Executive Summary

Radiation from Medical Procedures in the Pathogenesis of Cancer and Ischemic Heart Disease:

Dose-Response Studies with Physicians per 100,000 Population

John W. Gofman, M.D., Ph. D.
Professor Emeritus, Molecular and Cell Biology
University of California, Berkeley

Edited by Egan O'Connor

- Hypothesis-1: Medical radiation is a highly important cause (probably the principal cause) of cancer mortality in the United States during the Twentieth Century. Medical radiation means, primarily, exposure by xrays (including fluoroscopy and CT scans).

- Hypothesis-2: Medical radiation, received even at very low and moderate doses, is an important cause of death from Ischemic Heart Disease; the probable mechanism is radiation-induction of mutations in the coronary arteries, resulting in dysfunctional clones (mini-tumors) of smooth muscle cells.

First Edition: 1999
C.N.R. Book Division
Committee for Nuclear Responsibility, Inc.
Post Office Box 421993
San Francisco, California 94142
U.S.A.

Executive Summary

Radiation from Medical Procedures in the Pathogenesis of Cancer and Ischemic Heart Disease:

Dose-Response Studies with Physicians per 100,000 Population

John W. Gofman, M.D., Ph.D.
Professor Emeritus, Molecular and Cell Biology,
University of California, Berkeley

Edited by Egan O'Connor

November 1999

- This document reproduces the following parts of the book:

- The author's history is described on page viii and the rear cover.

Library of Congress Catalog Number: 99-045096.

Hardcover ISBN: 0-932682-97-9. 699 pages. $35.00
Softcover ISBN: 0-932682-98-7. 699 pages. $27.00
Available from online booksellers, library distributors, and the publisher.

The Committee for Nuclear Responsibility, Inc. (CNR) is a non-profit educational group organized in 1971 to provide independent analyses of the health effects and sources of ionizing radiation. Research in this field is not commercially viable. Most radiation research, analysis, and publications are funded, directly or indirectly, by governments and other sponsors whose activities cause exposure to ionizing radiation. By contrast, CNR's work is independent of sponsorship from such sources. The work is supported by persons who value "second opinions."

This book, *Radiation from Medical Procedures in the Pathogenesis of Cancer and Ischemic Heart Disease*, begins where the previous CNR study ended.

Library of Congress Cataloging-in-Publication Data

Gofman, John W.
Radiation from medical procedures in the pathogenesis of cancer and ischemic heart disease: dose-response studies with physicians per 100,000 population / John W. Gofman ; edited by Egan O'Connor.-- 1st ed.
p. ; cm.
Includes bibliographical references and index.
ISBN 0-932682-97-9 (hardcover) -- ISBN 0-932682-98-7 (soft cover)
1. Radiation carcinogenesis. 2. Coronary heart disease--Etiology. 3. Ionizing radiation--Health aspects. 4. Radiology, Medical--Health aspects. 5. Cancer--United States--Epidemiology. 6. Coronary heart disease--United States--Epidemiology. I. O'Connor, Egan. II. Committee for Nuclear Responsibility, Inc. III. Title.
[DNLM: 1. Neoplasms--mortality. 2. Neoplasms--etiology. 3. Myocardial Ischemia--mortality. 4. Myocardial Ischemia--etiology. 5. Radiography--adverse effects. 6. Dose-Response Relationship, Radiation. 7. United States--epidemiology. QZ 200 G612ra 1999]
RC268.55 .G628 1999
616.99'4071--dc21

99-045096

The Library of Congress Catalog Number (LCCN) is 99-045096.
This book is manufactured in the United States of America, at Consolidated Printers in Berkeley CA. It is available from the publisher, from online bookstores, and from library distributors.

Published by:
Committee for Nuclear Responsibility. Tel 415-776-8299.
Hardcover: ISBN 0-932682-97-9. $35.00. Paperback: ISBN 0-932682-98-7. $27.00.

Paper in both editions is pH neutral. There are 699 pages per book, and page-size is 8.5 x 11 inches upright (21.6 x 27.9 cm).

Both the hardcover and softcover editions are sturdy and durable. The hardcover has a glossy laminated casing (no jacket); the textblock is Smyth-sewn. Librarians can obtain additional details about the binding from the publisher.

Related books by John W. Gofman:

- *What We Do Know about Heart Attacks.* 1957.
- *Dietary Prevention and Treatment of Heart Disease.* Co-authors: Alex V. Nichols and E. Virginia Dobbin. 1958. LCCN 58-10072.
- *Coronary Heart Disease.* 1959. LCCN 58-14073.
- *Radiation and Human Health.* 1981. LCCN 80-26484.
- *Xrays: Health Effects of Common Exams.* Co-author: Egan O'Connor. 1985. LCCN 84-23527.
- *Radiation-Induced Cancer from Low-Dose Exposure: An Independent Analysis*. 1990. LCCN 89-62431.
- *Chernobyl Accident: Radiation Consequences for This and Future Generations*. 1994. ISBN 5-339-00869-X (Vysheishaya Shkola Publishing House, Minsk, Belarus).
- *Preventing Breast Cancer: The Story of a Major, Proven, Preventable Cause of This Disease*. 1995/96. LCCN 94-69129 (lst edition, 1995). LCCN 96-2453 (2nd edition, 1996).

Acknowledgments

The publisher takes great pleasure in thanking the following individuals and foundations for their support of CNR's publishing program on the health effects of exposure to ionizing radiation:

June Allen, M.Ed.
Phillip M. Allen, M.D., Ph.D.
Rodney Baird, in memoriam
Charles Bloomstein
David C. Bradley, M.D.
Paul F. Burmeister
Columbia Foundation
C.S. Fund
Richard Dorwin Davis, in memoriam
Leo and Kay Drey
Genevieve Ellis Estes, in memoriam
Robin M. Fleck, M.D.
Friendship Fund
Franklin L. Gage
John B. Gilpin
Richard and Rhoda Goldman Fund
The Grodzins Fund
Anne D. Hahn, in memoriam
Hahn Family Foundation
Betty Rhodes Latner
Robert Lowitz
James P. McGinley, M.D.
Mary R. Morgan
David T. Ratcliffe
Right Livelihood Award Foundation
Caroline H. Robinson Social Service Fund
Lawrence G. Tesler
May C. Tooker

Radiation from Medical Procedures in the Pathogenesis of Cancer and Ischemic Heart Disease

Dose-Response Studies with Physicians per 100,000 Population

SECTION ONE
Orientation, Materials, Methods

SECTION TWO
Cancer Mortality: Evidence that Medical Radiation Became a Principal Cause by 1940

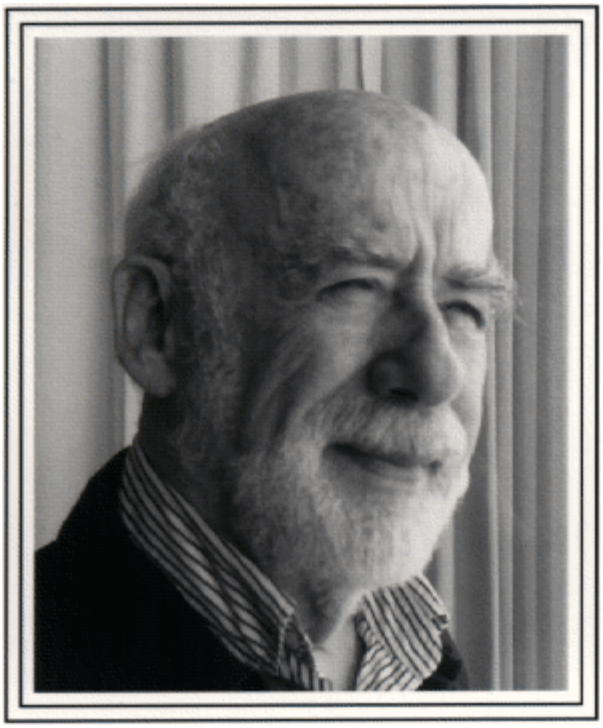
SECTION THREE
NonCancer NonIHD Mortality: Inverse Dose-Response with Medical Radiation

SECTION FOUR
Ischemic Heart Disease: Evidence that Medical Radiation Became an Important Cause by 1950

SECTION FIVE
Cancer and IHD Mortality after 1940: Fractional Causation by Medical Radiation

SECTION SIX
The Status of Hypotheses One and Two

APPENDICES



The Author's History
by Egan O'Connor

John William Gofman is Professor Emeritus of Molecular and Cell Biology, University of California at Berkeley, CA 94720-5706. He is also on the faculty at the University of California Medical School at San Francisco (UCSF). His life's work is divisible into three main areas, which converge for the first time in this monograph. Some of the earlier work is cited in the monograph's Reference List.

- **(1)** While a graduate student at U.C. Berkeley, Gofman earned his Ph.D. (1943) in nuclear/physical chemistry, with his dissertation on the discovery of Pa-232, U-232, Pa-233, and U-233, the proof that U-233 is fissionable by slow and fast neutrons, and discovery of the 4n + 1 radioactive series. His faculty advisor was Glenn T. Seaborg (who became Chairman of the Atomic Energy Commission, 1961-1971). Seaborg, Gofman, and Raymond W. Stoughton share Patent #3,123,535 on the slow and fast neutron fissionability of uranium-233, with its application to production of nuclear power or nuclear weapons. The work is recounted in Seaborg's book *"Nuclear Milestones"* (1972).

Post-doctorally, Gofman continued research related to the first atomic bombs --- particularly the chemistry of plutonium, at a time when the world's total supply was less than 0.25 milligram. He shares patents #2,671,251 and #2,912,302 on two processes for separating plutonium from the uranium and fission products of irradiated nuclear fuel. "We all were pushing the envelope in those years, and in the process, we learned the habit of observing details very closely."

- **(2)** After the plutonium work, Gofman completed medical school (1946) at UCSF, where the faculty and his classmates selected him to receive the annual Gold-Headed Cane Award for having the qualities of "a true physician."

In 1947, following his internship in Internal Medicine, Gofman joined the faculty at U.C. Berkeley (Division of Medical Physics), where he began his research on lipoproteins and Coronary Heart Disease at the Donner Laboratory. At the time, only two types of blood lipoproteins were known: Alpha and beta. By devising special flotation techniques with the ultracentrifuge, he and Frank T. Lindgren and co-workers at the Donner Lab began to reveal (1949-1950) the great diversity of very-low-density, intermediate-density, low-density, and high-density lipoproteins (VLDL, IDL, LDL, HDL) which truly exist in the bloodstream.

Their work on the chemistry of lipoproteins (e.g., the cholesterol-rich and triglyceride-rich varieties), and on dietary experiments, and on epidemiologic studies, soon produced evidence that high blood levels of the LDL, IDL, and VLDL lipoproteins are a risk-factor for Coronary Heart Disease.

In 1954, Gofman received the Modern Medicine Award for outstanding contributions to heart disease research. In 1965, he received the Lyman Duff Lectureship Award of the American Heart Association, for his research in atherosclerosis and Coronary Heart Disease. In 1972, he shared the Stouffer Prize for outstanding contributions to research in arteriosclerosis. In 1974, the American College of Cardiology selected him as one of twenty-five leading researchers in cardiology of the past quarter-century.

- **(3)** Meanwhile, in the early 1960s, the Atomic Energy Commission (AEC) asked Gofman to establish a Biomedical Research Division at the AEC's Livermore National Laboratory, for the purpose of evaluating the health effects of all types of nuclear activities. From 1963-1965, Gofman served as the division's first director and concurrently as an Associate Director of the full laboratory. Then he stepped down from the administrative activities in order to have more time for his own laboratory research on Cancer and chromosomes (the Boveri Hypothesis), on radiation-induced chromosomal mutations and genomic instability, and for his analytical work on the epidemiologic data from the Japanese atomic-bomb survivors and other irradiated human populations.

By 1969, Gofman and a Livermore colleague, Dr. Arthur R. Tamplin, had concluded that human exposure to ionizing radiation was much more serious than previously recognized. Because of this finding, Gofman and Tamplin spoke out publicly against two AEC programs which they had previously accepted. One was Project Plowshare, a program to explode hundreds or thousands of underground nuclear bombs in the Rocky Mountains in order to liberate (radioactive) natural gas, and to use nuclear explosives also to excavate harbors and canals. The second was the plan to license about 1,000 commercial nuclear power plants (USA) as quickly as possible. In 1970, Gofman and Tamplin proposed a 5-year moratorium on that activity.

The AEC was not pleased. Seaborg recounts some of the heated conversations among the Commissioners in his book *The Atomic Energy Commission under Nixon: Adjusting to Troubled Times* (1993). By 1973, Livermore de-funded Gofman's laboratory research on chromosomes and Cancer. He returned to teaching full-time at U.C. Berkeley, until choosing an early and active "retirement" in order to concentrate fully on pro-bono research into human health-effects from radiation.

His 1981, 1985, 1990, 1994, and 1995/96 books present a series of findings. His 1990 book includes his proof, "by any reasonable standard of biomedical proof," that there is no threshold level (no harmless dose) of ionizing radiation with respect to radiation mutagenesis and carcinogenesis --- a conclusion supported in 1995 by a government-funded radiation committee. His 1995/96 book provides evidence that medical radiation is a necessary co-actor in about 75% of the recent and current Breast Cancer incidence (USA) --- a conclusion doubted but not at all refuted by several peer-reviewers.

John W. Gofman is the son of David and Sarah Gofman --- who immigrated to the USA from czarist Russia in about 1905. JWG was born in Cleveland, Ohio, in September 1918.

INTRODUCTION

Overview, and Some Practical Implications of This Work

● Part 1. Practical Implications of Hypotheses One and Two

During the 1990s, approximately 23% of the U.S. deaths have been caused by Cancer, and 22% by Ischemic Heart Disease (also called Coronary Heart Disease, and Coronary Artery Disease).

