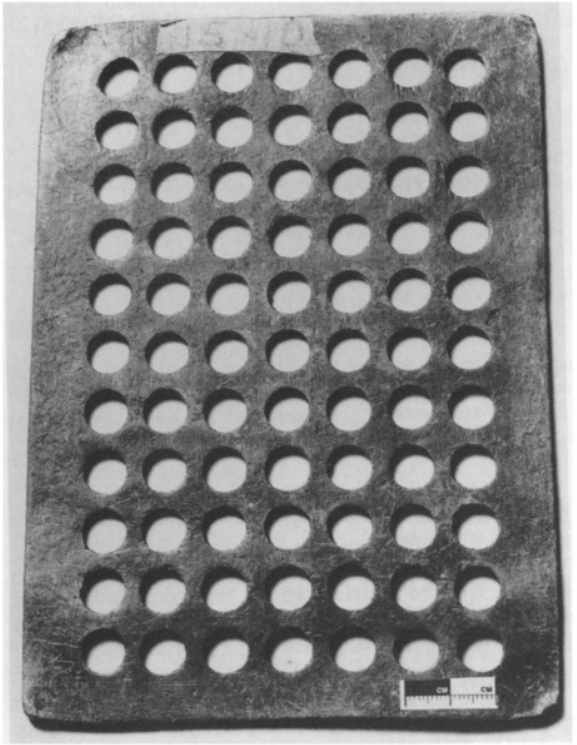
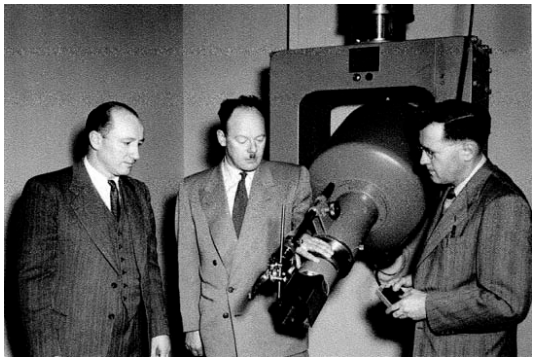
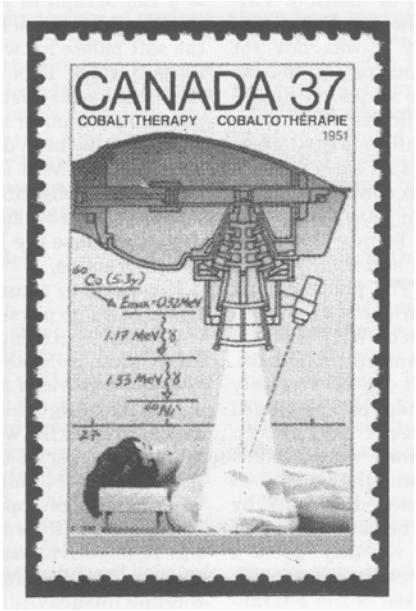


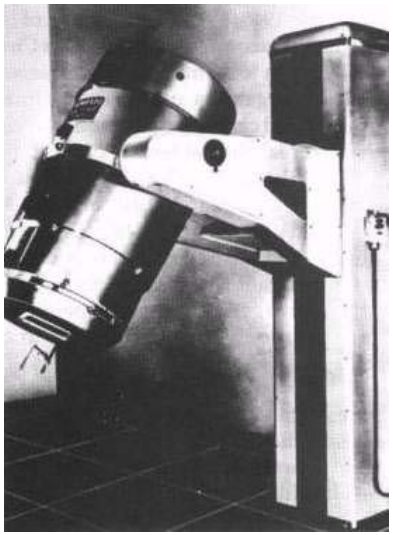
Figure 1. Lead sheet (4 mm thick) for use in grid therapy, with holes 10 mm in diameter with centres at 14 mm intervals.

The arrival of high energy beams I: Cobalt-60



Dr. T.A. (Sandy) Watson, John MacKay of ACME Machine and Electric, and Prof. Harold Johns Saskatchewan





Early cobalt-60 unit in the Victoria Hospital, London, Ontario.

Table HCT-1. First cobalt-60 treatments in the world, 1951

	Saskatchewan	W. Ontario
Cobalt-60 source delivered	July 30	October 16
Unit installed	August 17	October 23
Calibration	11 weeks	—
First patient treated	November 8	October 27

CS Houston, SO Fedoruk, http://esask.uregina.ca/entry/high-energy_cancer_treatment.html

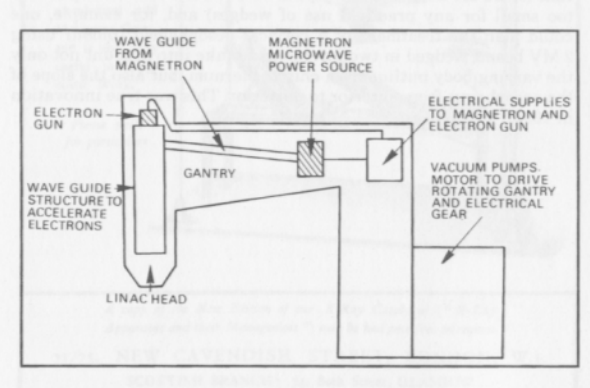
The arrival of high energy beams II: The betatron, 1950s

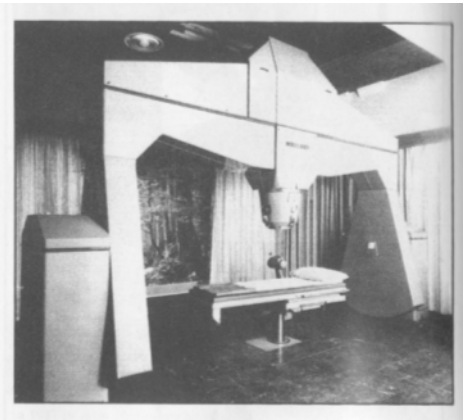
- First unit developed in 1940, U of Illinois (figure)
  - Electrons accelerated by magnetic fields and aimed at target to produce high energy x-rays
- First cancer treatment center with a betatron in Shorewood Hills, WI, ca. 1957
  - Higher energy beams mean good skin sparing for deep tumor treatment

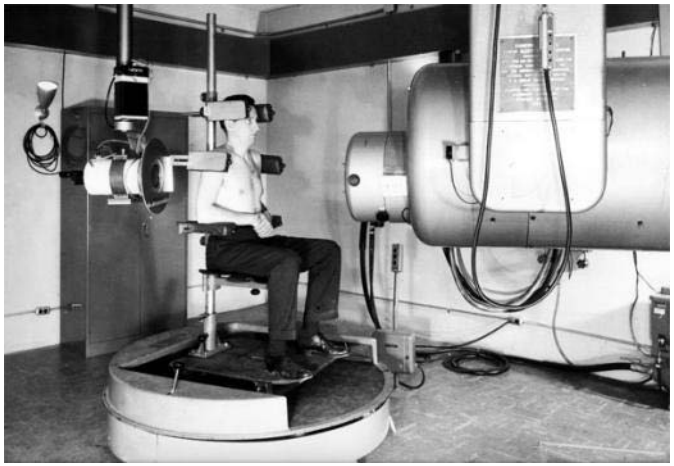
Dr Donald Kerst
Professor of Physics, U of I

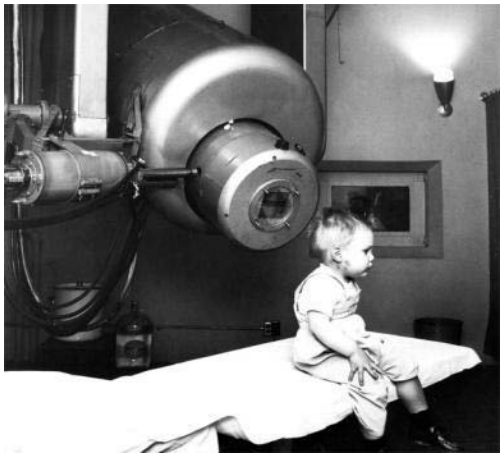
The arrival of high energy beams III: The linear accelerator, 1950s

