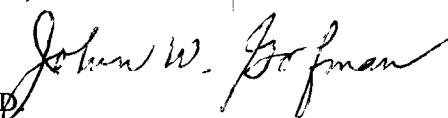## TO:

Docket 01N-0275. Re: 21 CFR 1020.30 - 33.
Dockets Management Branch (HFA-305)
US Food and Drug Administration
5630 Fishers Lane, Room 1061, Rockville MD 20852

FROM:

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WHAT:

**Comments on the Proposed Amendments to Reduce Fluoroscopic X-Ray
Doses to Patients and to Measure Such Doses, under the Federal
Performance Standards for Diagnostic X-Ray Systems.
March 31, 2003.**

    Integral parts of these comments are attachments 1, 2, 3:

    ● Attach-1: Gofman 2002, "What Are the Main Critiques
of the 1999 Study by Gofman..." (5 pages)
    ● Attach-2: Critique by Arthur C. Upton, Nov. 29, 1999.
(One page)
    ● Attach-3: Gofman 1999, "Executive Summary" (32 pages)
of the monograph "Radiation from Medical Procedures in the
Pathogenesis of Cancer and Ischemic Heart Disease:
Dose-Response Studies with Physicians per 100,000 Population."

TABLE OF CONTENTS FOR THESE COMMENTS:

01N-0275

C2

● Part 1. FDA's Goal: Reduce X-Ray Exposure to Patients

● This communication, with its three attachments, is offered in complete support of the U.S. Food and Drug Administration's (FDA) proposed performance standards for new x-ray fluoroscopic systems, under the Code of Federal Regulations 21 CFR 1020.30 to 1020.33.

● Our purpose here is to contribute scientifcally strong evidence that the FDA has greatly underestimated the health benefits of its own proposals (see Parts 4 and 7 below, elaborated in Attachments 1 and 3).

● The goal of the FDA's proposed amendments to the current standards is "to improve the public health by reducing exposure to and the detriment associated with unnecessary ionizing radiation from diagnostic x-ray systems, while assuring the clinical utility of the images ... These proposed amendments will require additional features on newly manufactured x-ray systems that physicians may use to minimize x-ray exposure to patients" (FR, pp.76057-58; please see FR 2002 in our Reference List.)

Main Target: FLUOROSCOPIC X-Ray Systems

● Most of the features apply to fluoroscopic x-ray systems, which use continuous x-ray beams to deliver real-time images to physicians during many common medical/surgical procedures, such as upper GI exams, cardiac catheterization, angiography, angioplasty, urinary/biliary stone removal, certain types of needle-biopsies, placement of catheters, stents, filters, etc.

● Fluoroscopy never irradiates the entire body, but exposes sections of it to x-rays at rates like 1 centi-gray (cGy) up to 20 cGy per minute, with cumulative doses per procedure ranging from less than 1 cGy to over 1,000 cGy (e.g., an estimated 60 cGy per stenosis dilated during angioplasty — NCRP 1989, p.31). The cGy and the rad are identical units of dose.

Some of the Newly Required Features, If Approved

● The required features for new fluoroscopic systems would, if approved, include the capability for last-image-hold ("freeze-frame"), which permits physicians to view and discuss an image during a procedure, without continuing to irradiate the patient. Cost per new system would be about $2,000 (FR, p.76078).

● Very importantly, also required would be display capability to show the operator the dose-rate per minute, the duration of exposure, and the accumulated skin-dose to the patient in "real-time" (during the procedure), and to record such doses. The estimated additional cost per new system is $4,000 (FR, p.76078), whereas addition of such display to a system designed without it is about $10,000 (FR, p.76078).

● Also required would be greater filtration of the x-ray beam (to eliminate many of the x-ray photons which only irradiate the patients but do not contribute to the images), better

collimation (to reduce irradiation of tissue not even within the image), and other common-sense features.

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● Part 2. The Benefit-Cost Estimate by the FDA

● How great will the health benefits be, if these features are approved, according to the FDA?

FDA's Estimate of Annual Benefits and Costs

● Using the customary rate of replacing older fluoroscopic systems by newer ones in the USA, the FDA expects that, within ten years, all such systems will include the required dose-reducing features (if approved).

● The FDA attempted to estimate the health benefits achieved during the first ten years while the new features are being phased in. It estimated the aggregate expected dose-reduction (based on only a few common procedures) during the ten years. Then it applied a value for the estimated dose which causes one fatal cancer. Then it made adjustments to an ANNUAL basis, taking account of gradual phase-in of the new features.

● How many "premature deaths associated with cancer" should be prevented ANNUALLY by that method of estimation? The FDA's median value is 223 such deaths per year (FR, p.76076) --- a very small number by comparison with over a half-million cancer deaths per year in the USA. The annual benefit associated with 223 prevented deaths is estimated at $320 million per year by the FDA (FR, p.76077).

● The FDA's estimate of annual cost, including one-time costs of re-designing equipment distributed over the ten years, is $40 million per year (FR, p.76079).

● This makes the FDA's benefit-cost ratio for the first ten years 8 to 1 in favor of the benefits ($320 / $40).

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● Part 3. Why Is a Federal Mandate Required?

● The FDA asks an important question (FR, p.76072): With such a favorable ratio of benefits over costs, why must a federal mandate be invoked? The FDA's answer: The "market" does not respond to the ratio because the costs accrue to the profession, but the benefits accrue to the patients.

● We believe that the above dynamic does operate, but that it operates only because the medical profession has been taught for decades that the cancer hazard from medical x-rays is negligible. That same message continues to be repeated today, not only by the FDA (Part 2, above), but elsewhere with greater vigor (Part 6, below).

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● Part 4. Gofman Evidence on Benefits from Dose-Reduction

● In great contrast to claims of very low hazards from customary medical x-ray practices (and thus, negligible health benefits from dose-reduction), we have uncovered powerful evidence that customary x-ray practices became and remain one of the necessary causal co-actors in over half of the fatal cases

of cancer AND over half of the fatal cases of ischemic heart disease (coronary artery disease) in the USA (Gofman 1999). The study's method and findings are most succinctly summarized in Attachment-1 (i.e., Parts 4 and 5 of Gofman 2002).

How Do X-rays Cause Coronary Artery Disease?

• Our Unified Model of Atherogenesis and Acute IHD Death (Gofman 1999, Chapters 44, 45, 46) proposes that a lipid-containing arterial plaque arises where atherogenic mutations (acquired after conception) produce a clone of dysfunctional cells (mini-tumors) which do an incomplete job of clearing the lipids out of that patch of dysfunctional arterial tissue and of protecting the arterial lumen from the accumulated thrombogenic lipids within the plaque.