Would anyone *not* welcome a simple, safe, and painless way either to postpone many cases of such diseases or to prevent many cases from occurring at all? The findings in this book, combined with already-published wisdom from some mainstream radiologists and radiologic physicists, identify such a way --- with certainty for Cancer, and with great likelihood for Ischemic Heart Disease (IHD).

The word "practical" is featured above, because prevention of these two diseases has always been our chief reason for investigating their causes. The evidence assembled and analyzed in this monograph identifies medical radiation as a very important cause of both diseases. The work is organized around two hypotheses.

1a. Statement of Hypothesis-1 (Cancer) and Hypothesis-2 (IHD)

● Hypothesis-1 is this: Medical radiation is a highly important cause (probably the principal cause) of cancer mortality in the United States during the Twentieth Century. (Hypothesis-1 is about causation, so it is silent about radiation-therapy used after a Cancer has been diagnosed.)

We are well aware of a belief that medical radiation causes only a very low percentage of cancer mortality. That belief rests on a few estimates whose input-data are highly unreliable and sometimes inherently irrelevant, for the reasons presented in Chapters 1, 2, and 67 (Part 5). By contrast, the evidence in this book strongly supports Hypothesis-1. We are confident --- for the reasons listed in Chapter 1 --- that our findings are far more credible, scientifically, than the low estimates. Also we are confident, for reasons stated in Part 5, that our findings do not conflict with estimates that more than half of the cancer rate is a result of smoking and poor diet.

● Hypothesis-2 is this: Medical radiation, received even at very low and moderate doses, is an important cause of Ischemic Heart Disease (IHD); the probable mechanism is radiation-induction of mutations in the coronary arteries, resulting in dysfunctional clones (mini-tumors) of smooth muscle cells. (Here at the outset, we can prevent some confusion about Hypothesis-2 by stating that **(a)** it was discovered decades ago that medical radiation at very high doses can damage the heart and its vessels, and that **(b)** the kinds of damage reported from very high-dose radiation seldom resemble the lesions of Ischemic Heart Disease --- details in Appendix J.)

Chapter 45 presents a Unified Model of Atherogenesis and Acute IHD Events which is consistent with the evidence in this book, is consistent with the findings (first by Earl Benditt in 1973) of monoclonal cells in atherosclerotic plaques, is consistent with well-established knowledge about atherogenic lipoproteins and other non-xray causes of fatal IHD, and is consistent with recent findings about the weaker connection than expected between degree of arterial stenosis and the fatal rupturing of specific atherosclerotic plaques.

1b. What Constitutes "Medical Radiation"?

Because not all readers will "arrive" here from the same fields, or with the same backgrounds, or with English as the native language, this book defines various terms and concepts in the fields of radiation, Cancer, Ischemic Heart Disease, and dose-response analysis. Definitions can be located with the combined Index and Glossary.

By medical radiation, Hypotheses One and Two mean primarily but not exclusively xrays (including fluoroscopy and CT scans).

There is no doubt that medical radiation can both be a cause of Cancer and also be used to treat Cancer. Cancerous activities are done by living cells, whose cancerous behavior can result from radiation-induced mutations of numerous types --- types which do not kill or sterilize the cells. When radiation is used for treatment of Cancer, it is used in very high doses which do enough damage to kill or sterilize cells. Clearly, dead or non-dividing cells cannot behave like cancer cells.

1c. Practical Implications of Hypotheses One and Two

The validity of Hypotheses One and Two is a question with major implications for future health, in the USA and elsewhere. Validity means that medical professionals and other humans have, already at hand, an opportunity which is guaranteed to achieve large reductions in *future* mortality-rates from Cancer and which is very likely to achieve similar reductions in Ischemic Heart Disease, in countries where medical radiation is widely in use.

Knowledgeable "mainstream" experts in radiology and radiologic physics have shown that xray dosage, from nontherapeutic diagnostic and interventional radiology in current medicine, could readily be cut by a factor of two or more (Chapter 1, Box 3) --- while still obtaining all the benefits of such radiology and without eliminating a single procedure (specifics in Chapters 1 and 2). Example: While radiographers have reduced the xray dose per mammographic examination by more than 10-fold, use of mammography has risen dramatically. The result of dose-reduction has certainly not been less mammography --- but rather, less-risky mammography.

Beyond diagnostic radiology, there is extensive and growing use of xray fluoroscopy, nondiagnostically, during placement of catheters and during surgical procedures. There is no doubt that dosage could be reduced many-fold during such procedures (Chapter 1, Box 3; Chapter 2, Part 3).

- **Part 2. Differing Origins of the Two Hypotheses**

How we happened to arrive at Hypothesis-1 is related in Chapter 2, Part 9. It deserves emphasis that Hypothesis-1 is not "Medical radiation can induce Cancer." Induction of Cancer in humans by ionizing radiation, including xrays, was proven long ago (Chapter 2, Part 4). The proof is so solid that it is accepted even by industries and professions which irradiate people.

Hypothesis-1 is that *medical* radiation causes a very *large* part of the nation's cancer problem. This book was undertaken in order to test, modify, or discard Hypothesis-1. In the process, the work also provides a bonus: Some of the most powerful evidence ever assembled *confirming* that ionizing radiation is a potent cause of virtually all types of human cancer.

By contrast, ionizing radiation was *not* a proven cause of Ischemic Heart Disease when Hypothesis-2 came into existence. Hypothesis-2 "fell out of the data" which we assembled in order to test Hypothesis-1. This book presents the first powerful evidence that ionizing radiation *is* a cause of Ischemic Heart Disease --- a very important cause.

- **Part 3. Some Rather Dazzling Results to Examine**

In approximately 50 years of biomedical research, we have rarely seen support for an hypothesis (Hypothesis-1), and indication for a new hypothesis (Hypothesis-2), "fall out of data" so strongly as they do in this monograph. Such events have to be taken seriously by objective analysts.

Even though the evidence is uncomplicated and the logic is straightforward, this book is long because we have the unusual policy of showing the steps which connect the raw data with the conclusions. For readers who want to know only the "bottom line," we provide an Abstract and Executive Summary (Chapter 1).

- **Part 4. Why Our Findings Do Not Challenge the Importance of Other Causes of Cancer and IHD**

Both Cancer and Ischemic Heart Disease are well established as multi-cause diseases. There is convincing evidence that several different causes increase the death-rate from Cancer, and likewise, that several different causes increase the death-rate from IHD. Moreover, it is safe to say that multiple causes generally (perhaps always) contribute to a *single case* of fatal IHD, and to a *single case* of fatal Cancer. The case would not occur when it does, without co-action by multiple causes.

The concept of *necessary* co-actors is an old one. For instance, in the famous 1964 "Surgeon General's Report" on cigarette smoking as a cause of Lung Cancer, the authors wrote (p.31): "It is recognized that often the co-existence of several factors is required for the occurrence of a disease, and that one of the factors may play a dominant role; that is, without it, the other factors (such as genetic susceptibility) seldom lead to the occurrence of the disease."

The assumption, of more than one cause per case of Cancer, arises from various lines of evidence. For example, the rate of Breast Cancer is higher in women who inherit one mutated copy of a "Breast Cancer Gene" than in women without that inheritance, but that inheritance certainly does not guarantee the development of Breast Cancer in every breast-cell --- even though every breast-cell contains the mutation. One or more additional causes are necessary in order to turn even one of those breast-cells into a Cancer.

The concept, that more than *one* cause is necessary to produce a case of Cancer, is embraced by the widely accepted initiator-promoter model of Cancer. In that model, inherited or acquired carcinogenic mutations require help from a "promoter" --- for example, a hormone or infectious agent. The concept of mutually dependent co-actors is also inherent in the widely accepted multi-mutation multi-step models of carcinogenesis --- i.e., Cancer "is typically a multi-step process resulting from an accumulation of as many as 10 genetic changes in a single cell" (p.471 in *Understanding Genetics: A Molecular Approach*, Norman V. Rothwell; Wiley-Liss Publishers, 1993).

By definition, absence of a *necessary* co-actor prevents the result. When two or more co-actors each have a required role, in producing a particular case of disease, then the absence of any *one* of them will prevent the case. We would regard such co-actors as equally important.

Thus, neither Hypothesis-1 nor Hypothesis-2 challenges the very important roles, already established, for various nonradiation causes of Cancer and IHD. When we propose that medical radiation is a highly important cause of Cancer and IHD mortality, we mean that in the *absence* of medical radiation, many or most of the cases would not have occurred when they did. While medical radiation has not been the *only* factor contributing to such cases, we mean that it has been a *necessary* co-actor in such cases. Discussion of co-action continues in Chapter 6, Part 6.

- **Part 5. How to Reconcile High Fractional Causations by Xrays, Smoking, Diet**

Fractional Causation refers to the fraction of the cancer mortality rate which would be absent (prevented) in the absence of a specified carcinogen --- which is medical radiation, in this monograph. Therefore, Fractional Causation is the fraction or percentage of the cancer mortality rate attributable to medical radiation --- or caused by medical radiation, in ordinary parlance.

A related term, widely in use, is "radiation-induced Cancer." The term is a brief and convenient way to refer to cancer cases which would have been absent in the absence of exposure to ionizing radiation. It does not mean that radiation is necessarily the *only* cause contributing to cases of radiation-induced Cancer. Similarly, when people refer to "occupationally-induced Cancer," they do not mean that occupation is the *only* cause contributing to such cases. They refer to cases which would have been absent in the absence of occupational exposure to carcinogens.

An Illustration of 100 Cancer Cases Resulting from Co-Action

Suppose that the evidence in this book indicates that Fractional Causation by medical radiation, of the national cancer death-rate, is 90% in a certain decade. Because of co-action, such a finding would *not* leave only 10% for all other causes combined --- as we will illustrate here with some hypothetical values. We will limit our illustration to only four carcinogens: Xrays, smoking, poor diet, and particular inherited mutations. For brevity, we exclude other workplace, at-home, and environmental carcinogens. Then, we arbitrarily specify that the total cancer death-rate per year is 100 cases per 100,000 population and that these 100 cases are the result of co-action as follows. Our First List (illustrative):

- 40 cases by co-action of xrays + smoking + poor diet.
- 25 cases by co-action of xrays + poor diet + inherited mutations.
- 25 cases by co-action of xrays + smoking + inherited mutations.
- 10 cases by co-action of smoking + poor diet + inherited mutations.

The meaning of the first row, above, is that xrays, smoking, and poor diet each make a *necessary* contribution to each case of Cancer in the first row. In the absence of any *one* of the necessary co-actors, the 40 cases in the first row could not occur. That is the meaning of "necessary." The meaning is similar for all four rows of hypothetical values.

A Second List, also adding up to 100 cases, would have very different implications if it were: 90 cases caused by xrays acting *alone*, 4 cases caused by a dietary factor acting alone, 3 cases caused by smoking acting alone, and 3 cases caused by an inherited mutation acting alone. In both lists, the sum of cases = 100 cases, but every case in the First List is the result of more than one cause per case, whereas every case in the Second List is the result of only one cause per case (no co-action in the Second List).

The Illustrative Fractional Causations
by Xrays, Diet, Smoking, and Inherited Mutations

Out of the mixture of cases in the First List, we will explore how many cases could be prevented if we could remove just *one* cause, while the other causes remain as they were. Xrays are a required co-actor in (40 + 25 + 25), or 90 cases per 100 total cases. Because absence of a required co-actor prevents the result, 90% of the cancer death-rate would be absent, in the absence of exposure to medical radiation. Fractional Causation = 90% by medical radiation.

Next, we put radiation back into the mixture, and we remove just "poor diet." In our supposition, it is a required co-actor in (40 + 25 + 10), or 75 cases per 100 total cases. Because absence of a required co-actor prevents the result, 75% of the cancer death-rate would be absent, in the absence of poor diet in this illustration. Fractional Causation = 75% by poor diet. In our hypothetical illustration, Fractional Causation = 75% by smoking and 60% by inherited mutations. It is obvious that a *high* Fractional Causation by xrays does not require a *low* Fractional Causation by any other cause of Cancer.

Because Fractional Causation means the fraction or percentage of the death-rate which would be absent (prevented) by the absence of a specified co-actor, *addition* of the separate Fractional Causations produces nonsense (a total greater than 100%). Such addition would be equivalent to counting the same cases of absent Cancer more than once.

Our warning against adding Fractional Causations applies to a statement in the 1999 report of the National Research Council's sixth Committee on the Biological Effects of Ionizing Radiation (the BEIR-6 Report, from the National Academy Press, 1999). The BEIR-6 Committee, referring to evidence of co-action between smoking and exposure to radon (and radon's decay-products), states that "Some lung-cancer cases reflect the joint effect of the two agents and are in principle preventable by removing either agent" (BEIR-6, p.33). Although Fractional Causation of such cases is 100% by radon and 100% by smoking, addition of the two Fractional Causations would clearly count each prevented case twice.

Implications of Co-Action for Progress in Preventing Cancer and IHD

When more than one cause is *required* per case of Cancer or Ischemic Heart Disease, it means that reducing exposure to a single necessary carcinogen or atherogen reduces the impact of all its partners. If one can identify a single agent which is a necessary co-actor in a high fraction of cases of Cancer and Ischemic Heart Disease, one can make real progress in preventing these diseases by reducing exposure to that cause. The evidence uncovered in this book strongly indicates that medical radiation is such an agent.

>>>>>>>>>>

ABSTRACT

Radiation from Medical Procedures in the Pathogenesis of Cancer and Ischemic Heart Disease:
Dose-Response Studies with Physicians per 100,000 Population.
John W. Gofman, M.D., Ph.D. 1999. 699 pages. LCCN 99-045096.
Hardcover: ISBN 0-932682-97-9. Softcover: ISBN 0-932682-98-7.
Committee for Nuclear Responsibility Books, San Francisco.