Christie Hospital, Newcastle Hospital, Stanford

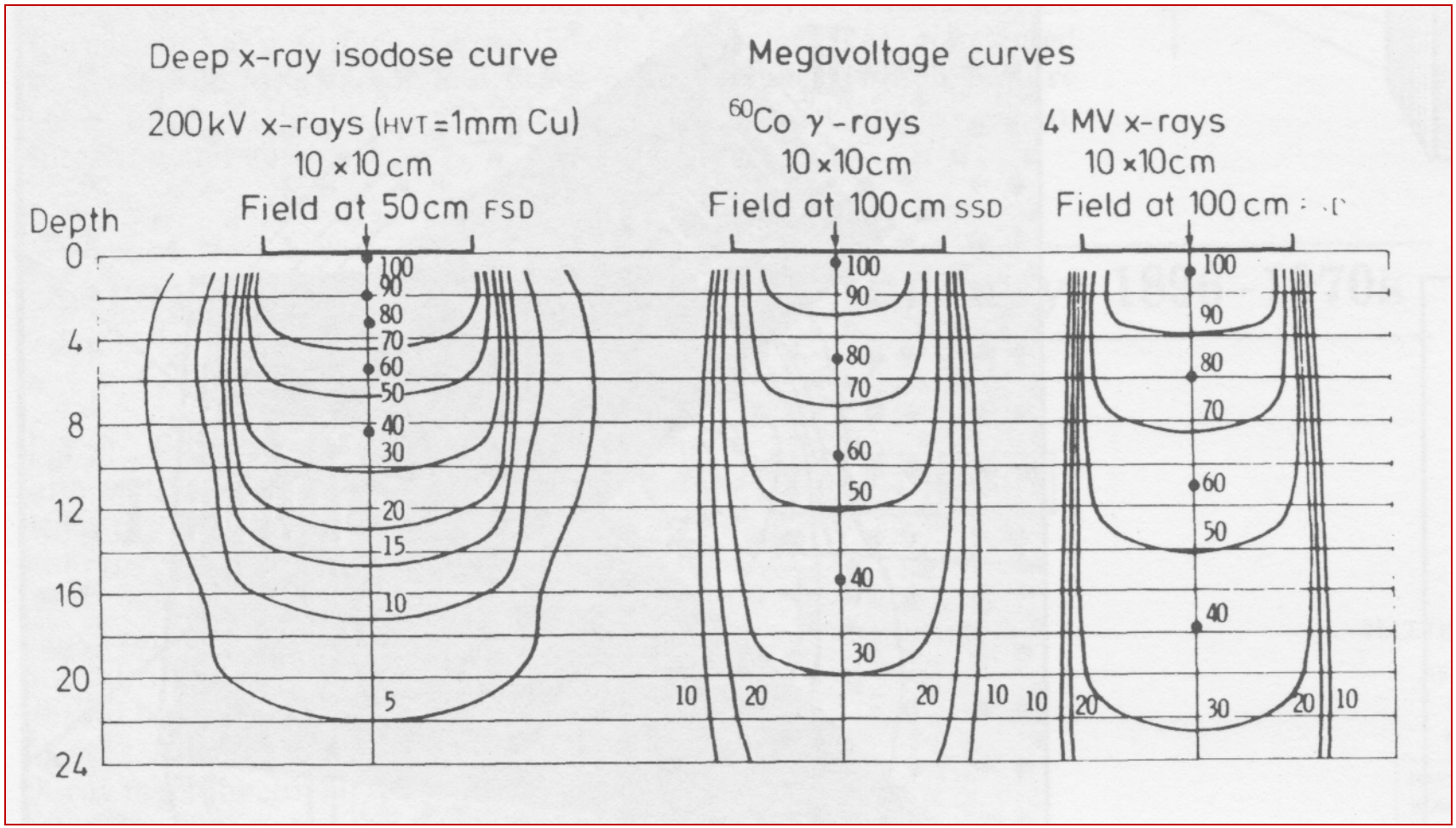








The key advantage of high energy: skin sparing



Mould RF. *Radiotherapy Treatment Planning*. Adam Hilger: Bristol, 1985

High dose palliative RT with high energy beams, late 1950s

- 22.5 MeV Betatron
  - Less skin dose the kV
- Typical once per week fractions of 5-12.5 Gy
- Generally palliative intent

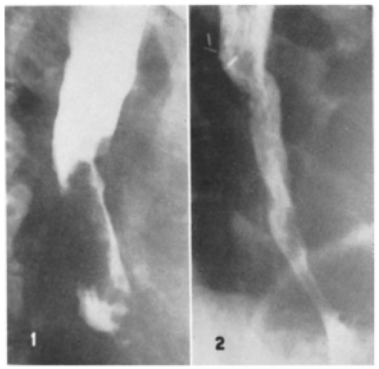


Fig. 1. Case I. Esophagram prior to therapy, showing involvement of distal esophagus by tumor.
Fig. 2. Case I. Five weeks after 2,500 r tumor dose given in eight days, divided into two fractions of 1,250 r each. Note re-establishment of esophageal lumen.

TABLE I: MASSIVE-DOSE RAPID PALLIATIVE RADIOTHERAPY

Site	Number	Subjective Improvement	Objective Improvement	Complications
Bladder	4	2	1	0
Breast	6	5	5	1
Lung	24	13	13	4
Head and neck	10	6	6	3
Esophagus and stomach	9	5	2	0
Misc.	10	6	2	1
TOTAL	63	37	29	9

HORRIGAN WD, ATKINS HL, TAPLEY ND. Radiology. 1962 Mar;78:439-44.

Columbia U series: case III, prior grid RT for thymoma, later 2 x 12.5 Gy for recurrence

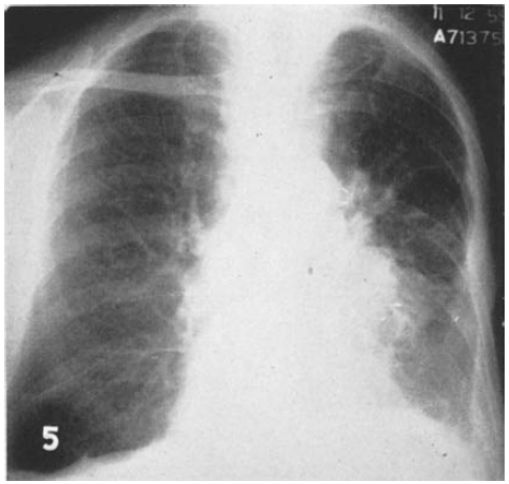


Fig. 5. Case III. Sixty-year-old white male had left forequarter amputation seventeen years before for fibrosarcoma. In 1954 a mediastinal thymoma was discovered at thoracotomy and the patient received 9,000 r air dose (250 kv radiation) through a grid. Film one month prior to therapy, showing recurrent mass in left chest.