• This model is consistent not only with previously established causal co-actors for IHD, but it also explains why arterial plaques occur only in discrete patches, surrounded by normal tissue. Some supplemental evidence for acquired atherogenic mutations is summarized in Note 1 of Attachment-1 (Gofman 2002).

Peer-Review of the 1999 Gofman Medical Monograph

• The new evidence presented in Gofman 1999 deserves serious consideration, according to Arthur C. Upton, M.D., former Director of the National Cancer Institute, and very active member of all the quasi-official radiation committees (BEIR, UNSCEAR, ICRP, NCRP). Dr. Upton's comment on the Gofman 1999 monograph, verbatim in its entirety, follows (Upton 1999, which is Attachment-2):

• "Thank you for kindly sending me a copy of your recent book entitled 'Radiation from Medical Procedures in the Pathogenesis of Cancer and Ischemic Heart Disease.' Your observations are impressive and are consistent with the linear-nonthreshold dose-response hypothesis for the genetic and carcinogenic effects of ionizing radiation, and they support the wisdom of the ALARA [as low as reasonably achievable] principle in radiation protection." And

• "At the same time, however, the associations you have so skillfully demonstrated cannot be taken as proof of causal relationships, owing to the possible influence of confounding variables. Just as the inverse relationship between lung cancer rates and county residential radon levels, as reported by Bernard Cohen, does not suffice to prove that low-level exposure to radon protects against lung cancer, neither do your observations suffice to establish medical radiation as a causal factor in the associations you have identified." And:

• "Nevertheless, I find your observations intriguing, and your interpretation of them to be thoughtful and constructively hypothesis-generating. I hope that your book stimulates the productive follow-up research that your findings clearly call for. Many thanks, again, for sharing your findings with me, and best wishes for continuing productivity in the new millenium. Arthur C. Upton."

• The Executive Summary of that 699-page medical monograph (Gofman 1999) and a discussion of its extensive peer-review (Gofman 2002) are provided as an integral part of this submission, as Attachments 1 + 3. So far, the main critiques of the 1999 monograph have produced no reason to

reject, modify, or ignore its conclusions.

Gofman's Estimated Annual Benefit from Dose-Reduction

● The correlations uncovered in Gofman 1999 strongly indicate that accumulated exposure to medical x-rays is a necessary causal co-actor in over half of the fatal cases of cancer and IHD in the United States. Those two diseases account for over one million deaths per year in the USA.

● The concept, "necessary causal co-actor," is very commonly accepted with respect to cancer and to ischemic heart disease (IHD). It means that every case has more than one cause. Thus, in the absence of ANY one of the case's necessary causal co-actors, the case could not happen as it did.

● From this, plus the observations in Gofman 1999, it follows that if there were NO exposure to medical x-rays, and if all other causal co-actors were held constant, the mortality rates from cancer and IHD would gradually fall in half or more.

● Also it follows, if all other things were held constant, that half of that half (i.e., about 250,000 premature cancer and IHD deaths per year) would be prevented over time, if customary x-ray doses were cut in HALF instead of completely eliminated. Part 5 discusses the feasibility.

● Part 5. How Much Can Fluoroscopic Doses Be Reduced?

● Fluoroscopy and CT scans account today for the bulk of the doses received by patients from medical x-rays. Because doses still are seldom measured or recorded, no one can presently know what share of the population's past or current average accumulated x-ray dose comes from fluoroscopy --- but the share must be a large one.

● Dr. Orhan H. Suleiman, health physicist with the FDA, estimates that "Doses from fluoroscopy can easily be reduced by orders of magnitude [well over 10-fold] when one uses currently available technologies such as a cumulative timer, pulsed fluoroscopy, more filtration, better collimation, last frame hold, dose and dose-rate display" (Suleiman 2001, p.8). Dr. Suleiman stands by that opinion, as ascertained by telephone on Feb. 27, 2003.

● Dr. Joel E. Gray, recently retired professor and medical physicist at the Mayo Clinic, warns that "Many users of hospital fluoroscopy equipment do not understand the basic principles of radiation protection and proper use of fluoroscopic equipment. [Many types of physicians besides radiologists use fluoroscopy.] It is necessary that physicians receive basic education about radiation and fluoroscopy before using the equipment. The [hospital's] Radiation Safety Committee can credential individuals who have obtained the appropriate education, and the hospital can grant privileges based on credentials. Continuing education should be required to maintain physicians' credentials and privileges" (Gray 1998, p.70).

● The Editor-in-Chief of AJR (American Journal of Roentgenology), Lee F. Rogers, M.D., has exhorted his readership --- mainly radiologists --- in an editorial (Rogers 2001, p.1): "The [fluoroscope] operator must be aware of the amount of radiation used during a procedure. Cavalier attitudes

about fluoro time, failure to record the time, and conscious avoidance of steps that minimize exposure are to be condemned and discouraged. Using intermittent fluoro, pulsed fluoro, simply taking your foot off the fluoro pedal, reviewing the previous run on video rather than repeating it --- there are many ways to reduce exposure without compromising a procedure, but you must recognize the need to do so. Some physicians, unfortunately, don't. As a result, some operators and their patients are needlessly overexposed. You can learn to do with less. It is all a matter of making a conscious effort to do so. You 'gotta wanta'!"

● Part 6. Claims of Threshold Doses and Hormesis (Protection against Cancer by Low-Dose Radiation): Not a Challenge to Gofman's 1999 Findings

   ● Will radiologists and other users of fluoroscopy want to reduce x-ray doses to their patients?

   ● A prime example of how radiologists receive assurance, that the harm from pre-cancer medical x-rays is negligible or non-existent, is the recent review article in the AJR by Dr. Bernard Cohen (Cohen 2002), in which Gofman 1999 and many other pertinent studies were not mentioned. Dr. Cohen concludes his review as follows (Cohen 2002, p.1141):

   ● "The evidence presented in this review leads to the conclusion that the linear no-threshold [LNT] theory fails badly in the low-dose region because it grossly overestimates the risk from low-level radiation. This means, for example, that the cancer risk from diagnostic radiography is much lower than is given by usual estimates, and may well be zero."

   ● Cohen 2002 summarizes nonhuman and human evidence suggesting that exposure to low doses of ionizing radiation (e.g., 0.2 cGy to 10 cGy) may temporarily stimulate production of DNA repair-enzymes, stimulate the apoptosis process (removal of damaged cells by cell-suicide), or stimulate the immune system. These effects, according to Dr. Cohen and some others, may create a non-linear dose-response, a threshold dose-level below which there is no cancer-risk, or a low-dose interval in which exposure is protective against cancer (the hormetic or J-shaped dose-response).