ORIENTATION:

For decades, xrays and other classes of ionizing radiation have been a proven cause, in vivo and/or in vitro, of virtually all types of mutation --- especially structural chromosomal mutations (such as deletions, translocations, and rings), for which the doubling-dose by xrays is extremely low. Additionally, xrays are an established cause of in vitro genomic instability.

This monograph looks at the impact of medical radiation --- primarily from xrays, including fluoroscopy and CT scans --- upon mortality-rates from both Cancer and Ischemic (Coronary) Heart Disease, from mid-century to 1990. The evidence in this book strongly indicates that medical radiation has become a necessary co-actor (but not the only necessary co-actor) in causing over 50% of the death-rates from Cancer and Ischemic Heart Disease (IHD) --- a finding which is consistent with participation of non-xray causes as necessary co-actors in the same cases (Introduction). In multi-cause diseases such as Cancer and IHD, more than one necessary co-actor per fatal case is very likely. Absence of any necessary co-actor, by definition, prevents such cases. The concept, of cases due to medical radiation, means cases which would be absent in the absence of medical radiation.

PURPOSE:

Xrays have been a well-established cause of human Cancer for decades. This monograph was undertaken **(a)** to quantify what share of U.S. age-adjusted cancer mortality, for each gender, is caused by medical radiation, and **(b)** to check on the

author's 1995 finding, based on completely different data, that exposure to medical radiation accounts for about 75% of Breast Cancer incidence in the USA. In the process of evaluating cancer mortality vs. noncancer mortality for this monograph, it became obvious that the impact of medical radiation upon death-rates specifically from Ischemic Heart Disease also demanded evaluation.

MATERIALS AND METHODS:

This study is based on mortality rates among 130-250 million persons --- namely, the entire United States population, 1940-1990. Age-adjusted cancer mortality rates (MortRates) per 100,000 population are available by gender for each of the Nine Census Divisions (USA), for the 1940-1990 decades, from Vital Statistics. Such rates for noncancer mortality rates also are available. For Ischemic Heart Disease, such rates are available starting in 1950, which means that NonCancer NonIHD MortRates, by Census Divisions, are available starting in 1950.

For reasons presented in Chapter 2 (Parts 2+3), there are no reliable estimates of average per capita population dose, accumulated from medical radiation, currently or in the past. Also not available, for reasons presented in Chapter 2 (Part 7c), are reliable estimates of cancer-risk per unit of dose from medical xrays. This monograph avoids these two types of uncertainty by using the number of physicians per 100,000 population (PhysPop) as a reasonable approximation of the *relative* magnitude of exposure from medical radiation in the Nine Census Divisions. The ranking of averaged PhysPop values by Census Divisions, over the 1940-1990 period, is remarkably stable.

MortRates are regressed upon PhysPop values, by Census Divisions, to determine the presence and direction of any dose-response. When a significant positive dose-response exists, the line of best fit is extended to the y-axis, where the intercept's value indicates what the MortRate would have been for that disease, if there had been *no* physicians per 100,000 population in a Census Division. The national MortRate for the disease under study, minus the intercept's value, provides a reasonable estimate of the share of that national MortRate which is due to medical radiation (i.e., the share which would be absent in the absence of medical radiation). Confidence limits are provided in Chapter 22, Box 1.

RESULTS:

Cancer and IHD MortRates each have very significant positive correlations with PhysPop, for males and females separately. By contrast, NonCancer NonIHD MortRates have a significant negative correlation with PhysPop. The following groups of Cancer were studied: All-Cancers-Combined, Breast Cancers, Digestive-System Cancers, Urinary-System Cancers, Genital Cancers, Buccal/Pharynx Cancers, Respiratory-System Cancers, Difference-Cancers (All-Except-Respiratory). Only female Genital Cancers failed to have a significant positive dose-response with PhysPop. The percentages, of the death-rates from Cancer and IHD caused by medical radiation (i.e., the shares which

would be absent, in the absence of medical radiation), are shown in Box 1 of Chapter 1. For example:

	Year	Percent	Year	Percent
• All-Cancers-Combined, m	1940	90%	1988	74%
• All-Cancers-Combined, f	1940	58%	1988	50%
• All-Cancer-Except-Genital, f	1940	75%	1980	66%
• Breast Cancer, f	1940	~ 100%	1990	83%
• Ischemic Heart Disease, m	1950	79%	1993	63%
• Ischemic Heart Disease, f	1950	97%	1993	78%

The growing impact of cigarette-smoking (Chapters 48, 49) almost certainly explains why the shares from medical radiation in 1980-1993 are somewhat lower than in 1940-50.

CONCLUSIONS:

Since its introduction in 1896, medical radiation has become a necessary co-actor in most fatal cases of Cancer and Ischemic Heart Disease (IHD).

It is proposed that, for radiation-induced IHD, the probable mechanism is radiation-induction of mutations in the coronary arteries, resulting in dysfunctional clones (mini-tumors) of smooth muscle cells. A Unified Model of Atherogenesis and Acute IHD Events is presented (Chapter 45), which is consistent with the findings in this book, is consistent with the findings (first by Earl Benditt in 1973) of monoclonal cells in atherosclerotic plaques, is consistent with well-established knowledge about atherogenic lipoproteins and other non-xray causes of fatal IHD, and is consistent with recent findings about the weaker connection than expected between degree of arterial stenosis and the fatal rupturing of specific atherosclerotic plaques.

The evidence in this monograph has major implications for prevention of Cancer and IHD. This monograph points to demonstrations, by others, of proven ways to reduce dose-levels of nontherapeutic medical radiation by 50% or considerably more, without eliminating a single diagnostic or interventional radiologic procedure and without degrading the information provided by medical radiation. Reduction of exposure to medical radiation can and will reduce mortality rates from both Cancer and Ischemic Heart Disease.

>>>>>>>>>>

CHAPTER 1

Executive Summary of This Book

Boxes, Figures, and Tables, in that (alphabetical) order, are located in this book at the ends of the corresponding chapters.

● Part 1. Orientation: What Is Old, and What Is New

The evidence presented in this book strongly indicates that over 50% of the death-rate from Cancer today, and over 60% of the death-rate from Ischemic Heart Disease today, are xray-induced as defined and explained in Part 5 of the Introduction. The finding means that xrays (including fluoroscopy and CT scans) have become a necessary co-actor --- but not the only necessary co-actor --- in causing most of the death-rate from

Cancer and from Ischemic Heart Disease (also called Coronary Heart Disease, and Coronary Artery Disease). In multi-cause diseases such as Cancer and Ischemic Heart Disease, more than one necessary co-actor per fatal case is very likely. Absence of any necessary co-actor, by definition, prevents such cases. The concept of xray-induced cases means cases which would be absent in the absence of exposure to xrays.

Xrays and other classes of ionizing radiation have been, for decades, a proven cause of virtually all types of mutations --- especially structural chromosomal mutations (such as deletions, translocations, and rings), for which the doubling dose by xrays is extremely low. Additionally, xrays are an established cause of genomic instability, often a characteristic of the most aggressive Cancers.

Not surprisingly, a host of epidemiologic studies have firmly established that xrays and other classes of ionizing radiation are a cause of most varieties of human Cancer. This monograph presents **(a)** the first compelling evidence that xrays are a cause also of Ischemic Heart Disease (IHD) --- a very important cause --- and presents **(b)** a Unified Model of Atherogenesis and Acute IHD Events (Part 7 of this chapter).

We have a high level of confidence that our findings, about the important causal role of medical radiation in both Cancer and IHD, are correct. Part 6 of this chapter identifies the features of the work which produce this confidence.

Part 9 of this chapter points to demonstrations, by others, of proven ways to reduce dose-levels of nontherapeutic medical radiation by 50% or considerably more, without eliminating a single diagnostic or interventional radiologic procedure and without degrading the information provided by medical radiation.

Reduction of exposure to medical radiation can and will reduce mortality rates --- from Cancer with certainty, and with very great probability from Ischemic Heart Disease too.

• Part 2. Some Key Facts about Xrays and Ionizing Radiation in General

---

Most physicians and other people appreciate the imaging capability of the xray, but --- through no fault of their own --- they are taught very little about the biological action of those xrays which never reach the film or other image-receptor. Part 2 provides some information about xrays and ionizing radiation in general. These facts are well supported in the peer-reviewed biomedical literature, in our text, and in our Reference List.

2a. Capacity to Commit Mayhem among the Genetic Molecules

The biological damage from a medical xray procedure does not come directly from the xray photons. The damage comes from electrons, which those photons "kick" out of their normal atomic orbits within human tissues. Endowed with biologically unnatural energy by the photons, such electrons leave their atomic orbits and travel with high speed and high energy through their "home cells and neighboring cells. Each such electron gradually slows down, as it unloads portions of its biologically unnatural energy, at irregular intervals, onto various biological molecules along its primary track (path).

The molecular victims include, of course, chromosomal DNA, and the structural proteins of chromosomes, and water. Even though each energy-deposit transfers only a portion of the total energy of a high-speed high-energy electron, the single deposits very often have energies far exceeding any energy-transfer which occurs in a natural biochemical reaction. Such energy-deposits are more like grenades and small bombs (Chapter 2, Part 4a). None of this is in dispute.

2b. The Free-Radical Fallacy

There is no doubt that, along the path of each high-speed high-energy electron described above, the energy-deposits produce various species of free radicals. Nonetheless, it is a demonstrated fallacy (Appendix-C) to assume equivalence between the biological potency of xrays and the biological potency of the free radicals which are routinely produced by a cell's own natural metabolism.

The uniquely violent and concentrated energy-transfers, resulting from xrays, are simply absent in a cell's natural biochemistry. As a result of these "grenades" and "small bombs," both strands of opposing DNA can experience a level of mayhem far exceeding the damage which metabolic free-radicals (and most other chemical species) generally inflict upon a comparable segment of the DNA double helix.

2c. Ionizing Radiation: A Uniquely Potent Mutagen

The extra level of mayhem is what makes xrays (and other types of ionizing radiation) uniquely potent mutagens. Cells can not correctly repair every type of complex genetic damage, induced by ionizing radiation, and sometimes cells can not repair such damage at all (evidence discussed in Appendix-B and Appendix-C). Not all mutated cells die, of course. If they all died, there would be very little Cancer and no inherited afflictions. Indeed, certain mutations confer a proliferative advantage on the mutated cells. Exposure to xrays is a proven cause of genomic instability --- a characteristic of many of the most aggressive Cancers (Chapter 2, Part 4b, and Appendix-D).

Unlike some other mutagens, xrays have access to the genetic molecules of every internal organ, if the organ is within the xray beam. Within such organs, even a single

high-speed high-energy electron, set into motion by an xray photon, has a chance (far from a certainty) of inducing the types of damage which defy repair. That is why there is no risk-free (no safe) dose-level (Appendix-B).

There is widespread agreement that, by its very nature, ionizing radiation at any dose-level can induce particularly complex injuries to the genetic molecules. There is growing mainstream acknowledgment that cellular repair processes are fallible, or entirely absent, for various complex injuries to the genetic molecules (Appendix-B and Appendix-C).

2d. The Very Low Doubling-Dose for Xray-Induced Chromosomal Mutations

---

The inability of human cells, to repair correctly every type of radiation-induced chromosomal damage, has been demonstrated in nuclear workers (who received their extra low-dose radiation at minimal dose-rates) and in numerous studies of xray-irradiated human cells at low doses. Besides demonstrating non-repair or imperfect repair, such studies have established that xrays have an extremely low doubling-dose for structural chromosomal mutations. (The doubling dose of an effect is the dose which adds a frequency equal to the pre-existing frequency of that effect.)

For instance, the doubling-dose for the dicentric mutation is in the dose range delivered by some common xray procedures, such as CT scans and fluoroscopy --- i.e., in the dose range of 2 to 20 rads (references in Chapter 2, Part 4b). The rad is a dose-unit which is identical to the centi-gray (Appendix-A). We, and many others, prefer the simpler name: Rad.

Xrays are capable of causing virtually every known kind of mutation --- from the very common types to the very complex types, from deletions of single nucleotides, to chromosomal deletions of every size and position, and chromosomal re-arrangements of every type. When such mutations are not cell-lethal, they endure and accumulate with each additional exposure to xrays or other ionizing radiation (Chapter 2, Part 8c; and Appendix-B, Part 2d).

2e. Medical Xrays as a Proven Cause of Human Cancer

Ionizing radiation is firmly established by epidemiologic evidence as a proven cause of almost every major type of human Cancer (Chapter 2, Part 4c). Some of the strongest evidence comes from the study of medical patients exposed to xrays --- even at minimal dose-levels per exposure (Appendix-B, Part 2d). Mounting mainstream evidence indicates that medical xrays are 2 to 4 times more mutagenic than high-energy beta and gamma rays, per rad of exposure (Chapter 2, Part 7).

● Part 3. No Doubt about Benefits from Medical Radiation

Radiation was introduced into medicine almost immediately after discovery of the xray (by Wilhelm Roentgen) in 1895.

There is simply no doubt that the use of radiation in medicine has many benefits. The findings in this book provide no argument against medical radiation. The findings do provide a powerful argument for acquiring all the benefits of medical radiation with the use of much lower doses of radiation, in both diagnostic and interventional radiology. (Interventional radiology refers primarily, but not exclusively, to the use of fluoroscopy to acquire information during surgery and during placement of catheters, needles, and other devices.)