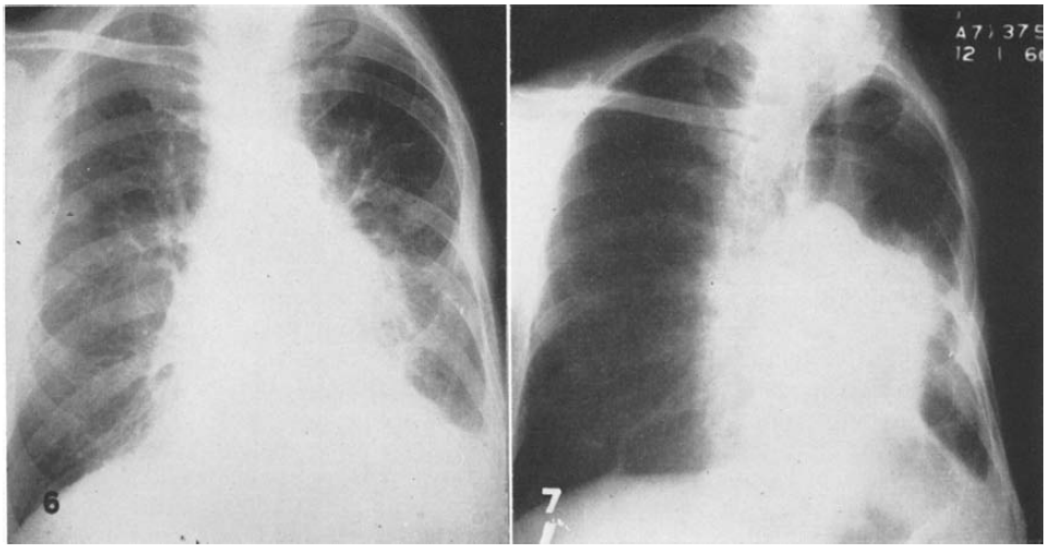


Fig. 6. Case III. Chest roentgenogram two weeks following completion of 2,500 r tumor dose in eight days (two fractions) through opposing 12 × 15-cm. portals. Reduction in size of mass.

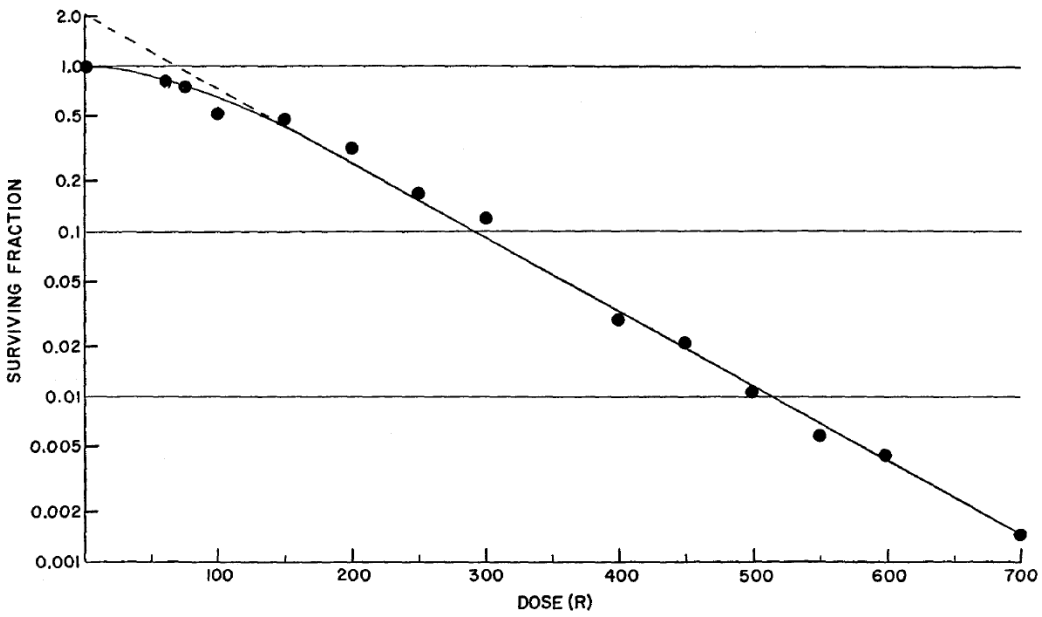
Fig. 7. Case III. Roentgenogram of chest one year following completion of therapy, showing marked fibrosis in field of irradiation. Patient was symptomatic at this time.

Pre-RT

2 weeks post-RT

1 year post-RT

Notable science, 1950s: Puck and Marcus, JEM 1956



TEXT-FIG. 2. Survival of reproductive capacity in HeLa cells as a function of x-ray dose. The points fit the equation $S = [1 - (1 - e^{-D/96})^2]$ within the limits of uncertainty of the experimental procedure.

ACTION OF X-RAYS ON MAMMALIAN CELLS*, ‡

BY THEODORE T. PUCK, PH.D., AND PHILIP I. MARCUS

(From the Department of Biophysics, Florence R. Sabin Laboratories, University of Colorado Medical Center, Denver)

(Received for publication, February 3, 1956)

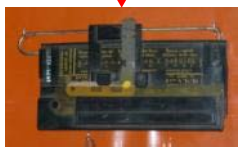
Timeline of Radiotherapy Philosophical Debate about how many treatments should be given

Slow and steady wins the race!

The race goes to the swift!

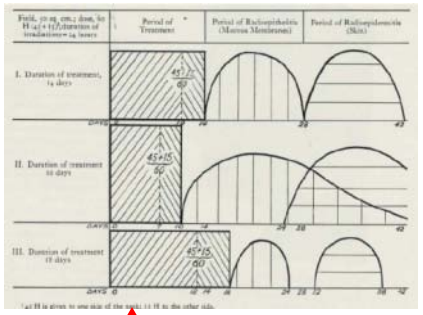
Go slow to monitor effect

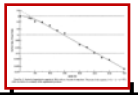
Don't cause cancer!



Do "expeditive" RT: and measure dose!

Be careful with normal tissues

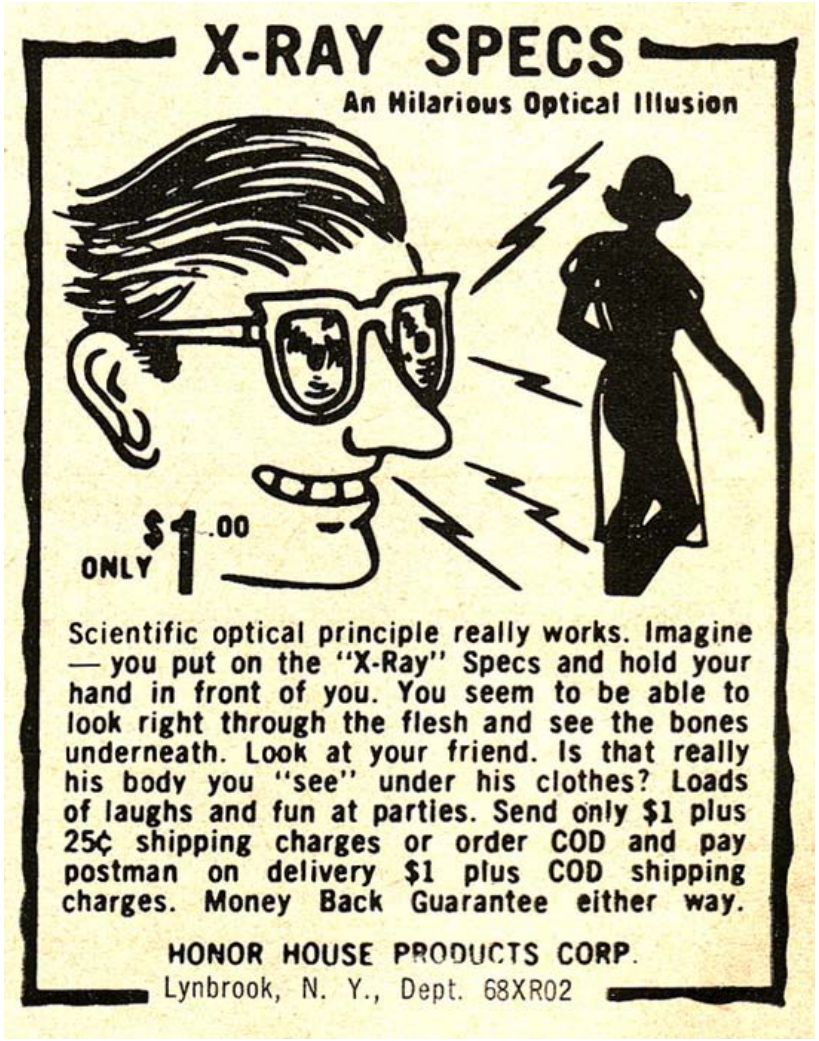




New technology can help us here!