Why Cohen's Article Is No Challenge to Gofman's Findings

   ● The 2002 Cohen article does not represent a challenge to the 1999 Gofman findings. Why not? Because Gofman 1999 observes and reports the harms which resulted from accumulated medical x-rays ANYWAY, despite any potential risk-reductions which might have occurred due to briefly stimulated DNA-repair, stimulated apoptosis, stimulated immune system, or hormetic "protection."

Shape of the Dose-Response

   ● The method of the 1999 Gofman study, described in both Attachments 1 + 3, means that the validity of its findings are completely compatible with any shape of dose-response: Linear, supra-linear, concave upward, S-shaped, or J-shaped. Whatever the true shape, the shape reflects a human biological response to ionizing radiation --- a response which will be alike

in all nine separate populations in the Nine Census Divisions into which the USA is divided.

• These nine populations demonstrated very strong positive and LINEAR nine-point dose-responses between physician-density and age-adjusted cancer and ischemic heart disease mortality-rates, by Census Divisions. But this observed linearity does not necessarily reflect the biological dose-response; it is also compatible with non-linear biological dose-responses. How? The observed linearity was discussed in Gofman 1999 (pp.93-94) as follows:

• "Physician-density is proportional to average accumulated per capita population dose from medical radiation because the more physicians there are per 100,000 population, the more radiation procedures are done per 100,000 persons. [Supporting evidence in Mettler 1987, p.134.] The increase in procedures occurs chiefly because MORE persons per 100,000 receive such attention --- not because the SAME persons get irradiated more often." [It would be unreasonable to think that physicians who realize they work in a Census Division having a high physician-density therefore decide to give each patient extra x-rays.] And:

• "In other words, the average per-PATIENT dose is about the same in the Census Divisions with low physician-density values as in Divisions with high physician-density values, but the average per-CAPITA dose is higher in high physician-density Census Divisions than in low physician-density Divisions because there are more PATIENTS per 100,000 population in high physician-density Divisions." And:

• "At the cellular level where x-ray-induced mutations occur, the average per-patient dose-level is likely to be very similar in all Nine Census Divisions. Therefore, the observed absence of curvature (e.g., the absence of supra-linearity) matches expectation, in dose-responses between physician-density and [age-adjusted] mortality rates."

Threshold and Hormesis: Some Evidence Omitted by Cohen

• The analysis in Gofman 1999 does not depend upon the no-threshold premise --- even though we and others have presented very strong evidence that no threshold-dose exists for low-LET ionizing radiation (for example, Gofman 1990, NRPB 1995, and other studies below --- none of which were mentioned in Cohen 2002).

• If either a threshold-dose or an hormetic dose-interval were actually to exist, it would mean that all the harms revealed by the observations in Gofman 1999 come from accumulated medical exposures each of which was higher in dose than the very low dose-range where there is any conceivable room left for either a threshold-dose or for a protective hormetic effect. A few examples suggest the upper limits of that potential dose-range:

• 7.5 cGy per exposure: The Nova Scotia fluoroscopy study (Boice 1978; not mentioned by Cohen) produced a host of excess breast cancer from serial absorbed doses to the breasts estimated at only 7.5 cGy each (BEIR 1980, p.276; Gofman 1990, Chapter 21).

• 2 cGy per exposure: The Lloyd Study (Lloyd 1988; not mentioned by Cohen), of human chromosome aberrations

induced in vitro by low-let radiation, showed a linear dose response right down to 2 cGy. Additionally, the Sutherland Study (Sutherland 2000, p.106; not mentioned by Cohen) yields evidence confirming that a single track of low-LET ionizing radiation is capable of causing clustered DNA damage and double-strand breaks.

● Less than 0.6 cGy per exposure: The Scoliosis Study (Doody 2000, pp.2057-2058; not mentioned by Cohen) revealed a clear excess of breast cancer in women who received, during childhood, serial x-ray doses to their breasts estimated at less than 0.6 cGy per exposure. For example, when the average number of radiographic exams was 76.2, the average cumulative dose to the breasts was estimated to be 32.6 cGy (Doody, Table 6).

● The dose-range of 0.6 cGy to 7.5 cGy per exposure is very commonly exceeded during medical x-ray imaging. Therefore, it is conceivable (but we do not think it is the reality) that the x-ray-induced cancer and IHD revealed by the 1999 Gofman analysis results exclusively from accumulated x-ray doses each of which was higher than (say) 7.5 cGy per exposure.

● Part 7. A Scientifically Powerful Reality-Check on Risks

● Dr. Cohen's article (2002) challenges operation of the linear no-threshold (LNT) dose-response in radiation's "low-dose region" (outset of Part 6 above). As explained in Part 6 above, the harms estimated in Gofman 1999 are not tied to assuming operation of the LNT in the low-dose region. Therefore, Dr. Cohen's challenge to the LNT does not conflict with any of the observations and conclusions of Gofman 1999 (Part 4 above).

● Nonetheless, Dr. Cohen assumes (at p.1141) that "failure" of the LNT in the low-dose region (if true) would mean that "the cancer risk from diagnostic radiography is much lower than is given by usual estimates, and may well be zero."

● By contrast, the evidence in Gofman 1999 provides the first scientifically powerful reality-check on all those "usual estimates" --- and shows that they have been gross UNDERestimates of the health risks from medical x-ray imaging procedures.

Why the "Usual Estimates" Have Been So Wrong

● Among the many reasons that the "usual estimates" have been so wrong is that there have been no reliable data for past or present decades on x-ray doses per procedure, the annual numbers of procedures, the collective ACCUMULATED doses by age and organ, and the corresponding risks per absorbed cGy of xray-dose (Gofman 2002, Part 3). Small studies of specific x-ray-exposed participants --- whose lifelong x-ray histories cannot be quantified --- have produced a wide range of risk-per-cGy values.

● Efforts to evaluate x-ray risk by substituting risk-per-cGy values from gamma-exposed populations (e.g., A-bomb survivors, nuclear workers) no doubt contribute to the underestimation of x-ray risk. Why? Not only are the participants' gamma doses poorly known and their x-ray histories rarely even considered, but also per cGy, 90 kVp

x-rays are probably two-fold to four-fold more mutagenic than such gamma rays (ICRU 1986; Gofman 1990, Chapter 13, Part 4; BEIR 1990, p.218; Gofman 1996, p.275, Box 5; Gofman 1999, pp.46-48).