Within the professions of radiology and radiologic physics, there are mainstream experts who have shown how the dosage of xrays in current practice could be cut by 50%, or by considerably more, in diagnostic and interventional radiology --- without any loss of information and without eliminating a single procedure (discussion in Part 9, below). Among the current leaders in dose-reduction education are Joel Gray, Ph.D. (recently retired from the Mayo Clinic's Department of Radiology in Rochester, Minnesota) and Fred Mettler, M.D. (Chief of Radiology, University of New Mexico School of Medicine in Albuquerque, New Mexico).

● Part 4. Role of Medical Radiation in Causing Cancer and IHD, Past and Present

This monograph has produced evidence with regard to two hypotheses.

● Hypothesis-1: Medical radiation is a highly important cause (probably the principal cause) of cancer mortality in the United States during the Twentieth Century. Medical radiation means, primarily but not exclusively, exposure by xrays --- including fluoroscopy and CT scans. (Hypothesis-1 is about causation of Cancer, so it is silent about radiation-therapy used after a Cancer has been diagnosed.)

● Hypothesis-2: Medical radiation, received even at very low and moderate doses, is an important cause of death from Ischemic Heart Disease (IHD); the probable mechanism is radiation-induced mutations in the coronary arteries, resulting in dysfunctional clones (mini-tumors) of smooth muscle cells. (The kinds of damage to the heart and its vessels, observed from very high-dose radiation and reported for decades, seldom resemble the lesions of IHD --- details in Appendix J.)

4a. These Hypotheses in Terms of Multi-Cause Diseases

Cancer and Ischemic Heart Disease are well established as multi-cause diseases. The concept, that more than one necessary co-actor is required per case, has already been discussed in Parts 4 and 5 of the Introduction. In efforts to prevent these multi-cause diseases, reduction or removal of any necessary co-actor is a central goal. The evidence in this book is that medical radiation has become a necessary co-actor in a high fraction of the U.S. mortality rates from *both* diseases. Fortunately, dosage from medical radiation is demonstrably reducible without eliminating a single procedure.

4b. Fractional Causation: Percentage of Death-Rates due to Medical Radiation

---

The tabulation below shows the percentages, of the age-adjusted death rates (m=male, f=female) from Cancer and IHD, due to medical radiation at mid-century and at the most recent year for which we have data. Box 1 at the end of this chapter shows percentages for several specific types of Cancer. Percentages for each intervening decade are shown in the appropriate chapters and assembled in Chapter 66.

When an entry of ~ 100% occurs, such a finding is fully consistent with the fact that these diseases occurred before the introduction of radiation into medicine, over a century ago. Other mutagens (including radiation exposure from nature itself) have been operative both before and after the introduction of medical radiation. A finding, of about 100% of the death-rate due to medical radiation in 1940, means that by 1940, a very low fraction of such deaths would have occurred without medical radiation as a co-actor.

	Year	Percent	Year	Percent
● All-Cancers-Combined, m	1940	90%	1988	74%
● All-Cancers-Combined, f	1940	58%	1988	50%
● Breast Cancer, f	1940	~ 100%	1990	83%
● All-Cancer-Except-Genital, f	1940	75%	1980	66%
● Ischemic Heart Disease, m	1950	79%	1993	63%
● Ischemic Heart Disease, f	1950	97%	1993	78%

The growing impact of cigarette smoking (Chapters 48, 49) almost certainly explains why the shares from medical radiation in 1980-1993 are somewhat lower than in 1940-1950.

A percentage such as 90% due to medical radiation (Fractional Causation by medical radiation = 0.90) means that about 90% of the death-rate would have been absent in the absence of medical radiation. Circumstantial evidence is strong that nonxray agents *also* were necessary co-actors in these same deaths. Thus, Fractional Causation of 90% by medical radiation certainly does not leave "just 10%" for all other causes combined, as already illustrated in Part 5 of the Introduction.

Fractional Causation, of a year-specific mortality rate (MortRate) by medical radiation, refers to whatever rate occurs in that year, and says nothing about whether the MortRate has been rising or falling over time. Indeed, changes over time, in the types and

concentrations of non-xray co-actors to which populations are exposed, can cause cancer MortRates simultaneously to rise for some organs, fall for other organs, and remain constant for still other organs (discussion in Chapter 67, Part 2).

The results in this book amply support Hypothesis-1 and the first part of Hypothesis-2. While the central estimates of Fractional Causation are statistically the most likely to be correct, of course the actual percentages could be either higher or lower. We note that percentages *very* much lower than the central estimates would support each hypothesis, too.

• Part 5. Our Method for Calculating Fractional Causation

When increments, in the death-rate from a disease, are proportional to increments in exposure to an identified cause, a linear dose-response exists between the causal agent and increments in the death-rate.

The evidence in this monograph repeatedly reveals a positive and tight linear dose-response, between dose from medical radiation and mortality rates from Cancer (discussion in Chapter 5, Part 5d). By "tight," we mean highly reliable (statistically). As we will explain, no group in our database escapes entirely from exposure to medical radiation. In order to estimate what the cancer mortality rates would be in the *absence* of medical radiation, we use the basic technique of linear regression analysis (Part 5c, below). After that basic step, it is not at all complicated to calculate Fractional Causation due to medical radiation (Part 5g, below).

5a. The Database for Age-Adjusted Mortality Rates (MortRates)

We acquired the age-adjusted cancer MortRates per 100,000 population in each of the Nine Census Divisions of the USA, from 1940 onward --- separately for males and females, and for all races combined (no exclusions). Such data are published by the U.S. Government (details in Chapter 4). For most types of Cancer, our data end in 1988-1990 (some end in 1980).

Also we acquired the comparable age-adjusted MortRates for All NonCancer Causes of Death --- as well as for selected individual causes (such as IHD, Stroke, Diabetes Mellitus, Influenza and Pneumonia, Accidents, etc.) --- in each of the Nine Census Divisions.

These MortRates, by Census Divisions, are the dependent variables (the responses) in our dose-response studies. Because the MortRates are age-adjusted, the Census Divisions are matched with each other for age.

5b. The Database for Dose: Physicians per 100,000 Population

During the 1985-1990 period, the number of diagnostic medical xray examinations performed per year in the USA was approximately 200 million, excluding 100 million dental xray examinations and 6.8 million diagnostic nuclear medicine examinations. The source of these estimates (the 1993 Report of UNSCEAR, the United Nations Scientific Committee on Atomic Radiation, p.229, p.275) warns that 200 million could be an underestimate by up to sixty percent.

Not only is the number of annual examinations quite uncertain, but the average doses per examination --- in actual practice, not measured with a dummy during ideal practice --- vary sometimes by many-fold from one facility to another, even for patients of the same size. The variation by facility has been established by a few on-site surveys of selected facilities, because measurement and recording of xray doses are not required for actual procedures (Part 9, below).

Fluoroscopy is a major source of xray dosage, because the xray beam stays "on" during fluoroscopy. Such doses are rarely measured. When fluoroscopic xrays are used during common diagnostic examinations, the total dose delivered varies with the operator. When fluoroscopic xrays are used during surgery and other nondiagnostic procedures, the total dose delivered varies both with the operator and the particular circumstances.

The uncertain number of procedures and the very uncertain doses per procedure combine to cause profound uncertainty about current average per capita population dose from medical radiation (Chapter 2, Part 3). Dose estimates for past decades are even *more* uncertain (Chapter 2, Part 2).

An Additional Gap in Knowledge: Risk-per-Rad Estimates

In most of the studies which produce estimates of cancer-risk per rad of xray dose, it is far from certain which participants received which xray doses over their lifetimes, because such doses were neither measured nor recorded. When a few participants are (unintentionally) assigned a wrong dose-estimate, the error can substantially alter the resulting risk-per-rad estimates. This contributes to the great uncertainty about the true risk-per-rad from xrays (Chapter 2, Part 7c). The uncertainty is no secret. For example, the fifth Committee on the Biological Effects of Ionizing Radiation stated in its 1990 report (National Academy Press, at pp.46-47): "A number of low-dose studies have reported risks that are substantially in excess of those estimated in the present report ... Although such studies do not provide sufficient statistical precision to contribute to the risk estimation procedure per se, they do raise legitimate questions about the validity of the currently accepted estimates."

A Solution to These Gaps in Knowledge

Medical radiation procedures are initiated by a physician, even if someone else actually performs the procedure. It is very reasonable to think that the more physicians there are per 100,000 population, the more radiation procedures per 100,000 population will be ordered. Thus, we arrive at the premise that average radiation dose, received per capita of population in a specific Census Division from medical procedures during a specific year, is approximately proportional to the number of physicians per 100,000 population in that same Census Division during that same year.

This common-sense premise is well supported in the 1988 and 1993 reports of the United Nations Scientific Committee on Atomic Radiation (details in our Chapter 3, Part 1a), and is supported specifically for the USA by data in a 1989 report from the National Council on Radiation Protection and Measurements (details in Chapter 3, Part 1a).

"PhysPop" Values in the Nine Census Divisions, over Many Decades

We use the abbreviation, "PhysPop," for the quantity "Physicians per 100,000 Population." A PhysPop value of 134 means 134 Physicians per 100,000 population, for the specified year and place.

PhysPop values for various calendar years have been compiled and published for each state by the American Medical Association over many decades (details in Chapter 3). It is a routine matter to combine such data appropriately, in order to obtain PhysPop values for the Nine Census Divisions (details in Chapter 3). Because substantial *differences* in PhysPop values exist among the Nine Census Divisions, it has been possible for us to do dose-response studies, with PhysPop values in each Census Division as surrogates for average per capita dose from medical radiation in each corresponding Census Division.

Of course, dose is cumulative (i.e., radiation-induced mutations are cumulative). Moreover, in a population of mixed ages (newborn to very advanced ages), the cancer-response to ionizing radiation is spread out over at least four to five decades (Chapter 2, Part 8). Thus, the age-adjusted cancer MortRates in any single year --- say 1990 --- incorporate cases which are due to radiation received in 1940, 1950, 1960, 1970, etc. It happens that, during the 1921-1990 period, the rank order of the Census Divisions --- by the size of their PhysPop values --- has been remarkably stable (details in Chapter 3, Box 1; see also Chapter 47, Table 47-A). Thus, PhysPop values are well-suited to be surrogates for the *relative* size of average *accumulated* per capita dose from medical radiation, among the Nine Census Divisions.

5c. Illustrative Regression (Input and Output), for All Cancers Combined

---

Linear regression analysis is a branch of mathematics which, among other things, evaluates how well correlated are sets of paired values. In our dose-response studies, there are always nine pairs of values, because there are Nine Census Divisions --- each

having its own age-adjusted MortRate (the y-variable) and its own PhysPop value (the x-variable). On the lefthand side of the next page, we show the input data for a regression whose output is shown on the righthand side.

In the output, two quantities measure the goodness (strength) of the correlation: The R-squared value, and the ratio of the X-coefficient divided by its Standard Error (X-Coef/S.E.).

- An R-squared value of 1.00 is perfection. An R-squared value of 0.70 is very good. Those who are familiar with the correlation coefficient, R, will recognize that R-squared values are lower than the corresponding R-values (for instance, when R = 0.83666, R-squared = 0.70; when R = 0.94868, R-squared = 0.90).

- A ratio of (X-Coef/S.E.) of about 2.0 generally indicates a statistically significant correlation. A ratio of 4.0 is a tight correlation. A ratio above 4.0 is very tight. The ratio describes the reliability of the slope in a line of best fit.

In Part 5d, the male 1940 MortRates per 100,000 population, for All-Cancers-Combined, are regressed upon the 1940 PhysPop values (which represent accumulated doses from earlier years of medical radiation). The regression reveals a spectacularly tight correlation: R-squared = 0.9508.

5d. Figure 1-A: Graph of the 1940 PhysPop-Cancer Dose-Response (Males, Females)

The regression output (below) provides all the information necessary to calculate and to graph the line of best fit for the nine pairs of real-world observations (listed below). Chapter 6, Part 3, shows how. The resulting graph is presented in the upper half of Figure 1-A, at the end o this chapter. The nine boxy symbols in Figure 1-A represent the nine pairs of actual observations from the x,y columns below. For example, the box farthest to the right represents the pair with the highest PhysPop value: The Mid-Atlantic pair.

Census Division	1940 PhysPop x	1940 All-Ca y
Pacific	159.72	122.9
New England	161.55	135.5
West North Central	123.14	110.9
Mid-Atlantic	169.76	140.9
East North Central	133.36	119.6
Mountain	119.89	99.8
West South Central	103.94	86.9
East South Central	85.83	73.6
South Atlantic	100.74	88.9

All-Cancer MortRates 1940 (males) vs. PhysPop 1940	
Regression Output:	
Constant	11.5484
Std Err of Y Est	5.4727
R Squared	0.9508
No. of Observations	9
Degrees of Freedom	7
X Coefficient(s)	0.7557
Std Err of Coef.	0.0650
X-Coef/S.E. =	11.6275

Figure 1-A also presents the comparable graph for females (borrowed from Chapter 7). It was prepared after regressing the female 1940 MortRates per 100,000 population, for All-Cancers-Combined, upon the 1940 PhysPop values (which represent accumulated doses from earlier years of medical radiation).

5e. The Dose-Response Findings for Specific Sets of Cancer

In addition to All-Cancers, we examined the dose-response for various sets of Cancers. With only one exception (female Genital Cancers), all the regression analyses revealed strong *positive* correlations between PhysPop and the 1940 Cancer MortRates, by Census Divisions. A summary of their R-squared values is in Column D of Box 1, after the text of this chapter.

5f. NonCancer Causes of Death: IHD Separates Itself from Other Causes

Before exploring the post-1940 decades, we asked, "Do the same strong positive correlations exist for noncancer causes of death?

They definitely do not. When we studied All Causes Except Cancer (Chapter 24), we found a nonsignificant *negative* relationship between PhysPop and MortRates. Curiosity drove us also to study *specific* noncancer MortRates in 1940 versus PhysPop. Almost all regression analyses revealed negative relationships between PhysPop and noncancer MortRates. There is a summary of those findings in the upper part of Box 2, at the end of this chapter. A negative X-coefficient means a downward slope.