1900 1910 1920 1930 1940 1950 1960 1970 1980 1990 2000 2010 2020

1960s image guidance technology



1970s: Dawn of the applied modeling era, featuring the LQ formulation

- Douglas & Fowler study was intended to determine means of adjusting RT schedules for same normal tissue effect
- 9000 mice irradiations!!!!

RADIATION RESEARCH 66, 401–426 (1976)

The Effect of Multiple Small Doses of X Rays on Skin Reactions in the Mouse and a Basic Interpretation

B. G. DOUGLAS[1] AND J. F. FOWLER

Gray Laboratory of the Cancer Research Campaign, Mount Vernon Hospital, Northwood, Middlesex, HA6 2RN, England

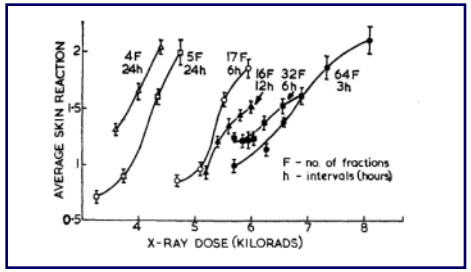
TABLE I

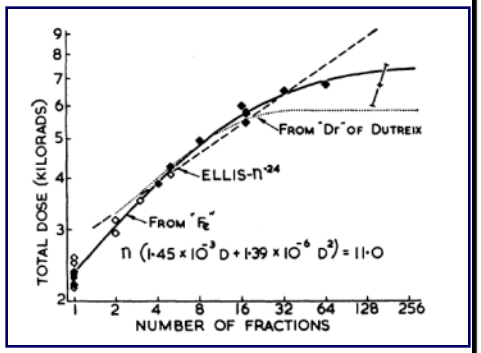
Mouse Foot Skin Reactions[a]

0.0	Normal
0.125	
0.25	Fifty–fifty doubtful if different from normal
0.375	
0.5	Slight hair loss and/or very slight reddening
0.625	
0.75	Definite but slight reddening ± hair loss
0.875	
1.0	Severe reddening, often with distended blood vessels or slight swelling
1.125	
1.25	Severe reddening with white scales and/or severe swelling; red "papery" skin when healing
1.375	
1.5	Moist breakdown of one small area (usually on bottom of foot first) with scaly appearance
1.625	
1.75	Moist desquamation in more than one small area or one slightly larger area (tips of toes stuck together with no other breakdown when healing)
1.875	
2.0	Breakdown of larger area and/or toes stuck together; possibly moist in places
2.125	
2.25	Breakdown of one-third skin area on foot
2.375	
2.5	Breakdown of one-half area of foot (usually first on bottom)
2.625	
2.75	Breakdown of about two-thirds area of foot
2.875	
3.0	Breakdown of most of the skin of foot, possibly with slight moist exudate
3.125	
3.25	Breakdown of entire skin of foot with slight moist exudate
3.375	
3.5	Breakdown of entire skin of foot with severe moist exudate; may be stuck to body fur

[a] It is the *area of skin* involved that is being scored rather than the severity of breakdown in that area. There is a temptation to give a higher score during the healing phase if, for example, half the skin is broken down but there is a nasty scab on it. This should be scored as 2.5 and not as a 3.0 on the basis of the moist exudate.

Douglas & Fowler, continued





APPENDIX C

The quadratic form obtained here for the cell survival curve is consistent with the postulate that cell death results from lethal interaction of two primary lesions placed close together in the cell. From Neary (*20*), the probability that primary lesions will occur in each of two cylindrical targets in one site in a cell is

$$1 - \exp(-mgk^2)[1 - \{1 - \exp(-mk + mgk^2)\}^2].$$

Here k is the probability that one track through the target will produce a primary lesion, g is the probability that a track that traverses one target will pass through the second target in the same site, and m is the mean number of tracks through the mean projected area of a target in the site.

Multiplying by the mean number of sites per cell N yields the mean number of sites per cell that contain lesions in both targets,

$$\lambda = N\{1 - \exp(-mgk^2)[1 - \{1 - \exp(-mk + mgk^2)\}^2]\}.$$

The possibility of cell death from radiation in the range of doses considered is assumed to be present only in cells with sites containing lesions in both targets. It is assumed that correct repair may be prevented by the interaction of the two lesions.

If the probability that both lesions will not be repaired correctly is p, then the probability of survival of a cell with Θ sites containing lesions in both targets is $(1 - p)^\Theta$. It is assumed that the distribution with respect to Θ is Poisson in form.

Summing over the Poisson distribution yields the surviving fraction s:

$$s = \sum_{\Theta=0}^{\infty} \frac{\lambda^\Theta e^{-\lambda}}{\Theta!}(1 - p)^\Theta = e^{-p\lambda}.$$

Substituting for λ,

$$s = \exp(-pN\{1 - \exp(-mgk^2)[1 - \{1 - \exp(-mk + mgk^2)\}^2]\}). \quad (24)$$

If $mk \ll 1$, the above can be approximated by taking the lowest terms in the expansion of the exponentials and

$$s = \exp(-pN\{mgk^2 + m^2k^2[(1 - gk)^2 - g^2k^2/2]\}).$$

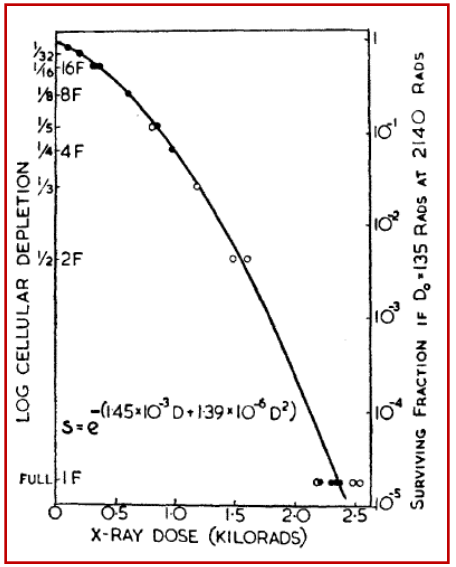
As m is proportional to D, where D is the dose in rads and p, N, g, and k are constants for a given quality of radiation, this can be written as

$$s = \exp[-(\alpha D + \beta D^2)],$$

where α and β are constants. The full equation (24) has the form

$$s = \exp(-\lambda_3[1 - e^{-\lambda_1 D}\{1 - (1 - e^{-(\lambda_2 - \lambda_1)D})^2\}]) \qquad [\text{Eq. (14)}],$$

where λ_2 and λ_1 are proportional to the inactivation constants for one and both members, respectively, of each pair of targets by a single photon, and λ_3 is pN above.