The Gofman Study: Not Based on "Thin-Air" Input

- One of the main scientific strengths of the 1999 Gofman Study is that it does not repeat the "usual" methods of estimating x-ray risk. Instead, it demonstrates a way to estimate the health impacts of accumulated exposure to medical x-rays without using the usual "thin air" dose estimates or the consequently unreliable estimates of risk-per-xray-cGy (Gofman 2002, Part 3).

- Part 8. "If You Care, You Measure" : A Moral Imperative

    - We acknowledge that no one, ourselves included, knows the average risk-per-cGy from medical x-rays. It is unknowable, thanks to failure to measure and record x-ray doses accumulated by patients over their lifespans. Is there a single patient anywhere who could find out his/her lifetime accumulated x-ray dose to any organ (e.g., breasts, lungs, heart, testes)?

    - But no doubt exists that low-LET ionizing radiations, including x-rays, are a proven mutagen and carcinogen. This has been demonstrated for decades. Within irradiated cells, low-LET radiations instantly deliver biologically unnatural amounts of energy (e.g., 60 ev) within a volume estimated at only 4 nanometers in diameter (Ward 1988, p.103). This unique physical property makes them capable of producing especially complex, unrepairable, and consequential mutations (discussion in Gofman 1999, Appendix-C).

A Moral Imperative, When Using a Potentially Lethal Agent

- Certainly not all x-ray-induced mutations are conse- quential, but when they are carcinogenic or atherogenic, the consequence can be fatal. Therefore, a moral medical imperative exists to reduce doses from medical imaging procedures to the lowest effective levels --- not just to the lowest convenient levels. And this imperative would exist even if our estimate of benefit from dose-reduction ever turns out to be too high.

- "If you care, you measure." This axiom reflects the well-known fact in business and education that, if you are SERIOUS about achieving a goal, you establish a system to measure progress or its absence. "What you measure improves." Without seeing the improvement, or knowing of its absence, people lack guidance and motivation, and are robbed of their pride in achievement.

- It is impossible to believe that doses during fluoroscopy will be cut in half (and much more) unless the MEASUREMENT of fluoroscopic x-ray dose becomes easy and automatic.

Medical Ethics and FDA's Proposed Performance Standards

- After more than ten years of study, the FDA is finally proposing performance standards which guarantee dose

measuring devices on new fluoroscopic equipment, plus some additional important dose-reducing features. In our opinion, further delay in acceptance of these performance standards would be medically unethical, for each additional year of delay causes irreversible, unnecessary, and deadly harm.

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What Are the Main Critiques of the 1999 Study by Gofman, after Three Years of Peer-Review? Six Critiques of "Radiation from Medical Procedures in the Causation of Cancer and Ischemic Heart Disease (IHD)."

November 2002, by

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   Molecular & Cell Biology, Univ. of Calif. Berkeley
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   Responsibility, Inc. (CNR), Publisher.

● **Part 1. What Are the Conclusions Under Review?**

   ● "Radiation from Medical Procedures in the Pathogenesis of Cancer and Ischemic Heart Disease" (Gofman 1999) is a massive dose-response study which began extensive circulation for peer-review among scientists in epidemiology, cancer etiology, IHD etiology, and health physics, immediately after its publication in November 1999.

   ● The study's two principal conclusions are 1) Medical radiation, introduced into medicine in 1896, became and remains a necessary causal co-actor in over half of the fatal cases of cancer in the USA, and 2) became and remains a necessary causal co-actor also in over half of the fatal cases of ischemic heart disease (coronary artery disease) in the USA.

   ● From these conclusions plus the fact that x-ray harm is approximately proportional to accumulated x-ray dose, it follows that a very great deal of future cancer and ischemic heart disease (IHD) could be prevented by reducing the dose-levels customarily administered during x-ray imaging procedures, especially CT and fluoroscopy. Indeed, it is very often feasible to get good images with half (or less) of the customary dose. Doing so could prevent about 250,000 premature deaths every year in the USA, by our estimate.

   ● The conclusions above are obviously so important for human health that they demand thoughtful, independent scrutiny, i.e., peer-review.

● **Part 2. What Has Peer-Review Produced So Far?**

   ● How have our conclusions held up under peer-review? Has someone shown a reason to discard them, to ignore them, or to modify them? Not so far.

   ● Valid critiques are often of two types: A demonstration that a better explanation exists for the same observations (Gofman 1999 Chapter 68), and/or a demonstration that the new conclusion is "impossible" because it contradicts some other conclusion of a scientifically incontrovertible nature (Gofman 1999 Chapter 67).

   ● So far, no critique has produced such a demonstration, as will be seen below when we summarize the six main critiques. (This document omits the favorable comments, due to space limits.)

   ● Why, then, are the findings not yet treated as one of the major medical breakthroughs of the past decade? Experience shows that it always takes time for humans to discard mistaken beliefs, especially when the beliefs are so comforting (e.g., "The harm from medical x-rays is trivial"). Still, patience may be no virtue when very many premature deaths could be prevented by a little speed (Gofman 1999 pp.17-20). We agree with the author, Kenneth Graham, who has observed:

   ● "The strongest human instinct is to impart information, and the second strongest is to resist it."

● **Part 3. Orientation: Why Our Study Was Done**

   ● In order to understand the six critiques at issue, one must have at least an overview of why and how the 1999 study was done. The starting point is that ionizing radiations, including x-rays, have been an established cause of human cancer for decades (affirmation in IARC 2000).

   ● The study, "Radiation from Medical Procedures ..." (Gofman 1999), was undertaken to find out if it is possible to make a scientifically credible estimate of how much cancer is caused in the USA by pre-cancer medical x-rays. The "conventional wisdom" is about 1% to 4% (e.g., Archer 1999 p.3; Doll 1981 p.1252; Evans 1986 p.810; Thun 2000 p.1).

   ● One important reason for our doubting the credibility of the 1% to 4% estimates is that they were derived from an estimate of average per capita x-ray dose in the USA. As a result of doing our earlier study of radiation-induced breast cancer (Gofman 1996), we learned that there is no way for anyone to make a reliable estimate of what the average per capita accumulated dose in the USA was — or is today — from pre-cancer medical x-rays.

   ● Past x-ray exposures cannot be ignored. Some 45 years after the 1945 exposure to A-bomb radiation, the Hiroshima-Nagasaki survivors are still producing excess cancer in a dose-dependent fashion (Pierce 1996 p.6). Some mutations induced by ionizing radiation persist in a dose-dependent fashion for decades (Lucas 1992 Figure 6; Kodama 1993), probably for the remaining lifespan. X-rays received 50 years ago or earlier can and do contribute to today's cancer mortality.