Strong *positive* Correlation between PhysPop and 1950 IHD MortRates

We arrived late at regressing Ischemic Heart Disease (IHD) MortRates on PhysPop, by Census Divisions, because there are no MortRate data for IHD until 1950. When we finally regressed the 1950 MortRates for IHD on PhysPop, we were astonished by the results (Chapters 40 and 41). What fell out of the data are very strong *positive* correlations with PhysPop --- which are graphed as Figure 1-B at the end of this chapter.

- Male IHD MortRates vs. PhysPop: R-sq = 0.95 and Xcoef/SE = 11.25.
- Female IHD MortRates vs. PhysPop: R-sq = 0.87 and Xcoef/SE = 6.75.

Such spectacular correlations do not happen by accident. They "demand" an explanation. The resemblance to the positive dose-response for Cancer is self-evident. These two diseases unambiguously sort *themselves* out from NonCancer NonIHD causes of death, with respect to medical radiation (PhysPop). The positive dose-response

between PhysPop and Cancer is no surprise, because xrays are a proven cause of Cancer. For IHD, the findings above invoke the Law of Minimum Hypotheses: Medical radiation is a cause of Ischemic Heart Disease, too. Our Unified Model of Atherogenesis (Part 7, below) proposes *how* radiation-induced dysfunctional clones of smooth muscle cells, in the coronary arteries, may interact with atherogenic lipoproteins to explain the strong positive correlations presented above.

Strong *negative* Correlation
between PhysPop and 1950 NonCancer NonIHD MortRates

When *both* Cancer and IHD are removed from Causes of Death, the correlation between PhysPop and MortRates for the remaining Causes of Death (NonCancer NonIHD) is not only *negative*, but it also is statistically significant. That relationship is depicted in Figure 1-C --- borrowed from Chapter 25. The contrast is dramatic, between Figure 1-C and the two preceding figures. Box 2, at the end of this chapter, presents the findings for specific NonCancer Non IHD causes of death.

5g. From Positive Dose-Response to Fractional Causation: The Calculation

---

The observed PhysPop values and the observed MortRates, by Census Divisions, reveal a positive, linear dose-response of great strength between medical radiation and the mid-century MortRates for Cancer and (separately) for Ischemic Heart Disease.

In order to estimate what *share* of the National MortRates for these diseases was due to medical radiation, we use the regression output to identify what the MortRates for each disease would have been at that time, if the population had received *no* medical radiation. The Constant is the value of the y-variable (the MortRate) when the x-variable (PhysPop) is zero. Obviously, if there had been no physicians per 100,000 population, there would have been no medical radiation. On our graphs, the Constant is the value of y where the line of best fit intercepts the vertical y-axis.

Example from Part 5d, above: In the regression output, the Constant = 11.5 --- matching the y-intercept in the upper graph of Figure 1-A. From Chapter 6, Table 6-B, we have the datum that the 1940 *national* age-adjusted male MortRate from All Cancers Combined was 115.0 fatal Cancers per 100,000 male population. Of these 115.0 cases, only 11.5 cases would have occurred if there had been no medical radiation. The number of fatal cases (per 100,000 population) in which medical radiation was a required co-actor was (115.0 minus 11.5), or 103.5 cases. And the Fractional Causation by medical radiation was 103.5 / 115.0, or 0.90 --- 90%.

This is the manner in which Fractional Causation by medical radiation is estimated, both for Cancer and for IHD MortRates, throughout this book. For the decades beyond mid-century, one adjustment was required (and executed in plain view) for the impact of

cigarette smoking, an important co-actor whose intensity was not matched across the Nine Census Divisions (Chapter 48).

Returning to the example from Part 5d, we want to estimate the Upper and Lower 90% Confidence Limits on the Fractional Causation by medical radiation of the male 1940 National All-Cancer MortRate. These limits are, respectively, 99% and 75%. These limits are derived from the reliability of the slope of the line of best fit, because its slope (the X-coefficient) determines the value of the y-intercept (the Constant). The regression output in Part 5d provides the required values: The X-coefficient is 0.7557 units of y per unit of x, with a Standard Error of 0.0650. Calculation of the Confidence Limits is first demonstrated in Chapter 6, Part 4.

• Part 6. Eight Features Which Confer High Credibility on the Findings

---

This monograph presents evidence that medical radiation is an important cause of both fatal Cancer and fatal Ischemic Heart Disease in the USA. There are eight features of our findings which endow us with high confidence that the findings are correct, and so we call those features to the attention of readers:

• First, the findings occur from data which were collected long ago for other purposes --- namely the collection of Vital Statistics from each state on the causes of death per 100,000 population, and the collection of information from each state on the number of physicians per 100,000 population (PhysPop values). Thus, these databases are free from any conceivable bias with respect to Hypothesis-1 or Hypothesis-2. This is no small matter. The first obligation of objective analysts is to be able to assure themselves and the public that the raw data which they employ are trustworthy and neutral with respect to the topic.

• Second, the findings occur from an enormous database: The entire U.S. population. (132 million in 1940; 247 million in 1990). It is hard to imagine a larger prospective study than one which "enrolls" the entire U.S. population in its nine dose-cohorts (Chapter 22, Part 4). All other things being equal, the larger the database, the more reliable are the results.

• Third, the findings occur without dependence on permanently uncertain dose-estimates in medical rads and without dependence on unsettled estimates of cancer-risk per medical rad (Part 5b, above). Instead, the *relative* sizes of medical doses, proportional to PhysPop values in the Nine Census Divisions, directly reveal the magnitude of Fractional Causation, by medical radiation, of the death-rates from Cancer and from Ischemic Heart Disease. This aspect of the method itself is a source of enormous credibility for the results.

• Fourth, the findings are not the product of elaborate statistical manuevers and adjustments occurring, beyond realistic review, in a computer. While statistical

operations are an essential part of epidemiology, we regard findings in the biomedical literature as unreliable, if they are the product of layer upon layer of such operations. In this monograph, we have confined ourselves to one layer of statistical operation: The basic linear regression with just one independent variable. (Every step in our findings --- from the raw data to the estimated values of Fractional Causation by medical radiation --- has been presented in the open.)

- Fifth, the mid-century dose-responses between PhysPop and the MortRates for Cancer and for Ischemic Heart Disease are extremely strong. There is nothing marginal about the findings. They are almost spectacular in their strength. Even without linear regression, it would be clear from Figures 1-A and 1-B that the nine real-world observations (the boxy symbols) cluster very closely around a straight and upward line. The nearly perfect correlations provide a solid foundation for confidence in the resulting estimates of Fractional Causation by medical radiation, both for Cancer and for Ischemic Heart Disease.

- Sixth, MortRates from diseases in *general* very definitely do not share a strong positive correlation with PhysPop values. On the contrary. PhysPop discriminates among diseases. Figure 1-C displays the significant *negative* correlation between PhysPop and all NonCancer NonIHD Causes of Death at mid-century --- and the negative correlation persists through subsequent decades (Chapter 25, Box 1).

Box 2 summarizes the findings for specific as well as combined NonCancer NonIHD Causes of Death, and contrasts them with the findings for All-Cancers, specific Cancers, and IHD.

A mountain of powerful evidence is summarized on that single page. The real-world observations clearly show that Cancer and Ischemic Heart Disease belong together, and not with the other diseases, with respect to PhysPop. These observations "demand" an explanation, which is supplied by the proportionality between PhysPop and average accumulated per capita dose from medical radiation.

Figure 1-A has a ready explanation, based on two undisputed facts: **1)** Physicians cause exposure to medical radiation, and **2)** Radiation is a proven cause of Cancer. Figure 1-B also has an explanation which is tied to real-world evidence: **1)** Physicians cause exposure to medical radiation; **2)** Radiation is a proven cause of mutations of virtually every sort; and **3)** Some evidence exists, prior to this monograph, that acquired mutations *are* co-actors in atherogenesis (Chapter 44, Parts 8 and 9). In contrast to the evidence-based explanations above, various speculations are possible (Chapter 68). For example, perhaps physicians do something additional (besides causing exposure to radiation) which causes both Cancer and Ischemic Heart Disease. If that speculation seems credible, then clearly the National Institutes of Health should give top priority to *identifying* what the physicians do.

- Seventh, the conclusion, that medical radiation is a major cause of both fatal Cancer and fatal Ischemic Heart Disease, very reasonably explains the tight positive

correlations between PhysPop and the MortRates for Cancer and for IHD (and the absence of such correlations for NonCancer NonIHD MortRates), while various alternative proposals fall short (Chapter 68). Moreover, the conclusion does not produce conflicts with well-established facts (Introduction, and Chapters 46 and 67). Indeed, the conclusion helps to explain some of them (Chapter 46).

- Eighth, this monograph --- although employing completely independent data and methods from our 1995/96 monograph about Breast Cancer --- nonetheless produces remarkably similar estimates of the Fractional Causation of recent Breast Cancer rates by medical radiation (Chapter 67, Part 5c).

- **Part 7. Our Unified Model of Atherogenesis, and NonXray Co-Actors in IHD**

As noted above, this monograph's real-world evidence clearly shows that Cancer and Ischemic Heart Disease belong together, and not with the other causes of death, with respect to PhysPop. The positive dose-response between PhysPop and Cancer is certainly not strange. Cancer is the single cause of *death* already well-proven (prior to this monograph) to be inducible by ionizing radiation --- and average population exposure to ionizing radiation from medical procedures is approximately proportional to PhysPop.

The surprise is our unambiguous finding of a tight positive correlation between PhysPop and IHD MortRates, a result which indicates strongly that Ischemic Heart Disease also is inducible by medical radiation. With respect to "surprise," a reminder is appropriate: The kinds of damage to the heart and its vessels, observed from very high-dose radiation and reported for decades, seldom resemble the lesions of IHD --- details in Appendix-J.

Our monograph is essentially the first, large prospective study on induction of fatal Ischemic Heart Disease by medical radiation. The results are stunning in their strength. Such strong dose-response relationships do not occur by accident.

7a. Earl Benditt's Work on Monoclonality in Atherosclerotic Plaques

---

We might be less surprised, by the strong positive dose-response between medical radiation and IHD MortRates, if we (and others) had paid more attention to a different type of evidence, available since 1973. We mean evidence supporting a role for mutagens in atherosclerosis. Such evidence came into existence at the University of Washington School of Medicine, Department of Pathology, when Earl Benditt and colleagues found evidence of monoclonality in atherosclerotic plaques in 1973 --- findings which have been replicated several times (Chapter 44, Parts 8 + 9). The fact, that ionizing radiation is a uniquely potent mutagen, provides the foundation for the second part of Hypothesis-2 --- our Unified Model of Atherogenesis (Part 7c, below).

7b. A Reality-Check, for Consistency in Our Findings

Our dose-response evidence, that medical radiation is an important cause of both Cancer and Ischemic Heart Disease, elicits a "prediction." The MortRates for the two diseases should show a persistent positive correlation with each *other*, by Census Divisions, over time --- and should simultaneously show a distinctly *different* relationship with MortRates for NonCancer NonIHD Causes of Death, which are *not* inducible by ionizing radiation. The expectation is well met, as we show in Appendix-N.

7c. Our Unified Model of Atherogenesis and Acute IHD Events

Our Unified Model of Atherogenesis and Acute IHD Events (Chapter 45) combines the evidence in this book, that medical radiation has an important causal role in mortality from Ischemic Heart Disease, with the abundant evidence elsewhere that certain lipoproteins in the bloodstream also have an important causal role in mortality from Ischemic Heart Disease (Chapter 44, Parts 3,4,5,6,7).

Our view (shared by many others) is that the plasma lipoproteins have no physiologic function in the intimal layer of the coronary arteries, and that under normal circumstances, their rate of entry and exit from the intimal layer is in balance. We propose that what disrupts this lifelong egress of lipoproteins from the intima --- with the disruption occurring only at specific locations --- are mutations acquired from medical radiation and from other mutagens.

In our Unified Model, some mutations acquired by smooth muscle cells render such cells dysfunctional *and* give such cells a proliferative advantage --- so that they gradually replace competent smooth muscle cells at a localized patch of artery (a mini-tumor). And this patch of cells, unable to process lipoproteins correctly, becomes the site of chronic inflammation, resulting in construction of an atherosclerotic plaque --- whose fibrous cap is sometimes too fragile to contain the highly thrombogenic lipid-core within the plaque. The Unified Model is described in more detail in Chapter 45. Then Chapter 46 describes how the model helps to explain, or is consistent with, established observations --- including the existence of many additional co-actors in the causation of mortality from Ischemic Heart Disease.

● Part 8. A Personal Word: The Xray Deserves Its Honored Place in Health

The finding, that radiation from medical procedures is a major cause of both Cancer and Ischemic Heart Disease, does *not* argue against the use of xrays, CT scans, fluoroscopy, and radioisotopes in diagnostic and interventional radiology. Such uses also

make very *positive* contributions to health. We deeply respect those contributions, and the men and women who achieve them.

This author is most definitely not "anti-xray" or "radio-phobic." As a graduate student in physical chemistry, I worked very intimately with radiation, in the quest for the first three atomic-bombs. Subsequently, in medical school, I considered becoming a radiologist. In the late 1940s, I did nuclear medicine with patients having a variety of hematological disorders. In the 1960s, I did chemical elemental analysis of human blood by xray spectroscopy. In the early 1970s, our group at the Livermore National Laboratory induced genomic instability in human cells with gamma rays.

In short, I fully appreciate the benefits and insights (in medicine and other fields) which ionizing radiation makes possible.