Same end result formula as Lea & Catcheside

Different derivation

Building on the LQ formalism

$$s = \exp[-(\alpha D + \beta D^2)]$$

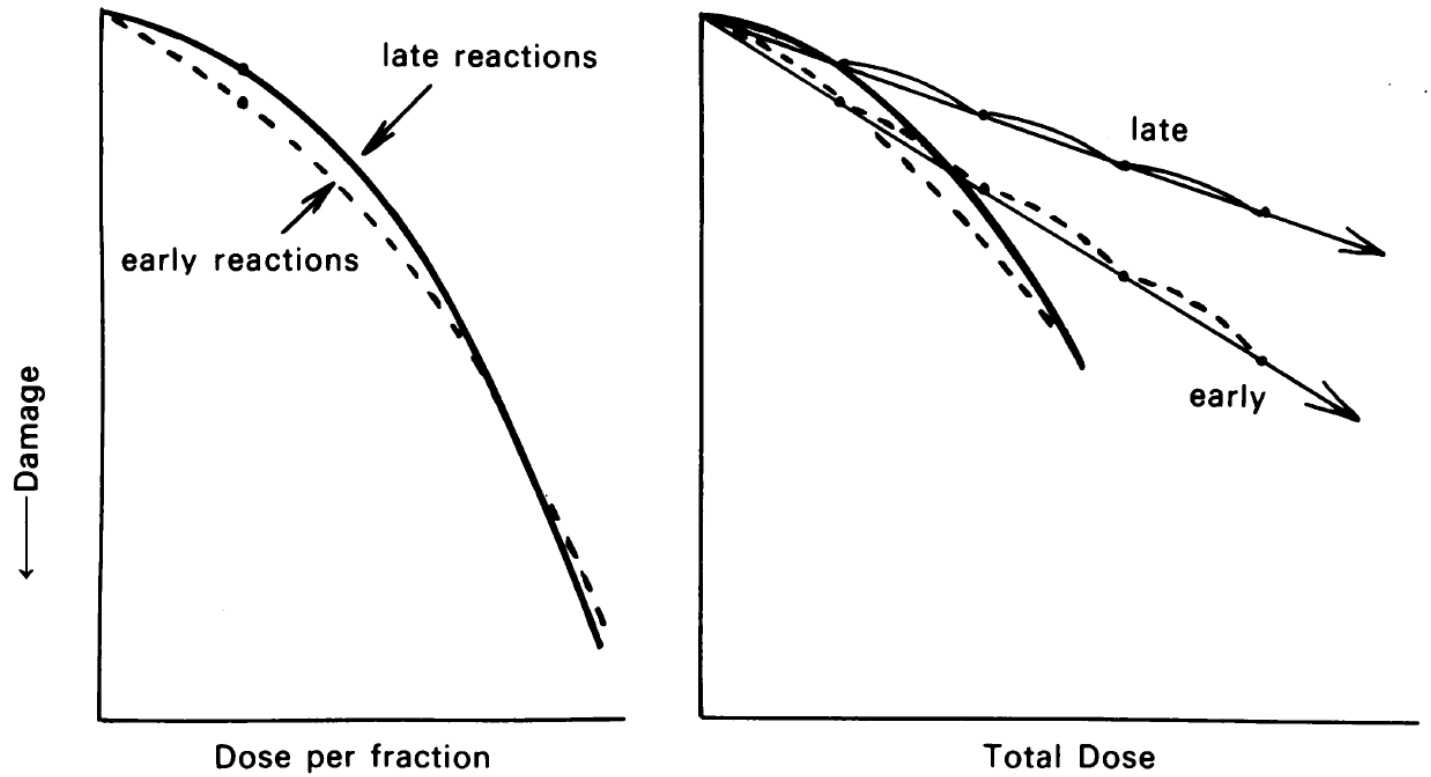
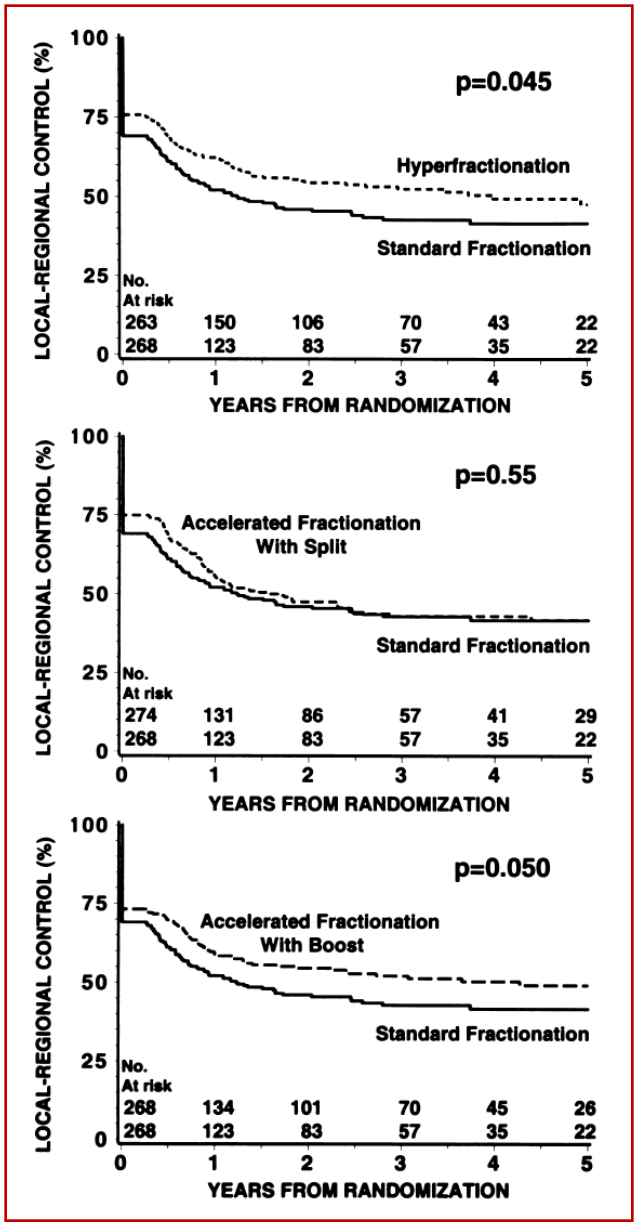


Figure 6 The difference in shape between the dose-response curves for early or late reactions, matched at 200 cGy per fraction. Smaller doses per fraction would require a larger increase of total dose for late than for early reactions.

Fowler, Br J Cancer 1984

RTOG 90-03

- Standard 2 Gy/d to 70 Gy versus 2 alternatives:
  - Hyperfractionated RT (1.2 Gy bid) to 81.6 Gy
  - Accelerated RT via concomitant boost (1.8/1.5) or 1.6 BID with split



Fu et al, 2000

Hypofractionation: lessons from complications

Gilbert H. Fletcher

Department of Clinical Radiotherapy, The University of Texas, M.D. Anderson Cancer Center, Houston, TX, U.S.A.

Late complications in patients with Stage III cancer of the cervix free of disease in the pelvis (from Singh [25]).

	Group I	Group II
	40 Gy whole pelvis in 20 daily fractions (TDF:66), then intracavitary gamma-ray, then 10 Gy to pelvic walls in 5 daily fractions (minimum follow-up 24 months)	5 weekly doses of 5.8 Gy (TDF:66), then same intracavitary gamma-ray, then 1 fraction of 5.8 or 6.7 Gy depending on thickness of the patient (minimum follow-up 12 months)
No. of patients	19	20
No complications	11	0
Proctitis lasting over 6 months	8	8
Severe bowel complications	0	10 (3 dead)
Rectovaginal fistula	0	2
Edema of vulva, months, etc.	0	2

TABLE I

Failures and severe complications in patients treated with protracted irradiation alone with ^{60}Co (from Montague [21]).

Breast: 60 Gy/8 wk + 20–40 Gy boost over tumor*
Axilla: 50 Gy/5 wk + 10–20 Gy boost over palpable tumor through small appositional portal*
5 days per week: 88 patients
3 days per week: 57 patients

% of severe complications	5 fractions/wk	3 fractions/wk
Severe axillary fibrosis and frozen shoulder	2	11.5
Chest wall necrosis and fibrosis; multiple rib fractures	3	13

* The tangential portals for the breast were treated on alternate days. The AP and PA portals covering the shoulder and axilla were treated every day.

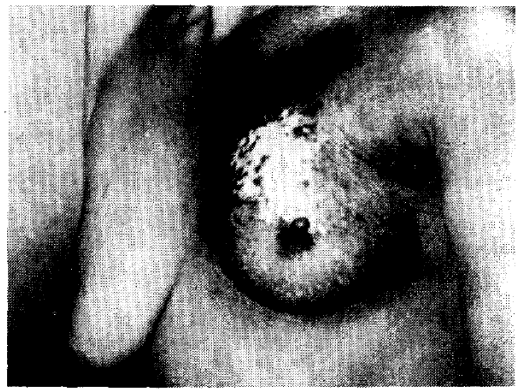


Fig. 1. Breast cancer patient 2 years after radiotherapy (5 × 670 rad once a week) "The breast was supple with no evidence of fibrosis 2 years after radiotherapy" (from Dvivedi and Pradhan [11]).