The Absence of Measured X-Ray Doses

   ● Although x-rays have been widely used in medical practice for over 100 years, in no decade have x-ray doses been measured — indeed, for about the first 40 years, the response of the skin was the only "measure."

   ● Even after measurement became technically possible, it was not done in practice — and is very rarely done today. We venture to assert that there is no one in the USA who knows or could find out what his/her accumulated dose of pre-cancer x-rays is to any part of the body (e.g., breasts, testes, lung, heart).

   ● From one type of procedure to another, the x-ray dose can vary by 100-fold. There are only very loose estimates of how many procedures of which type were given in any decade. A leading figure in radiology, Henry D. Royal, M.D., estimates that average per capita x-ray doses are 2 or 3 times higher now than they were in 1980, due to expanded use of CT (in Veterans 2000 pp.260-261).

   ● Moreover, even for the same procedure, on patients of the same size, sporadic sampling programs show that x-ray doses vary widely from facility to facility, and even within a single facility.

The Scientific Challenge

   ● Given the lack of dose data about x-rays in the USA, we consider the widely used average per capita dose-estimates — past and present — to rest on "thin air." A colleague of ours commented, "Well, you have undertaken an inquiry where there will never be any data!"

   ● So, our scientific challenge was to try designing a study which could produce a scientifically better estimate of the impact of pre-cancer x-rays on cancer mortality, by entirely avoiding the very flimsy ("thin air") dose-estimates — and by avoiding also the consequently unreliable estimates of risk per dose-unit.

● Part 4. Orientation: How Our Study Was Done

● Instead of using any dose-estimates, we used the premise that average per capita dose per 100,000 population is approximately proportional to the number of practicing physicians per 100,000 population (physician density) --- supporting evidence in Mettler 1987 p.134 --- because physicians order x-rays even when others perform them. Thus the RELATIVE magnitude of physician-density values in the nation's nine permanent Census Divisions should reflect the RELATIVE magnitude of the per capita x-ray dose delivered in each Census Division. The earliest year is 1921 for which we obtained the density data for all nine Census Divisions (Pennell 1952; later decades, see AMA).

● Our design was to see if any correlation (dose-response) exists between magnitude of physician density and magnitude of age-adjusted cancer mortality rates, by Census Divisions. Nine Divisions make each test a nine-point correlation.

● The year 1940 marks the first decade for which every state reported mortality data for all major causes of death, including cancers (Grove 1968; later decades, see Natl. Center). The main reason for doing the analysis by Census Divisions (not counties or states) is to minimize degradation by migration. Prior to World War Two, there was far less migration from one Census Division to another than after 1940. To a first approximation, people accumulated their x-ray doses over a lifetime in the same Census Division where they died. The number of states per Division ranges from 3 to 8.

● Our dose-response study would not have been possible, however, if the rank order of physician-density values had switched so much over time that the population in every Census Division accumulated about the SAME average x-ray dose. But it turns out that the rank order of the nine Census Divisions, with respect to physician density, has been remarkably stable (Gofman 1999 p.66) --- stable enough that you can predict the national age-adjusted cancer mortality rates (male, female) rather well for 1940 by examining relative physician density by Census Divisions in 1921, 1931, and 1938 (Gofman 1999 p.214, p.222; for IHD in 1950, see p.296).

● And so we undertook a mammoth dose-response study, enrolling the entire US population (131.7 million people in 1940).

Forty Dose-Response Tests

● Our 1999 dose-response study tested for the existence or absence of a dose-response between physician density and age-adjusted 1940 mortality, separately for males and females, for all-cancers combined, breast cancer, digestive-system cancers, urinary-system cancers, genital cancers, mouth and pharynx cancers, respiratory-system cancers (12 cancer dose-response tests).

● Exceedingly importantly, our dose-response study tested the noncancer causes of death too, separately for males and females: Combined noncancer causes, combined noncancer nonIHD causes, IHD (ischemic heart disease), appendicitis, strokes, chronic nephritis, diabetes mellitus, hypertensive disease, influenza and pneumonia, fatal motor-vehicle accidents, other fatal accidents, rheumatic fever and rheumatic heart disease, syphilis and sequelae, tuberculosis, ulcer of stomach and duodenum (28 noncancer dose-response tests).

● Part 5. The Results of Our 40 Dose-Response Tests

● Eleven of the 12 cancer studies produced statistically significant, positive dose-responses between physician-density and age-adjusted cancer mortality rates in 1940; only female genital cancers showed no relationship with physician density. In all other tests, as physician density rose, so did the age-adjusted cancer mortality rates. Indeed, the correlation was so nearly perfect in 8 of the 11 tests that the R-squared values ranged from 0.86 to 0.96; in the other 3 tests, R-squared values ranged from 0.72 to 0.78 (all tabulated in Gofman 1999 p.217).

● The 11 strong correlations permitted us to estimate the impact of medical radiation upon 1940 cancer mortality --- without using any "thin air" dose estimates or any unreliable values for risk per unit dose.

● How? We extended each correlation's "line of best fit" down to ZERO physician density (no medical x-rays), and thus we obtained the estimates of what the cancer mortality rates would most probably have been in the ABSENCE of accumulated exposure to medical x-rays.

Results of Twenty-Eight Noncancer Dose-Response Tests

● To our astonishment, one of the noncancer entities --- ischemic heart disease (IHD) --- produced spectacularly strong and positive

dose-responses between physician density and age-adjusted mortality rates in 1950 (the first decade in which all states reported mortality data for IHD). For males, the R-squared value was 0.95; for females, 0.83 (Gofman 1999 Chapters 40, 41). And again, we could estimate the impact of x-rays on IHD-causation by extending the best-fit line to ZERO physician density (no medical radiation).

● All the other noncancer dose-responses (Chaps. 24-37) were either negative --- higher physician density going with lower death rates --- or flat, with the only exceptions being male and female diabetes (see explanation, Gofman 1999 p.247) and, male G.I. ulcers (barely statistically significant; see comment in Gofman 1999 bottom of p.22).

● Combined, all noncancer nonIHD causes of death had a statistically very significant negative correlation with physician density --- in great contrast with the very strong positive correlations for cancer and for IHD with physician density.