But no one *honors* the xray by treating it casually or by failing to acknowledge that it is a uniquely potent mutagen. One honors the xray by taking it seriously. While doses from diagnostic and interventional radiology are very low *relative to doses used for cancer therapy*, diagnostic and interventional xray doses today are far from negligible (some examples in Chapter 2, Part 7e). The widely used CT scans, and the common diagnostic examinations which use fluoroscopy, and interventional fluoroscopy (e.g., during surgery), deliver some of the largest nontherapeutic doses of xrays. In 1993, the United Nations Scientific Committee on the Effects of Atomic Radiation warned, appropriately, in its Annual Report:

"Although the doses from diagnostic xray examinations are generally relatively low, the magni- tude of the practice makes for a significant radiological impact" (UNSCEAR 1993, p.228/40). In the USA until about 1970, fetal irradiation occurred during ~ 1 pregnancy per 14 Chapter 2, Part 2d).

• Part 9. Every Benefit of Medical Radiation: Same Procedures, Lower Dose-Levels

The fact that ionizing radiation is a uniquely potent mutagen, and the finding that radiation from medical procedures is a major cause of both Cancer and Ischemic Heart Disease, clearly indicate that it would be appropriate in medicine to treat dosage of ionizing radiation at least as carefully as we treat dosage from potent medications. In the medical professions, we do not administer unmeasured doses of powerful pharmaceuticals, and we do not take a casual view of a 5-fold, 10-fold, even 20-fold elevation in dosage of such medications.

By contrast, in both the past and the present, unmeasured doses of xrays are the rule --- not the exception (Chapter 2, Parts 2, 3a, and 3e). When sampling has been done, in which actual measurements are taken, dosage has been found to vary from one facility to another by many-fold, for the same procedure for patients of the same size. The reason for large variation is obvious from the list of numerous proven ways to reduce dosage

(Box 3 at the end of this chapter). Facilities which apply all the measures can readily achieve average doses more than 5-fold lower than facilities which apply very few measures.

Certain Spinal Xrays: A Dramatic Demonstration

The potential for dose-reduction may far exceed 5-fold for some common xray exams. This has already been demonstrated for the spinal xrays employed to monitor progress in treating idiopathic adolescent scoliosis, a lateral curvature of the spine. An estimated 5% of American children, or more, have this disorder. In a most responsible way, Dr. Joel Gray and co-workers at the Mayo Clinic developed radiologic techniques for scoliosis monitoring which can reduce measured xray dose to various organs as follows (Gray 1983 in *J. of Bone & Joint Surgery* 65-A: 5-12):

- Abdominal exposure: 8-fold reduction.

- Thyroid exposure: 20-fold reduction (with a back to front radiograph), and 100-fold reduction (with a lateral radiograph).

- Breasts: 69-fold reduction (with a back to front radiograph), and 55-fold reduction (with a lateral radiograph).

They report, "These reductions in exposure were obtained without significant loss in the quality of the radiographs and in most instances, with an improvement in the overall quality of the radiograph due to the more uniform exposure.

9a. Dose-Measurement: Low Cost and High Importance

Incorporated in Box 3's list, under the term "Quality Assurance," is measurement of dose-levels. Only frequent measurements can provide the feedback required to make continual dose reductions --- and also to prevent continual dose increments. The combination of frequent measurements, with an enhanced recognition that each xray photon matters, can achieve a very great deal all by themselves. Nearly everyone takes pride in doing better and better. The evidence, that a series of small improvements can amount to a big difference in result, is abundant elsewhere in medicine and pharmacology.

Fortunately, it is extremely easy to measure entrance-doses during a radiation procedure. One just presses on a small self-adhesive patch called a TLD (thermo-luminescent dosimeter), which does not interfere at all with the procedure. Moreover, the cost for a TLD, including its subsequent "reading," is just a few dollars.

We note that no major equipment purchases are required either to achieve the benefits of quality control (an estimated 2-fold reduction in average dose-level in

radiography, Box 3) or to achieve better operator-techniques in fluoroscopy (an estimated 2-to-10-fold reduction in dose, Box 3). Cost is not a big obstacle to taking dose-reduction seriously. The big obstacle is the recognition that it really matters.

Mammography: A Model of Success

The importance of dose-reduction for the mammographic examination has been recognized, and such doses have been reduced by about a factor of *ten* in recent years. "Where there is a will, there is a way." In certified mammography centers today, doses are routinely verified periodically, and measurements provide the feedback required, in order to achieve constant dose-reduction instead of upward creep.

9b. The Benefits of Every Procedure --- with Far Less Dose

Dose-reduction can be a truly safe measure. It is clear that average per patient doses from diagnostic and interventional radiology could be reduced by a great deal without reducing the medical *benefits* of the procedures in any way. We can summarize from Box 3:

- Radiography: Quality-assurance (dose-reduction by an average factor of 2), beam-collimation (by a factor up to 3), rare-earth screens (by a factor of 2 to 4), rare-earth filtration (by a factor of 2 to 4), use of carbon-fibre materials (by a factor of 2), gonadal shielding (by a factor of 2 to 10 for the gonads).

- Digital Radiography: Decrease in contrast resolution, when such resolution is not needed (dose-reduction by a factor of 2 to 3), use of a pulsed system (by a factor of 2).

- Fluoroscopy: Changes in the operator's technique (dose-reduction by a factor of 2 to 10), variable aperture iris on TV camera (by a factor of 3), high and low dose-switching (by a factor of 1.5), acoustic signal related to dose-rate (by a factor of 1.3), use of a 105mm camera (by a factor of 4 to 5). Additional methods not specified in the list: Use of a circular beam-collimator when the image-receiver is circular (Chapter 2, Part 3d), adoption of "freeze-frame" or "last-image-hold capability, and restraint in recording fluoroscopic images (Chapter 2, Part 3e).

- Part 10. An Immense Opportunity: All Benefit, No Risk

The evidence in this monograph, on an age-adjusted basis, is that most fatal cases of Cancer and Ischemic Heart Disease would not happen as they do, in the absence of xray-induced mutations. We look forward to responses to our findings.

We have also presented findings, from outside sources, that average per patient radiation doses from diagnostic and interventional radiology could be reduced by a great deal, without reducing the medical *benefits* of the procedures in any way. The same procedures can be done at substantially lower dose-levels (Part 9, above).

10a. Does the Public Need a Denial, "For Its Own Good" ?

One type of response to this monograph may be that the findings need to be denied immediately (without examination), lest the public refuse to accept the benefits of xray procedures.

This type of response, insulting to the public, would not be consistent with reality. In reality, the public accepts a host of dangerous medications and procedures, in exchange for their demonstrable benefits --- sometimes, for undemonstrated benefits. Very few people will forego the obvious benefits from diagnostic and interventional radiology, just because such procedures confer a risk of subsequent Cancer and IHD. The only change will probably be that people will demand that the same degree of care, now exercised with respect to dosage of potent medications, be exercised with respect to dosage of radiation from each procedure. They will want to avoid a dose-level of, say, ten rads --- if the same information could be acquired with one rad. They do not deserve "one useful part of information, and nine unnecessary parts of extra risk of Cancer and IHD." Patients will want more measurements, and fewer assumptions, about the doses delivered. But they will *not* reject the procedures themselves.

10b. Do Nothing Until the Work Is Independently Confirmed?

A second response, to the evidence in this monograph, may be that doses in diagnostic and interventional radiology should not be reduced until our work is independently confirmed.

The concept, "independent confirmation," is meaningless without equally credible, but independent, sets of data. If one is seriously interested in new prevention-measures for Cancer and Ischemic Heart Disease, then one really needs to ask: Will it ever be possible to conduct a *more* reliable evaluation --- of Fractional Causation, by medical radiation, of Cancer and IHD --- than the evaluation provided by the databases we used in this book? We doubt it, for the reasons described in Part 5b above. As for replication of our results from the *same* databases (PhysPops and age-adjusted MortRates, by Census Divisions), that could be promptly achieved.

It is worth emphasis that validity of the first part of Hypothesis-2 (medical radiation is an important cause of IHD) does not depend on the validity of the second part of Hypothesis-2 (our Unified Model of Atherogenesis --- Part 7c, above). The Unified

Model will definitely need independent testing. This might consume decades. Meanwhile, why deny patients the benefits of eliminating uselessly high doses of medical radiation?

10c. The "Advocacy Issue" and the Hippocratic Oath

It is very often said that, if scientists advocate any action based on their findings, they undermine their scientific credibility. If such scientists stand to benefit financially from the actions they advocate, such suspicion occurs naturally. But even in such circumstances, if their work is presented in a way which anyone can replicate, it should be impossible for their advocacy to diminish the scientific credibility of their work.

Our findings are not encumbered either by financial interests or by any barriers to replication. We have high confidence in the scientific credibility of the results, for the reasons presented in Part 6. The findings stand on their own, whether or not we advocate any action.

I have spent a lifetime studying the causes of Ischemic Heart Disease, and then Cancer, in order to help prevent such diseases. So it would be pure hypocrisy for me to feign a lack of interest in any preventive *action* which would be both safe and benign. And when sources, completely independent from me, set forth their findings that such action is readily feasible --- namely, significant dose-reduction in diagnostic and interventional radiology --- it would be worse than silly for me to pretend that I have no idea what action should occur. After all, as a physician, I took the Hippocratic Oath: "First, do no harm." Silence would contribute to the harm of millions of people.

10d. Why Wait? What Is the Purpose?

Although it is commonly assumed that radiation doses are "negligible" from modern medical procedures, the assumption is definitely mistaken. In reality, estimated dose-levels today from some common xray procedures are far from negligible, as illustrated in Chapter 2, Part 7e. Both the downward and upward forces upon post-1960 dose-levels are discussed in Chapter 2, Part 3. The net result is unquantifiable.

An estimated 35% to 50% of some higher-dose diagnostic procedures are currently received by patients below age 45 (details in Chapter 2, Part 3f) --- when the carcinogenic impact per dose-unit is probably stronger than it is after age 65 or so.

In diagnostic and interventional radiology, dose-reduction would be wholly safe, quite inexpensive, and guaranteed beneficial --- because induction of Cancer by ionizing radiation has been an established fact for decades. (The contribution of radiation-induced mutations, to all types of inherited afflictions, is beyond the scope of this book.) It seems

to us that anyone who contemplates Part 9 of this chapter, on known methods of dose-reduction in radiology, has to ask: Why wait? What is the purpose of waiting, when only benefit, and no harm, can come from reducing uselessly high doses as rapidly as possible?

10e. A Mountain of Solid Evidence That Each Dose Matters

The fact, that xray doses are so seldom measured, reflects the false assumption that such doses do not matter. This monograph has presented a mountain of solid evidence that they do matter, enormously. And each bit of additional dose matters, because any xray photon may be the one which sets in motion the high-speed high-energy electron which causes a carcinogenic or atherogenic mutation. Such mutations rarely disappear. The higher their accumulated number in a population, the higher will be the population's mortality-rates from radiation-induced Cancer and Ischemic Heart Disease.

The xray is a proven mutagen and a proven cause of Cancer, and the evidence in this book strongly indicates that it is also a very *important* cause of Cancer and a very important atherogen. From the existing evidence, it is clear that average per patient doses from diagnostic and interventional radiology could be reduced by a great deal without reducing the medical benefits of the procedures in any way (Part 9, above): Same procedures, at lower doses. Unless effective measures are taken, to eliminate uselessly high dosage, medical radiation will continue in the next century to be a leading cause of Cancer and Ischemic Heart Disease in the United States, and will become a leading cause in the "developing" world, too.

10f. A Prudent Position from Which No One Loses, Everyone Gains

---

Whether diseases are common or rare, a prime reason for studying their causation is *prevention*. Cancer and Ischemic Heart Disease, combined, accounted for 45% of all deaths in the USA during 1993 (Chapter 39, Part 4).

If we in the medical professions take the position, that we should *not* press for reducing doses from medical radiation until every question has been perfectly answered, then we can never un-do the harm inflicted during the waiting period, upon tens of millions of patients every year. By contrast, if we take the prudent position that dose-reduction should become a high priority without delay (and if humans do not start exposing themselves to some *other* potent mutagen), the evidence in this monograph indicates that we will prevent much of the future mortality from Cancer and Ischemic Heart Disease, without causing any adverse effects on health. No one loses, everyone gains.

>>>>>>>>>>

Box 1 of Chapter 1

Final Summary for Fractional Causation, by Medical Radiation, of Cancer and Ischemic Heart Disease.

☛ The range of values below represents the earliest year and the most recent year named in Column A. Values for the intervening decades are provided in the listed chapters (e.g., Ch49). The values below come from the "A" or "AA" tables in Chapters 49 - 65. "Diff-Ca" = All Cancers Except Respiratory. AllExcGen" = All except Genital Cancers. Mortality rates in Column B are age-adjusted to the reference year 1940.