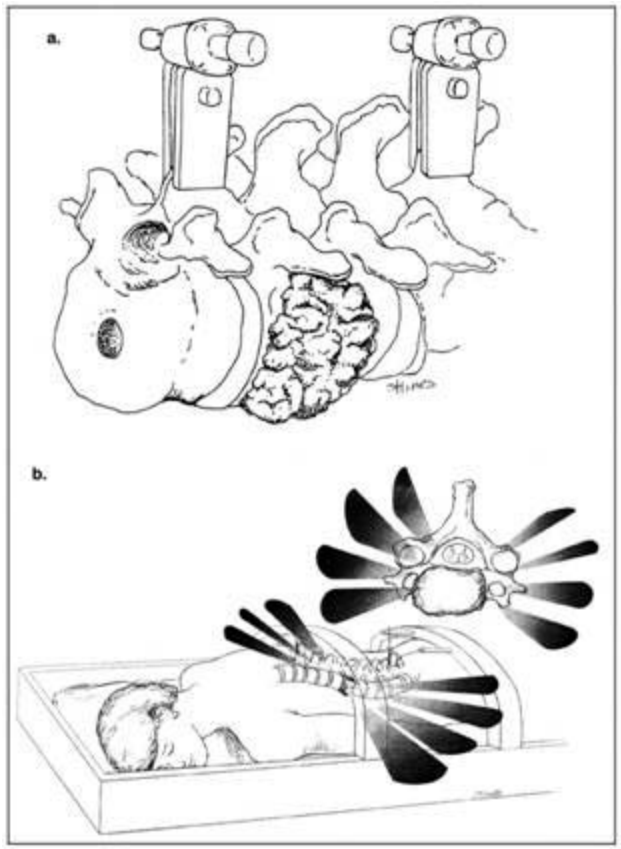
Radiotherapy and Oncology, 20 (1991) 10–15

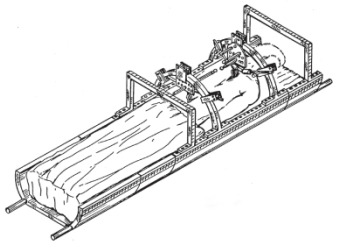
…brevity is the soul of wit…

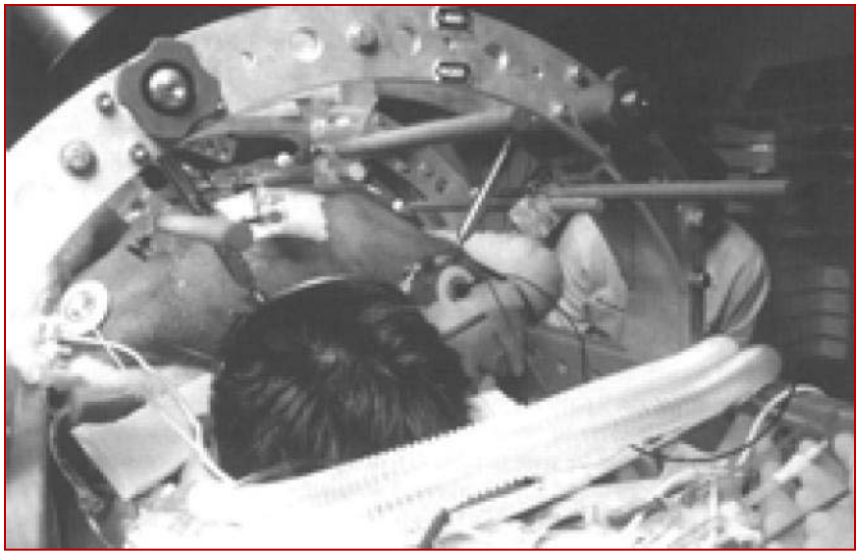
Polonius, in *Hamlet*, Act 2, Scene 2
W. Shakespeare

- Early interest in hypofractionated treatment regimens as long ago as the 1960s
  - Largely driven by resource limitation, not tumor biology
- Sir Laurence Olivier
  - *Actor*
  - *prostate cancer survivor*
- Treated in 1967 on an experimental protocol involving 6 fractions of 6 Gy
  - 22 yrs NED after that

Earliest “high dose” extracranial stereotactic treatment: Hamilton et al, Neurosurgery,1995







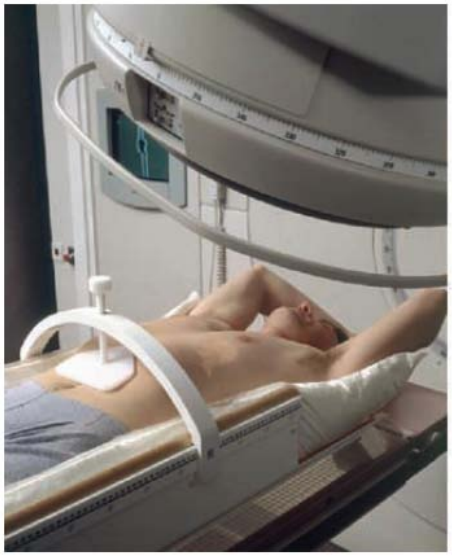
Rigid clamps connected to vertebral bodies, a la rigid head frame
5 patients treated, modest dose by today’s standards

STEREOTACTIC HIGH DOSE FRACTION RADIATION THERAPY OF EXTRACRANIAL TUMORS USING AN ACCELERATOR

Clinical experience of the first thirty-one patients

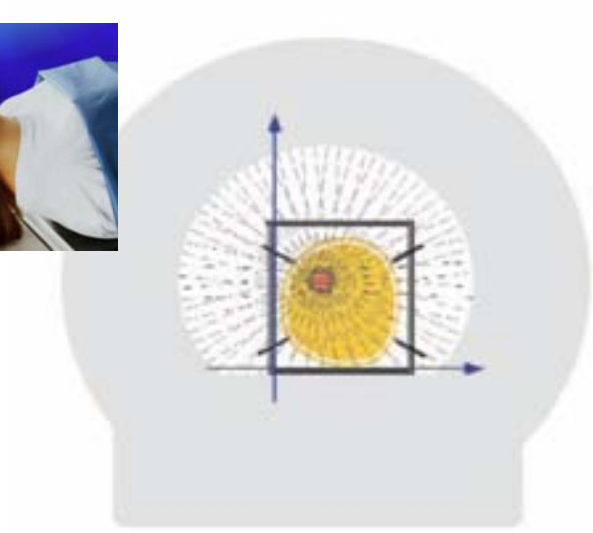
HENRIC BLOMGREN, INGMAR LAX, INGEMAR NÄSLUND and RUT SVANSTRÖM

Blomgren et al, Acta Oncol 1995

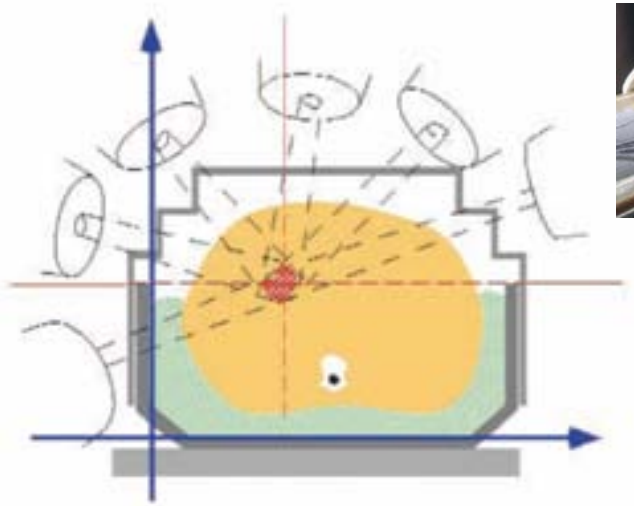


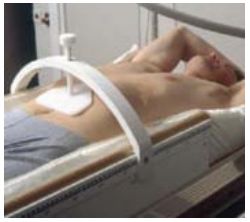
SBRT: operational definition

- *Stereotactically* localized, ultra-high-dose radiotherapy
  - Given to discrete tumor nodules in *extracranial* locations
  - Within a *hypofractionated* regimen (1-5 treatments)
    - Unlike typical 6-7 week course of radiotherapy
  - Analagous to cranial stereotactic radiosurgery (SRS)