● Part 6. First Critique: Correlation vs. Causation

● One of the first critiques we received belongs to the "maybe there is a better explanation" class. It comes from Arthur C. Upton, M.D., former director of the National Cancer Institute (1977-1979), member of all the main radiation committees, including the National Research Council's Committee on the Biological Effects of Ionizing Radiation, 1972, 1980, 1990 (chair). We quote his critique (Upton 1999) in its entirety:

● "Dear Dr. Gofman: Thank you for kindly sending me a copy of your recent book entitled 'Radiation from Medical Procedures in the Pathogenesis of Cancer and Ischemic Heart Disease.'

"Your observations are impressive and are consistent with the linear-nonthreshold dose-response hypothesis for the genetic and carcinogenic effects of ionizing radiation, and they support the wisdom of the ALARA principle [As Low As Reasonably Achievable] in radiation protection.

"At the same time, however, the associations you have so skillfully demonstrated cannot be taken as proof of causal relationships, owing to the possible influence of confounding variables. Just as the inverse relationship between lung cancer rates and county residential radon levels, as reported by Bernard Cohen, does not suffice to prove that low-level exposure to radon protects against lung cancer, neither do your observations suffice to establish medical radiation as a causal factor in the associations you have identified.

"Nevertheless, I find your observations intriguing, and your interpretation of them to be thoughtful and constructively hypothesis-generating. I hope that your book stimulates the productive follow-up research that your findings clearly call for. Many thanks, again, for sharing your findings with me, and best wishes for continuing productivity in the new millennium. Arthus C. Upton."

Our Response: Agreement on Inherent Limitations

● Dr. Upton is not suggesting that our study was designed to prove whether or not x-rays are a cause of cancer. That was established decades ago. Nor was our study intended to prove whether or not x-rays are a cause of IHD. Results of our IHD tests astonished us (Part 5, above).

● Instead, Dr. Upton is agreeing with a reality stressed repeatedly in our study, namely that correlations are inherently unable to prove causation, by themselves. Correlations can and do occur without being causal.

● So, whenever a correlation is observed in biomedical research, there is inevitably room to challenge the identity of what truly caused the correlation to occur --- even in the widely accepted Atomic Bomb Survivor Study, for instance. In Chapters 48 and 68 of our 1999 study, we ourselves look for non-xray explanations of the many correlations uncovered by our work.

● Importantly, we explore cigarette smoking as a potential non-xray explanation. The evidence is that smoking has a NEGATIVE correlation with physician density, by Census Divisions, and so smoking cannot be a valid cause of the observed POSITIVE correlations (physician density with cancer and IHD mortality, by Census Divisions).

● Establishing causation in medicine is particularly difficult, not only because of inherited biochemical individuality, but because of the different external forces experienced by free-living humans. Before causation is considered proven, correlations do need support from supplemental evidence or logic, especially about a plausible biological mechanism of causation (e.g., how xray-induced mutations could cause IHD; see end of Note 1, and Gofman 1999 Chapters 44, 45, 46).

● Part 7. Is "Urbanization" a Better Explanation?

● Critique #2. Several peer-reviewers have speculated that the positive correlations between physician density and cancer, by Census Divisions, may be caused by a positive correlation between "urbanization" and physician density.

● For example, Gofman 1999 was reviewed on November 29, 2000 by the U.S. Department of Veterans Affairs, Office of Adjudication, Veterans Advisory Committee on Environmental Hazards. The transcript of that meeting is Veterans 2000 in our list. Some on the Committee were highly skeptical that x-rays could be the correct explanation. Said Theodore Colton, Sc.D., Boston University School of Public Health:

● "I don't know what the obvious flaw is, but one of the limitations of ecologic studies is the fact that they're very prone to confounding variables. And it just seems to me that there's some obvious confounding variable that affects both physicians per capita and cancer mortality that's not being taken into account..." (Veterans 2000 p.272).

● Soon, Henry D. Royal, M.D., Nuclear Medicine Division of the Mallinckrodt Institute of Radiology, suggested urbanization as the confounding variable:

● "Well, we do know that rural versus urban, that there's a difference in cancer rates with rates being higher in urban settings. Certainly physicians per population is going to be weighted to those urban settings, so that's certainly one confounding variable" (Veterans 2000, p.274).

Our Response: What Makes City Life Carcinogenic?

● Dr. Royal and some other peer-reviewers appear to assume that living in cities was a cancer-risk during the decades leading up to 1940 (the first year analyzed in Gofman 1999). And they must also assume, for the period leading up to 1940, that the more urbanized Census Divisions had higher physician density than did rural Census Divisions. Suppose that we share those assumptions (Gofman 1999 Chapter 68).

● City living is not itself a biological agent. But x-rays are. And they are a proven carcinogen. According to Dr. Royal's own logic, x-rays could explain WHY urban areas have higher cancer mortality rates. With more physicians per 100,000 persons in urban areas, there are more x-rays given per 100,000 persons --- and thus the average per capita accumulated x-ray dose is higher in the urbanized Census Divisions than in the more rural Divisions.

● In summary, urbanization is not a "confounding variable" in our study. It is not a "better explanation" than x-rays for the correlations uncovered by our work. Instead, higher exposure to medical x-rays can provide a good explanation of WHY urban areas may have higher cancer rates.

Some Tests for Validating a Speculation

● It is easy to speculate that some agent OTHER than medical x-rays is the true cause of the observed correlations in Gofman 1999. After all, many proven and suspected non-xray causes exist for cancer and IHD. However, none can provide a valid alternative to the x-ray explanation, for the correlations uncovered in Gofman 1999, unless the alternative can explain the observations equally well. In order to do so, an alternative agent would have to pass all of the following tests:

(1) o Public exposure to the non-xray agent would need a very strong correlation with physician density, by Census Divisions.

(2) The correlation by Census Divisions would have to be a positive one (not negative).

(3) The correlation by Census Divisions would have to persist over time, in order to yield the predictions described in Part 4, above.

(4) The non-xray agent would have to be a potent cause of nearly every type of fatal cancer.

(5) The non-xray agent would have to be a potent cause of ischemic heart disease (IHD).

(6) The non-xray agent would have to be NOT a cause of noncancer, nonIHD causes of death. Could reviewers show evidence to establish that "urbanization" is NOT a cause of noncancer, nonIHD causes of death?

● Part 8. Correlations Show Only that Doctors and Sick People Want to Be in the Same Place?

● Critique #3. Two reviewers proposed in private communications that maybe cancer and IHD mortality rise where physician density rises, by Census Divisions, only because doctors and sick people want to be in the

The monograph, "Radiation from Medical Procedures..." (Gofman 1999) was sent for peer-review to Dr. Richard R. Monson, chair of the BEIR-7 Committee (the Nat'l Research Council's Com'tee on the Biological Effects of Ionizing Radiation), with our offers (a) to supply a copy for every member and (b) to respond to any critiques. Dr. Monson replied (Monson 2000, 2002) that he would read the study with interest, but that his Committee's deliberations are confidential and afford us no chance to respond to any critiques. The BEIR-7 Report is expected in 2003.