Col.A: M = Male. F = Fem.	Col.B: Nat'l Age-Adjusted Mortality Rate	Col.C: Col.E: X-Coefficient XCoef/Std.Error	Col.D: Col.F: Frac. Causation Ratio of by Medical Radn	R-squared
Ch49, 1940-88, Big net rise.				
All-Cancer: M	115.0 --> 162.7	0.93 0.76 --> 0.75	90% --> 74% 11.6 --> 10.1	0.95 -->
Ch50, 1940-88, Net decline.				
All-Cancer: F	126.1 --> 111.3	0.87 0.53 --> 0.34	58% --> 50% 6.6 --> 6.9	0.86 -->
Ch51, 1940-88, Enormous rise.				
Resp'y Ca: M	11.0 --> 59.7	0.78 0.12 --> 0.27	~100% --> 74% 6.8 --> 5.0	0.87 -->
Ch52, 1940-88, Enormous rise.				
Resp'y Ca: F	3.3 --> 24.5	0.90 0.02 --> 0.13	97% --> 83% 13.4 --> 7.8	0.96 -->

|Ch53, 1940-88, Approx. flat. | |

|Diff-Ca: M 104.0 --> 103.0 | 84% --> 72% | 0.93 -->
0.92 0.64 --> 0.46 10.0 --> 8.7 |

| | | |

|Ch54, 1940-88, Big decline. | |

|Diff-Ca: F 122.8 --> 86.8 | 57% --> 48% | 0.85 -->
0.84 0.50 --> 0.25 6.3 --> 6.1 |

| | | |

|Ch55, 1940-90, Flat. | |

|Breast-Ca: F 23.3 --> 23.1 | ~100% --> 83% | 0.92 -->
0.89 0.19 --> 0.12 8.7 --> 6.7 |

| | | |

|Ch56, 1940-80, Flat. | |

|AllExcGen: F 94.0 --> 94.8 | 75% --> 66% | 0.87 -->
0.93 0.51 --> 0.43 6.8 --> 9.6 |

| | | |

|Ch57, 1940-88, Big decline. | |

|Digest-Ca: M 60.4 --> 38.8 | 97% --> 82% | 0.91 -->
0.87 0.43 --> 0.20 8.3 --> 7.0 |

| | | |

|Ch58, 1940-88, Big decline. | |

|Digest-Ca: F 50.1 --> 23.5 | 80% --> 68% | 0.76 -->
0.86 0.29 --> 0.10 4.6 --> 6.7 |

| | | |

|Ch59, 1940-80, Approx. flat. | |

|Urinary-Ca: M 7.4 --> 8.2 | ~100% --> 83% | 0.92 -->
0.61 0.08 --> 0.05 9.0 --> 3.3 |

| | | |

|Ch60, 1940-80, Decline. | |

|Urinary-Ca: F 4.0 --> 3.0 | 86% --> 78% | 0.94 -->
0.91 0.02 --> 0.02 10.4 --> 8.5 |

| | | |

|Ch61, 1940-90, Some rise. | |

|Genital-Ca: M 15.2 --> 16.9 | 79% --> 47% | 0.77 -->
0.79 0.09 --> 0.05 4.9 --> 5.2 |

| | | |

|Ch63, 1940-80, Approx. flat. | |

|Buccal-Phar: M 5.1 --> 4.6 0.73 0.04 --> 0.03		~100% --> 81% 4.3 --> 4.4		0.72 -->
|Ch64, 1950-93, Enormous fall.				
|IHD: M 256.4 --> 131.0 0.73 1.49 --> 0.50		79% --> 63% 11.2 --> 4.3		0.95 -->
|Ch65, 1950-93, Enormous fall.				
|IHD: F 126.5 --> 64.7 0.68 0.90 --> 0.30		97% --> 78% 6.8 --> 3.9		0.87 -->

Box 2 of Chapter 1
Comparison of Results: All Causes, NonCancers, NonCancers NonIHD, Cancers, IHD.

All the comparisons below are based on the relationship between 1940 PhysPops and 1940 MortRates, except for 3 pairs of 1950 MortRates. "Sig." means statistically significant. When XCoef/SE = 2, then P = roughly 0.05. See Chap.38.

	Relationship, MortRates w. PhysPops by CensusDiv.		R-Squared	X-Coef.	XCoef/Std Err
|Ch23: All Causes Combined	Inverse, but not sig.	Male	0.1299	Neg.	-1.02
|	Inverse, and marginal.	Fem	0.2823	Neg.	-1.66
|Ch24: All Noncancer Combined	Inverse, and marginal.	Male	0.2841	Neg.	-1.67
|	Inverse, and significant.	Fem	0.4362	Neg.	-2.33
|Ch25: All Noncancer NonIHD	Inverse, and very sig.	Male	0.7933	Neg.	-5.18
|	Inverse, and very sig.	Fem	0.7037	Neg.	-4.08
|Ch26: Appendicitis	None.	Male	0.0179	Neg.	-0.36

	Fem	0.0010	Neg.	-0.08
None.				
Ch27: CNS Vascular (Stroke)	Male	0.4000	Neg.	-2.16
Inverse, and significant.				
	Fem	0.2882	Neg.	-1.68
Inverse, and marginal.				
Ch28: Chronic Nephritis	Male	0.4561	Neg.	-2.42
Inverse, and significant.				
	Fem	0.2687	Neg.	-1.60
Inverse, and marginal.				
Ch29: Diabetes Mellitus	Male	0.6435	Pos.	3.55
Positive, and quite sig.*				
	Fem	0.6005	Pos.	3.24
Positive, and quite sig.*				
Ch30: Hypertensive Disease	Male	0.3564	Neg.	-1.97
Inverse, and significant.				
	Fem	0.2056	Neg.	-1.35
Inverse, and very marginal.				
Ch31: Influenza and Pneumonia	Male	0.8344	Neg.	-5.94
Inverse, and highly sig.				
	Fem	0.8849	Neg.	-7.34
Inverse, and highly sig.				
Ch32: Fatal Motor Vehicle Accid.	Male	0.0195	Neg.	-0.37
None.				
	Fem	0.0003	Neg.	-0.04
None.				
Ch33: Other Fatal Accidents	Male	0.0901	Neg.	-0.83
None.				
	Fem	0.4440	Neg.	-2.36
Inverse, and significant.				
Ch34: Rheum.Fever/Rheum.Heart	Male	0.0021	Pos.	0.12
None.				
	Fem	0.0550	Pos.	0.64
None.				
Ch35: Syphilis and Sequelae	Male	0.3278	Neg.	-1.85
Inverse, and marginal.				
	Fem	--	--	--
--				
Ch36: Tuberculosis, All Forms	Male	0.2067	Neg.	-1.35
Inverse, and very marginal.				
	Fem	0.6381	Neg.	-3.51
Inverse, and quite sig.				
Ch37: Ulcer: Stomach, Duoden.	Male	0.3864	Pos.	2.10
Positive, and significant.**				
Ch6+7: All Cancers Combined	Male	0.9508	Pos.	11.63
Positive, and highly sig.				
	Fem	0.8608	Pos.	6.58
Positive, and highly sig.				
Ch8: Breast Cancer	Male	--	--	--
--				
	Fem	0.9153	Pos.	8.70
Positive, and highly sig.				
Ch9+10: Digestive-Syst. Cancers	Male	0.9078	Pos.	8.30
Positive, and highly sig.				

	Fem	0.7550	Pos.	4.64
	Positive, and very sig.			
Ch11+12: Urinary-Syst. Cancers	Male	0.9208	Pos.	9.02
	Positive, and highly sig.			
	Fem	0.9395	Pos.	10.43
	Positive, and highly sig.			
Ch13+14: Genital Cancers	Male	0.7182	Pos.	4.22
	Positive, and very sig.			
	Fem	0.0683	Pos.	0.72
	None.			
Ch15: Buccal & Pharynx Cancers	Male	0.7234	Pos.	4.28
	Positive, and very sig.			
	Fem	--	--	--
	--			
Ch16+17: Respiratory-Syst. Canc.	Male	0.8673	Pos.	6.76
	Positive, and highly sig.			
	Fem	0.9625	Pos.	13.40
	Positive, and highly sig.			
Ch40+41: Ischemic Heart Disease	Male	0.9475	Pos.	11.24
	Positive, and highly sig.			
	Fem	0.8337	Pos.	5.92
	Positive, and highly sig.			

* Diabetes Mellitus (DM): After the rules changed in 1949 for reporting the underlying cause of death in diabetics, DM MortRates abruptly fell in half and our R-sq. values dropped abruptly to 0.11 and 0.20 (Chap.29). The significant R-sq. values in 1940 very probably denote a correlation between PhysPop and xray-induced deaths during 1940 from Ischemic Heart Disease in people having diabetes (Chapters 29, 40, 41).

** Ulcer Deaths: The positive correlation between Ulcer Deaths in 1940 and PhysPop might be due to erroneous reporting in 1940 of deaths, truly from Stomach Cancer, as deaths from Stomach Ulcers.

Box 3 of Chapter 1
Procedures to Reduce Collective Dose Equivalent in Diagnostic Xray Examinations.

● - This box, with its title above and footnotes below, is borrowed without alteration from the 1988 UNSCEAR Report (Annex C: Exposures from Medical Uses of Radiation, Table 23 at p.282). UNSCEAR = United Nations Scientific Com'tee on the Effects of Atomic Radiation. An almost identical table appears also in the 1989 NCRP Report (Report No. 100, Table 3.21, at p.37). NCRP = National Council on Radiation Protection (USA). Details for UNSCEAR 1988, NCRP 1989, and the references cited below, are in the Reference List of this monograph.

Area	Procedure	Entrance-Dose Reduction-Factor	Reference
All Types	Elimination of medically unnecessary procedures	1.2	Cohen 1985.
	Introduction of Quality Assurance programme (general)	2*	Cohen 1985.
Radiography	Decrease in rejected films through Quality Assurance programme	1.1	Gallini 1985. Properzio 1985.
	Increase of peak kilovoltage	1.5	Wiatrowski 1983.
	Beam collimation	1 to 3	Johnson 1986. Morris 1984.
	Use of rare-earth screens	2 to 4	Kuhn 1985. Newlin 1978. Segal 1982. Wagner 1976.
	Increase of filtration	1.7	Kuhn 1985. Montanara 1986. Wiatrowski 1983.
	Rare-earth filtration	2 to 4	Tyndall 1987.

	Change from photofluorography to chest radiography	4 to 10	Jankowski 1984. Mustafa 1985. Neamiro 1983.
	Use of carbon fibre materials	2.0	Huda 1984.
	Replacement of CaW04 screens with spot film technique	4.0	Kuhn 1985.
	Entrance exposure guidelines	1.5	Laws 1980.
	Gonadal shielding	2 to 10 **	Poretti 1985.
Pelvimetry	Use of CT topogram	5 to 10	Stanton 1983.
Fluoroscopy	Acoustic signal related to dose rate	1.3	Anderson 1985.
	Use of 105 mm camera	4 to 5	Rowley 1987.
	Radiologist technique	2 to 10	Rowley 1987.
	Variable aperture iris on TV camera	3.0	Leibovic 1983.
	High and low dose switching	1.5	Leibovic 1983.
Digital radiography	Decrease in contrast resolution	2 to 3	Rimkus 1984.
	Use of pulsed system	2	Rimkus 1984.

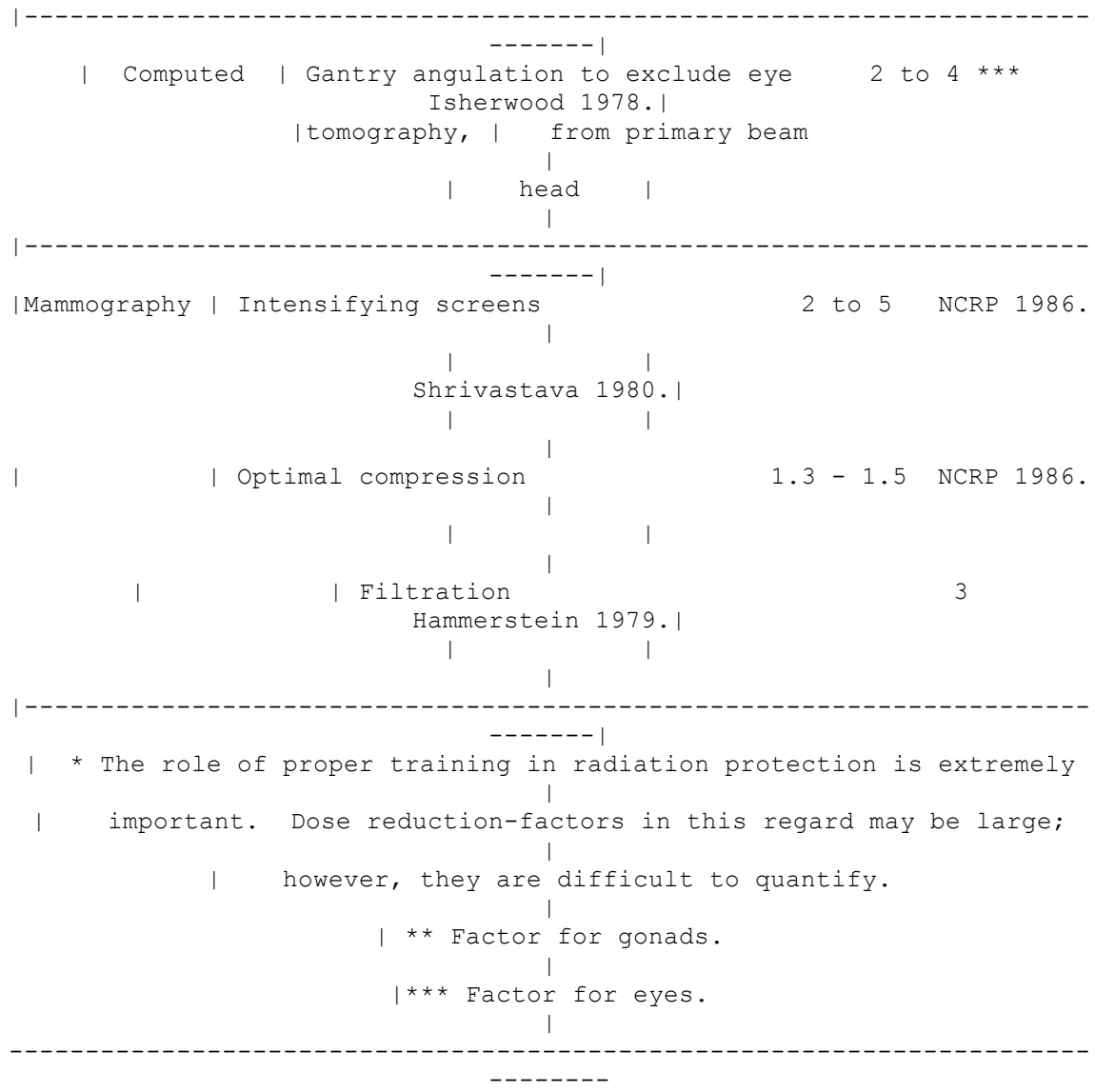
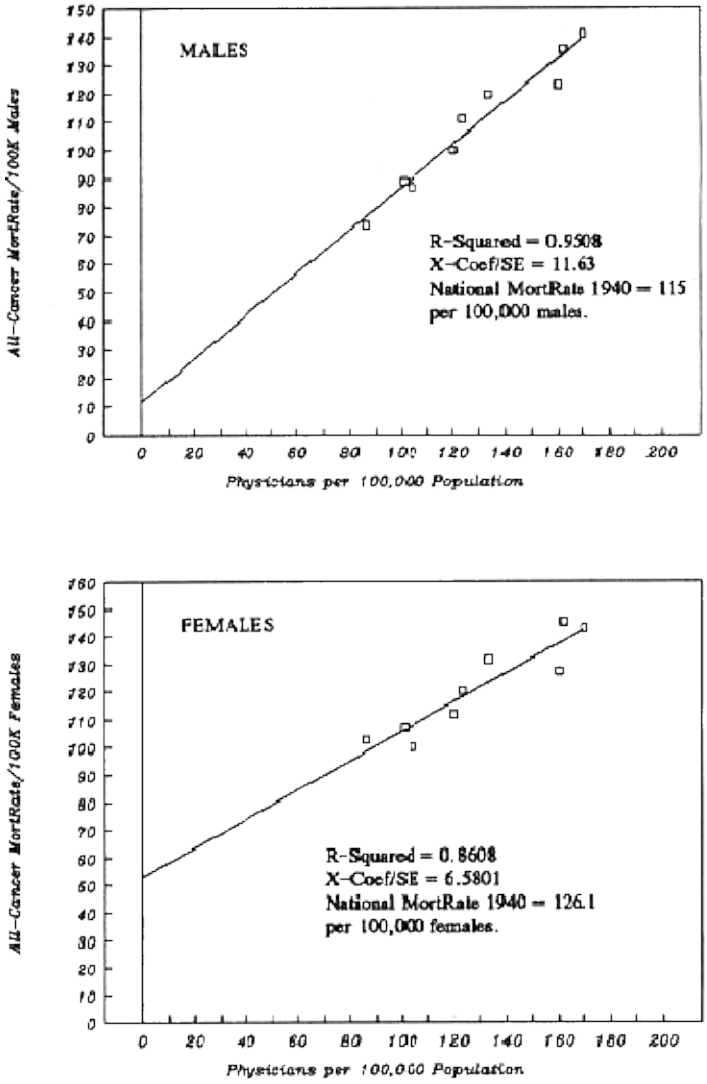