Head frame-based cranial SRS





Body frame-based cranial SRS

Early SBRT experience Karolinska Institute

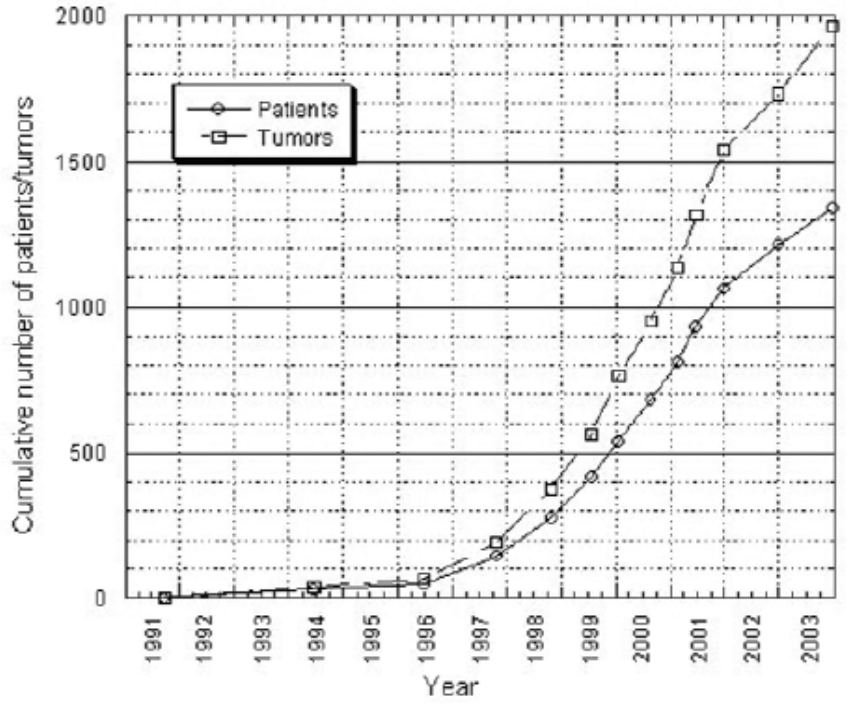


FIGURE 7. Diagram shows the cumulative number of patients and tumors treated during the years 1991 to 2003.

TABLE 2 Anatomic Distribution of 1965 Tumors That Have Been Treated with Stereotactic Body Radiation Therapy at the Karolinska Hospital from 1991 to 2003.

Organ	*No. Tumors*
Lungs	997
Mediastinum	78
Liver	484
Pancreas	149
Suprarenal glands	30
Abdomen[a]	118
Skeleton	25
Miscellaneous[b]	46

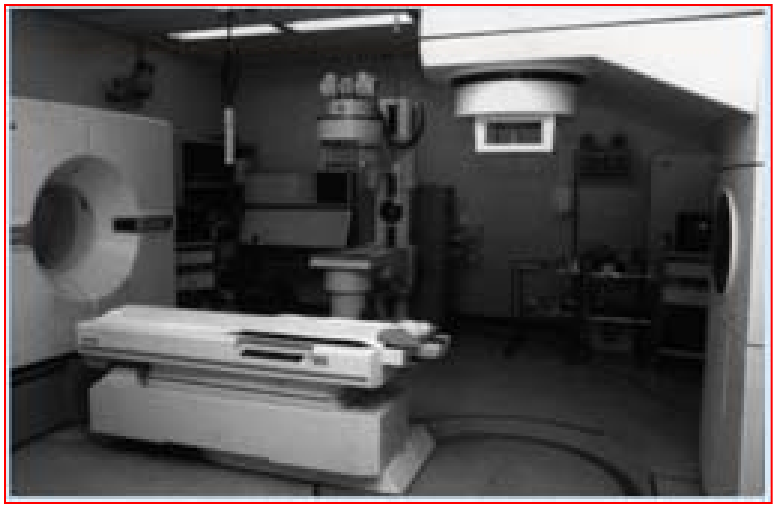
[a]Mainly kidneys and para-aortic regions.
[b]Pelvic area, muscles, and so forth.

1990's:
SBRT pioneers on 3 continents

Lax & Blomgren (Karolinska)

Uematsu (Saitama), Nagata (Kyoto)

Timmerman & Papiez (Indiana U)



Original "FOCAL" Unit,

(Fusion of CT and LINAC)

Defense Medical College, Saitama, Japan

Common denominators:

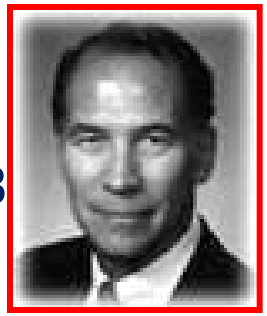
- Average equipment
- Clever low-tech solutions to allow high-tech treatments

Common goal:

- *Kill more cancer, more efficiently*

1st use of term "oligometastases"

Hellman S, Weichselbaum RR. J Clin Oncol. 1995;13(1):8



EDITORIAL

Oligometastases

CANCER TREATMENT is based on an often unstated paradigm of disease pathogenesis. Since 1894, when W.S. Halsted[1,2] clearly elucidated a mechanism of breast cancer spread and used it to design and support the radical mastectomy, surgical and radiotherapeutic approaches to most cancers have been based on this theory. The Halsted theory proposed that cancer spread is orderly, extending in a continuous fashion from the pri-

more about the multistep nature of the development of malignancy.[11-13] Once tumors become invasive, they may gradually acquire the properties necessary for efficient and widespread metastatic spread.[14] Therefore the likelihood, number, and even sites of metastases may reflect the state of tumor development. This suggests that there are tumor states intermediate between purely localized

"Conformal radiotherapy now being investigated for the treatment of primary tumors may find the treatment of oligometastases its most important application…

This technique allows both an increase in the tumor dose and a reduction in normal tissue toxicity by restricting…the radiation to the…tumor while avoiding critical normal tissues…

It requires … precise reproducible … radiation delivery…"

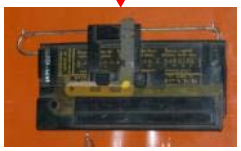
Timeline of Radiotherapy Philosophical Debate about how many treatments should be given

Patience is a virtue!

He who hesitates is lost!

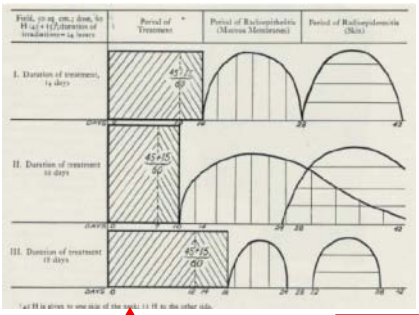
Go slow to monitor effect

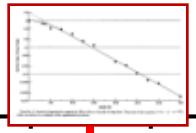
Don't cause cancer!

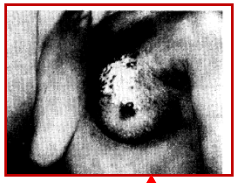


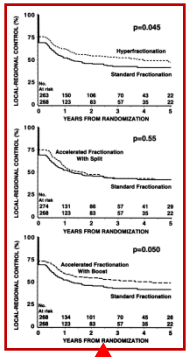
Do "expeditive" RT: and measure dose!