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same place. In other words, there may be a strong positive correlation between physician density per 100,000 people and sick people per 100,000 people --- a proposition that we, too, considered (Gofman 1999 Chap.68).

● By itself, such a correlation would be reasonable --- and certainly consistent with the premise that where physician density is higher, the number of x-ray procedures per 100,000 population is higher too.

Our Response: You Can't Discard the Noncancer NonIHD Facts

● Because they assume a positive correlation between physician density and the density of sick people, by Census Divisions, these two reviewers think "of course" mortality rates rise where physician density rises.

● Not so. The age-adjusted noncancer nonIHD mortality rates FALL where physician density rises (Part 5, above) --- and noncancer nonIHD mortality rates account for about HALF of total mortality rates at midcentury and subsequently.

● Neither the reviewers nor we can ignore the NEGATIVE correlations between physician density and noncancer, nonIHD causes of death, by Census Divisions. To be a "better explanation" for the observations, a proposition must be consistent with all the key observations.

● Critique #3 cannot explain the noncancer nonIHD observations. When pressed, one reviewer proposed that only people having cancer and IHD want to be near doctors, but people having other fatal illnesses do not feel the same desire. The other reviewer conceded that her proposition cannot explain all of the key observations.

● But the x-ray explanation can. Cancer and IHD behave differently with respect to physician density because rising physician density means rising average accumulated per capita x-ray exposure. Noncancer causes of death are not known to be inducible by x-rays, whereas x-rays are a proven human carcinogen (via mutations). So a different response would be expected, to rising physician density.

● As for IHD, our study provides the first powerful epidemiologic evidence that x-rays (via mutations) are very probably an atherogen as well as a carcinogen. Long before 1999, some independent, supplemental evidence aleady existed that mutations acquired after conception have a role in atherogenesis, but we and many others either were unaware of it or paid it too little attention --- until our 1999 monograph. Some of the supplemental evidence on IHD is described in Note 1, on page 5.

● Part 9. Correlations Show Only that People Live Long Enough to Die of Cancer or IHD Where Doctor Density Is High?

● Critique #4. Two other reviewers proposed, as a "better explanation" for the positive correlations uncovered in Gofman 1999, that "With an increased number of physicians per 100,000 population, better medical care, the population lives longer making death from an age-related disease (cancer or heart disease) more likely" (Arvid Zuber, Ph.D., April 15, 2000, in a critique sent to the magazine "World and I"). The other reviewer used different words to convey the same idea.

Our Response: Age-Adjusted Mortality Rates Equalize the Number of Persons Reaching Each Age

● These two reviewers are thinking of what is called "crude" mortality rates. But every mortality rate used in Gofman 1999 was an age-adjusted mortality rate. There is a big difference in their meaning.

● By definition, age-adjusted mortality rates for each of the nine Census Divisions are adjusted for the SAME age-distribution, and are based on the observed age-specific observations of deaths per 100,000 persons in a Census Division who DO REACH each specific age (sample calculation shown in Gofman 1999 p.87).

● These two reviewers have no explanation for why the cancer and IHD mortality rates are higher, per 100.000 persons who DO REACH

advanced ages, where physician density is higher than where it is lower, by Census Divisions. So they have not identified a "better explanation" than the higher accumulated per capita dose of x-rays, where physician density is higher —— as subsequently acknowledged by one of the reviewers who offered Critique #4.

● Part 10. "Ecologic Studies" Are Inherently Weak

● Critique #5. The fact that our study can be labeled "an ecologic study" helps people to dismiss it (see Part 7, above). Dr. Colton pointed out, "You can't say that everybody has been exposed to physicians and everybody who's had cancer and who's died from cancer has had these x-rays" (Veterans 2000, p.273). An ecologic dose-response study leaves open the possibility that the response is coming from people who received no dose.

Our Response: By 1940, Nearly Everyone Was X-ray Exposed

● While few people have x-rays every year, what counts is the accumulated dose. The mutations accumulate. The body remembers.

● X-rays ("roentgen rays") were discovered in December 1895, and were introduced so rapidly into medicine that until about 1906, x-rays "were tried out [as therapy] on nearly every chronic disease" (MacKee 1938 pp.15-16). After World War One, a radiologist commented to his colleagues about "the large number of internists who have placed fluoroscopes in their offices, not with the idea of specializing in the work, but simply wishing to have conveniently at hand an x-ray control of their physical findings ... The simplified apparatus which has developed from war-time [battlefield] practice is conspicuous" (Hickey 1923). "Fluoroscopy, I venture to assert, will become a routine measure in every physician's office before very long" (Bishop 1922).

● And so it came to pass that, in 1937, Dr. Eugene Leddy of the Mayo Clinic wrote: "Roentgenologic methods of diagnosis are so important that no investigation of a patient is considered complete without roentgenologic examinations, which generally include roentgenoscopy [fluoroscopy]" (Leddy 1937 p.924). One expert has estimated that the average x-ray dose per fluoroscopy was 65 rads (Moeller 1953, p.58-59).

● We consider it highly unlikely that in the United States, more than a very small share of people dying in 1940, of any illness, escaped x-ray exposure during their lifetimes.

● Part 11. Is It "Impossible" for X-Rays to Be a Necessary Causal Co-Actor in Over Half the Cancer and IHD Mortality?

● Critique #6 was presented, separately, by two health physicists: By Dr. Roland Finston, orally at a breast cancer forum (2001), and by Dr. Brian Wowk in the magazine, "Life Extension" (Wowk 2002 p.75).

● Their critique asserts that our conclusion, that x-rays are a necessary causal co-actor in over half the cancer and IHD mortality, cannot be correct because the average annual radiation dose from natural background radiation is about 6 times higher than the average annual accumulated dose from medical x-rays. Therefore, even if ionizing radiation were a necessary causal co-actor in every fatal case of cancer and IHD, x-rays could contribute only a small share compared with natural background radiation.

Our Response: The Dose-Ratio Deserves Reversal

● Dr. Wowk accepts the common estimate that annual per capita dose from medical imaging is, today, about 0.05 rem or centi-sievert (cSv), as does Dr. Finston. They just ignore the fact that this is necessarily a "thin air" estimate (Part 3, above). The "thin air" estimate does not even approach the status of a scientifically incontrovertible fact. Therefore, our conclusion is certainly not invalidated just by being incompatible with the 0.05 rem estimate.