Figure 1-A.
All-Cancers-Combined: Dose-Response between PhysPop and MortRates.

Please refer to Parts 5a-5d of this chapter. In each graph, the line of best fit results from regressing the 1940 All-Cancer Mortality Rates (male, female) on the 1940 PhysPop values. PhysPop (physicians per 100,000 population) is a surrogate for accumulated dose from medical radiation. The nine boxy symbols denote the observed values in the Nine

Census Divisions. Full details are in Chapters 6 and 7.

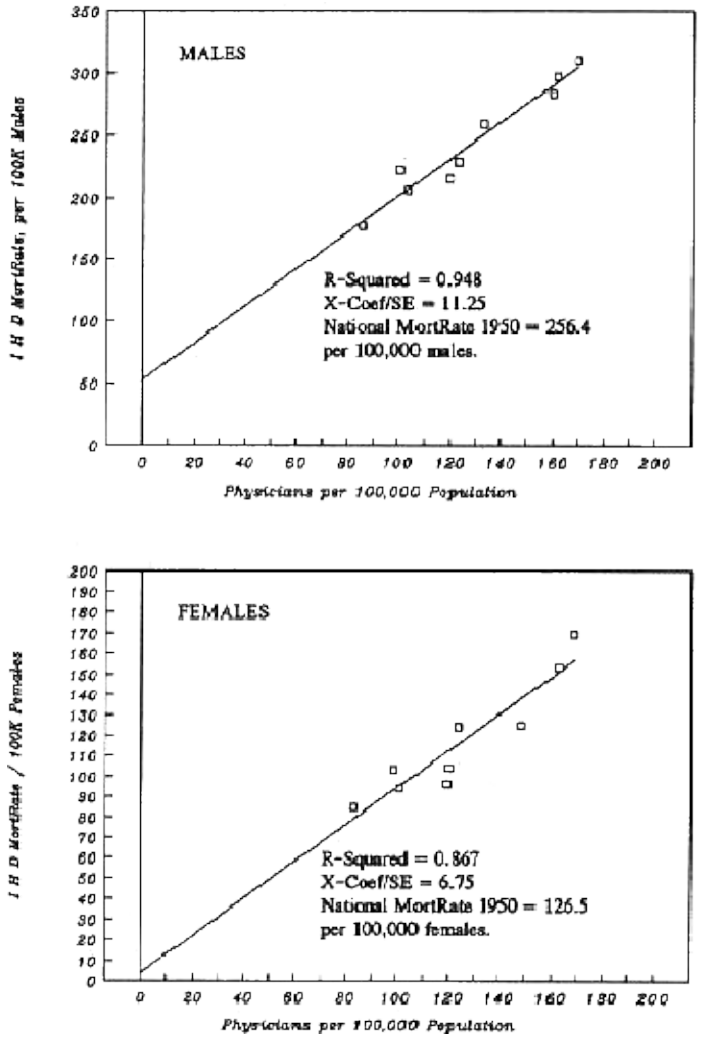


Related text = Paris 5a - 5d.

Figure 1-B.
Ischemic Heart Disease: Dose-Response between PhysPop and MortRates.

Please refer to Part 5f of this chapter. In the upper graph, the line of best fit results from regressing the age-adjusted male 1950 Mortality Rates from Ischemic Heart Disease on the 1940 PhysPop values. PhysPop (physicians per 100,000 population) is a surrogate for

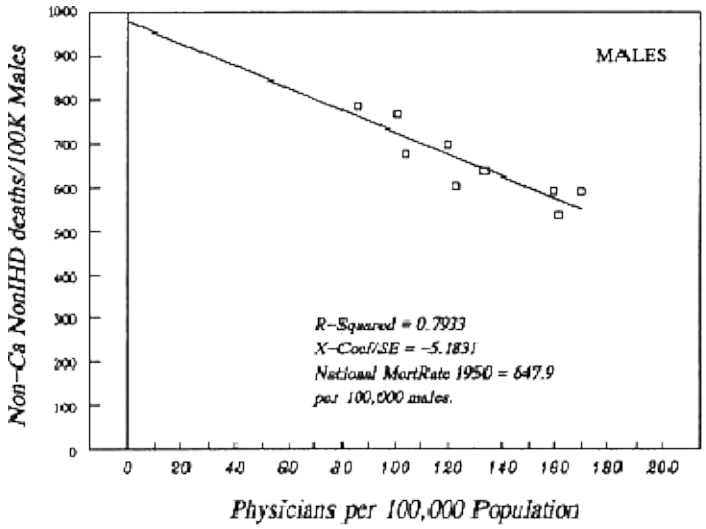
accumulated dose from medical radiation. The nine boxy symbols denote the observed values in the Nine Census Divisions. In the lower graph (females), we show 1950 PhysPop values. When female 1950 age-adjusted IHD MortRates are paired with 1950 PhysPops, R-squared = 0.8669; with 1940 PhysPops, R-squared = 0.8337 --- a trivial difference. Full details are in Chapters 40 and 41.

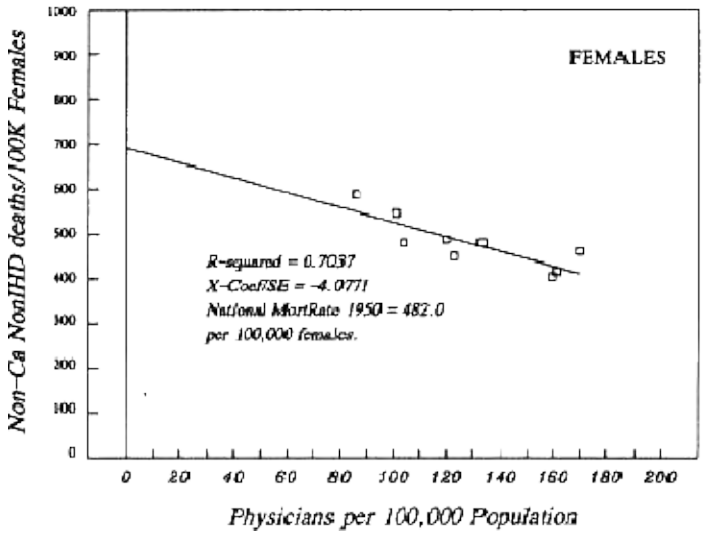


Related text = Part 5f.

Figure 1-C.
NonCancer NonIHD Deaths: Dose-Response between PhysPop and MortRates.

Please refer to Part 5f of this chapter. In each graph, the line of best fit results from regressing the 1950 age-adjusted NonCancer NonIHD MortRates (male, female) on the 1940 PhysPop values. PhysPop (physicians per 100,000 population) is a surrogate for accumulated dose from medical radiation. The nine boxy symbols denote the observed values in the Nine Census Divisions. The dose-response is inverse (negative). Full details are in Chapter 25.





Related text = Part 5f.

Some Comments about Dr. John Gofman's Earlier Work and Books.

- In 1972, Dr. Gofman shared the 1972 Stouffer Prize, one of the top awards for research in combatting arteriosclerosis. The 1972 Prize Committee was chaired by Professor Ulf S. von Euler, M.D., former chairman of the Nobel Prize Committee for Physiology and Medicine. The Committee's citation:

"The 1972 Stouffer Prize is awarded to Dr. John W. Gofman for pione ering work on the isolation, characterization and measurement of plasma lipoproteins, and on their relationship to arteriosclerosis. His methods and concepts have profoundly stimulated and influenced further research on the cause, treatment, and prevention of arteriosclerosis."

Radiation and Human Health. 1981. ISBN 0-87156-275-8.

- From the *Journal of the American Medical Assn*., March 19, 1982, p.1637, a review by Victor E. Archer, M.D.: "This remarkable and important book enables any intelligent person with a high school education to understand the complexities involved in assessing the risks to man from low levels of ionizing radiation. Gofman not only demonstrates his mastery of this complex subject but carefully explains the basic concepts of epidemiology, genetics, birth defects, carcinogenesis, radiobiology, physics, chemistry and even mathematics, which are necessary to an understanding of the subj ect."

Xrays: Health Effects of Common Exams. 1985. ISBN 0-87156-838.1. E.O'Connor, co-author.

- From the *New England Journal of Medicine*, Feb. 6, 1986, p.393, a review by Maurice M. Greenfield, M.D. (radiologist): "This book is practical and important. It is destined to represent a watershed in the controversial field of low-dose radiobiology and will be of inestimable value to radiologists, other physicians, dentists, and patients."

- From the *American Journal of Roentgenology*, April 1986, p.774, a review by David S. Martin: "From a radiologist's point of view, this book represents a well organized and concise attempt to quantify the cancer risk from diagnostic xray exposures by age, gender, organ, and examination. As such, it is a useful starting point for comparisons."

Radiation-Induced Cancer from Low-Dose Exposure. 1990. ISBN 0-932682-89-8.

- From the *New England Journal of Medicine*, Feb. 14, 1991, p.497, a review by G. Theodore Davis, M.D., and Andre J. Bruwer, M.D. (radiologist) of two books jointly: The 1990 book by Gofman (above) and the 1990 BEIR-5 Report from the National Research Council, National Academy Press: "Both these works agree that previous assessments of the dangers of radiation underestimated the risk, but they reach substantially different conclusions about the magnitude of the risk, especially when the

radiation is at lower doses (below 10 rem) and the doses are delivered slowly ... We strongly recommend both these excellent and timely books for physicians, engineers, and public health officials concerned with radiation, the environment, and public health."

Preventing Breast Cancer. 1995. ISBN 0-932682-96-0 (Second Edition).

- From the *Journal of the American Medical Assn*. "Medical News & Perspectives," August 2, 1995, a two-page feature (pp.367-368) by Andrew A. Skolnick about Gofman's book: "A respected authority on the biological effects of ionizing radiation has just published a book claiming that the vast majority of breast cancers in the United States were caused by ... medical xrays ..." Skolnick quotes from interviews with the author and with critics of the book.

- On August 3, 1995, Channel 3 in Britain telecast a report ("The Xray Effect") featuring the book's findings. The 1995 broadcast included these statements:

"John Gofman is a superb analyst and has always been at the cutting edge of medical science, particularly when it comes to protecting people." - Mortimer Mendelsohn, M.D., Ph.D., then Assoc. Director of the Radiation Effects Research Foundation (the A-Bomb Survivor Study).

"Dr. Gofman is owed a debt of gratitude by the scientific community because he was one of the first people to raise the issue of cancer risks from radiation exposure." - Edward P. Radford, M.D., epidemiologist and Chairman of the 1980 Committee on the Biological Effects of Ionizing Radiation (BEIR-3) of the National Academy of Sciences, National Research Council.

Single copies of the Executive Summary: $5.00 each, includes handling and postage. For a price on multiple copies to a single address, please inquire at Tel: 415-776-8299.

back to RMP | CNR | radiation | rat haus | Index | Search | tree