Be careful with normal tissues



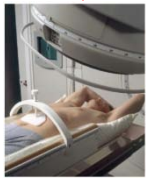






1900 1910 1920 1930 1940 1950 1960 1970 1980 1990 2000 2010 2020

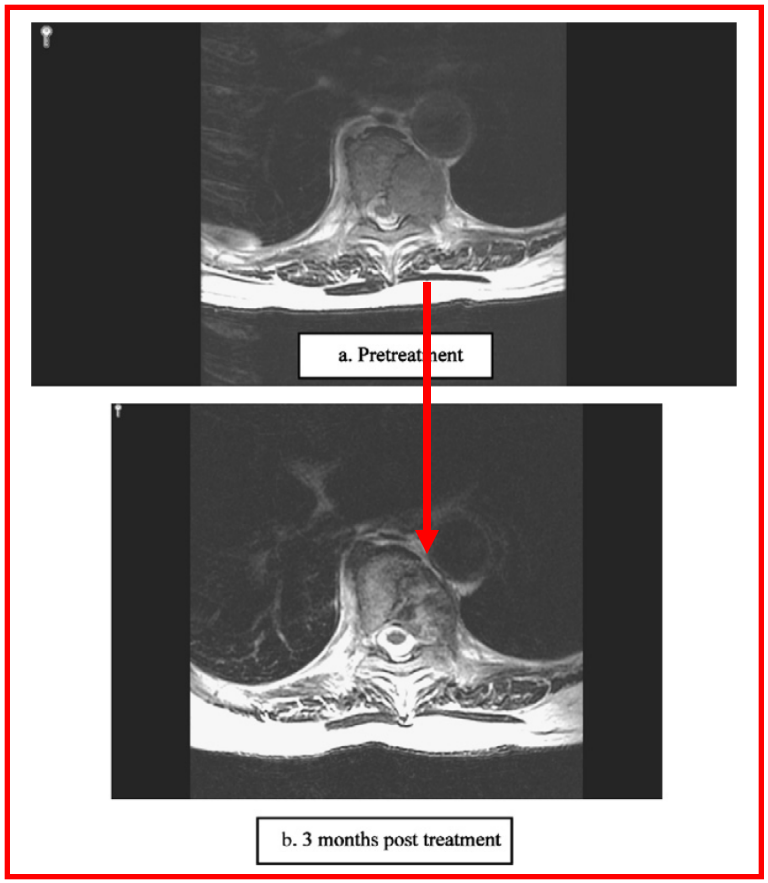
New technology can help us here!



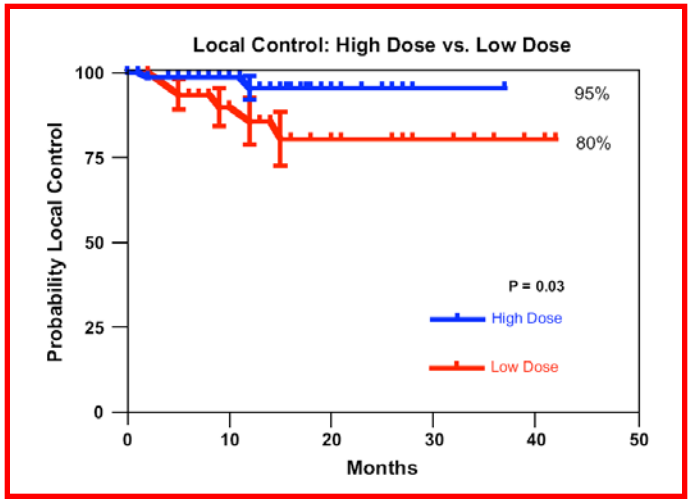
21st century radiobiology

Radiation as potent anti-angiogenic:

Obervations from the MSKCC spinal SBRT experience



Metastatic colorectal ca example



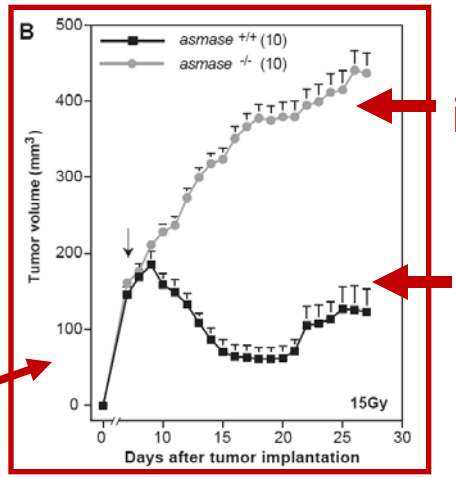
- 93 patients, 103 lesions
  - No spinal cord compression
- Single fraction 18-24 Gy
  - Spinal cord max 12-14 Gy
- Better control at higher dose (24 Gy) than lower (above)

Yamada et al, Int J Rad Oncol Biol Phys 2008; 71(2):484-90

MSKCC argument why SBRT works so well:

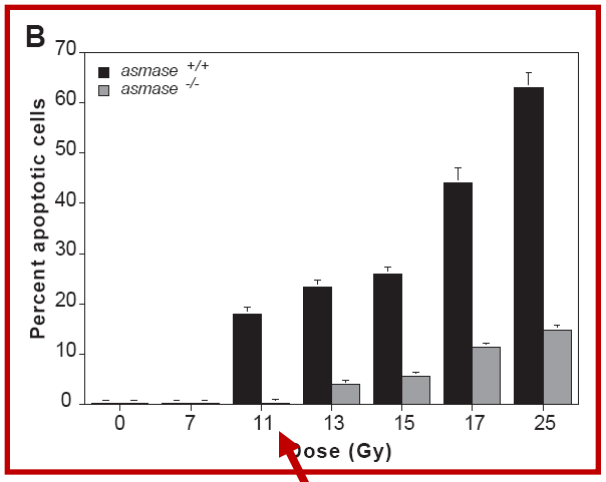
Tumor response to high dose radiotherapy is largely driven by endothelial cell apoptosis

- Fibrosarcoma and melanoma models
- Growth delay after RT influenced by apoptotic capacity
- Dose-dependence of percent apoptosis in endothelial cells



Apoptosis-incompetent

Apoptosis-competent



Threshold?

Garcia-Barros et al, Science, 2003

Sources of guidance for SBRT normal tissue dose constraints

- AAPM TG 101 report
  - Benedict et al, Med Phys, Aug 2010
- Selected RTOG SBRT studies
- QUANTEC papers
  - very limited SBRT, mostly conventional
- Timmerman RD. Sem Rad Onc 18(4): 215-222, 2008
  - Mostly unvalidated but well considered estimates for 1, 3, and 5 fractions

Timeline of Radiotherapy Philosophical Debate about how many treatments should be given: what really happened

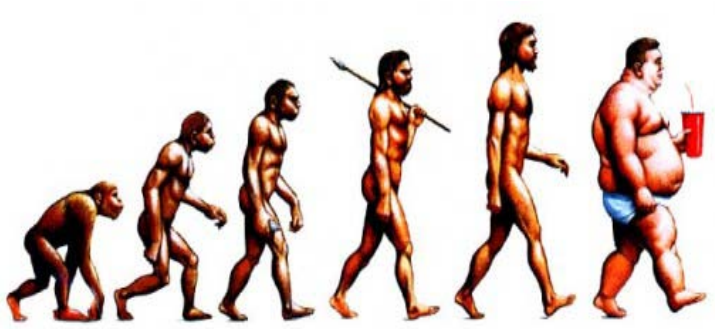
Don't be a fool!

Concurrent chemotherapy explodes everything and makes the nuances of conventional fractionation discussion almost completely disappear

1900 1910 1920 1930 1940 1950 1960 1970 1980 1990 2000 2010 2020

Don't be a Luddite!

Like it or not, this is where radiation oncology has evolved, and there is no end insight to the use of large doses per treatment



Thanks for your attention!