● These reviewers, in addition, say nothing at all about average per capita PAST doses, which are the relevant ones, here. Our study begins with the 1940 mortality rates, for which the x-ray doses accumulated between 1900 and 1940 are the only ones which matter.

● In Appendix K of Gofman 1999, we explored this issue by trying to make an estimate of what the annual per capita x-ray dose may have been prior to 1940. Using papers by Donaldson (1951) and Moeller (1953), plus clearly stated assumptions and logic, we estimate that the average annual per capita whole-body dose from medical imaging in 1950 was in the region of 0.65 rad, excluding non-imaging (therapeutic) uses of

x-rays, radium, and excluding all dental x-rays. We challenge anyone to show that some lower estimate for midcentury is more credible than 0.65 rad.

● Indeed, 0.65 rad is likely to be quite an underestimate, because of all the x-ray procedures it omits. It properly omits uses for cancer therapy (because we are investigating cancer causation). But 0.65 rad also excludes numerous x-ray therapies for "benign" noncancer ailments, including 80 skin disorders (cumulative doses of many hundred rads per treatment), enlarged thymus gland, mastitis, tuberculosis, asthma, pneumonia, tendonitis, certain kinds of pain, and more (see MacKee 1938, Gofman 1996).

● "It has been said that radiation therapy has been used promiscuously, on every disease there is, and probably so," wrote the radiologist, Stephen B. Dewing (Dewing 1965 p.ix).

Comparing Two Kinds of Doses: X-Rays and Natural Background

● A medical RAD is not directly comparable with the estimated average annual whole-body dose of 0.3 REM or cSv from natural background radiation. Evidence from radiation track analysis indicates that a reasonable conversion factor, from rads to rems for medical x-rays, is about 1.7 (see tabulation, text, and references in Gofman 1999 p.47).

● Multiplication of 0.65 rad (medical) times 1.7 rem per rad yields 1.1 rem as a credible estimate of the average annual per capita whole-body dose from medical x-rays during the first half of the 20th century. It compares with an average dose of only 0.3 rem from natural background, including 0.2 rem from radon (BEIR 1990 p.18). The 0.3 rem estimate (natural) is itself a very uncertain estimate, strongly affected by several key assumptions. Nonetheless, we will use it.

● These two values (1.1 rem, medical, and 0.3 rem, natural) mean that the annual per capita whole-body dose at midcentury from x-rays could easily have been about 3.7 times HIGHER than the dose from natural sources (1.1 / 0.3).

● This is quite a reversal of the ratio assumed by the two reviewers.

● Even though we assume that average per capita x-ray doses are no longer as high as the midcentury estimate, we are mindful that x-ray practices in 1950 affect cancer and IHD mortality rates for the subsequent 50 years and probably longer —— by producing some carcinogenic and atherogenic mutations which endure (Part 3, above).

● Fortunately, after 1955 or so, radiation has been seldom used therapeutically, except for cancer therapy. On the other hand, two large UPWARD forces on average per capita x-ray dose have been introduced during the 1970-2000 period. Uses of fluoroscopy —— delivering x-rays at 2 to 20 rads per minute —— have greatly expanded, e.g., during catheterizations, surgeries, and other common procedures (Gofman 1996). Another large upward force on average per capita x-ray dose is the replacement of many "planar" x-ray images by CT procedures during the 1980-2000 period (see Part 3, above).

● In summary, nothing in Critique #6 invalidates the conclusions of Gofman 1999, that medical x-rays were and remain a necessary co-actor in over half the U.S. mortality rates from cancer and IHD.

● Part 12. Conclusion: A Biologically Consistent Picture

● We have studied the relationship of age-adjusted mortality rates and physician density with 40 separate tests (Part 4, above). The findings sort themselves out in a biologically consistent way, almost without exception (Part 5, above). Such correlations do not happen just by ACCIDENT. Moreover, they have happened in the way one would expect, if medical x-rays are the CAUSE.

● No critique thus far of the findings, concerning medical x-rays in the causation of cancer and coronary artery disease, provides a better explanation of all the observations in Gofman 1999, and no critique shows that the new conclusions are "impossible" due to any contradiction of a scientifically incontrovertible fact.

● At issue is prevention of some 250,000 premature deaths per year in the USA, by cutting average per capita x-ray exposure in half (Part 1, above). Does this not suggest that the medical profession needs to use more speed in taking the findings seriously?

# # # # #

The Reference List, and Note 1, are located on page 5.

NOTE 1.

Some Supplemental Evidence for Atherogenic Mutations

● Human Pathologic Evidence. In 1973, Earl Benditt and co-workers reported that human atherosclerotic plaques were far more monoclonal than adjacent non–atherosclerotic tissue (summary in Gofman 1999 Chapter 44). Others confirmed those pathologic observations. Do those findings indicate that such plaques arise due to mini–tumors? Research on the cause of such monoclonality continues at the University of Washington Pathology Department.

● In addition, Arthur Elkeles published papers in 1961, 1966, and 1968, reporting unusually high concentrations of alpha activity (a type of densely ionizing radiation, definitely mutagenic) at the calcified plaque sites of atherosclerosis cases.

● Experimental Animal Studies. In 1977, Roy Albert and co-workers published evidence that weekly injections of strong chemical carcinogens "resulted in large, proliferating plaques in the abdominal aorta in cockerels" (from Penn 1989 p.190). Penn himself showed, in a series of papers (1981, 1986, 1988, 1989, 1991), that DNA from the coronary artery plaques of some human patients can transform NIH 3T3 fibroblasts, which thereby acquire the power to produce tumors in nude mice, and that injection of experimental animals with a variety of established chemical carcinogens and mutagens promotes expansion of arterial plaques in such animals. See Penn 1990 and Gofman 1999 Chapter 44.

● Ionizing radiation at high therapeutic doses has also been explored as an atherogen in nonhumans. In 1976, Richard A. McReynolds et al summarized evidence as follows: "When irradiation is given to animals (rabbits or rats) on high cholesterol diets, severe coronary atherosclerosis results, far more severe degrees of atherosclerosis than that resulting from the hypercholesterolemia alone. Irradiation and hypercholesterolemia appear to act synergistically to produce considerably more atherosclerosis than that produced by either radiation or hypercholesterolemia alone" (McReynolds 1976 pp.44–45).

Atherogenic Mutations as a Necessary Co-Actor in IHD Deaths

● Our "Unified Model" (Gofman 1999 Chapters 45, 46) builds upon prior evidence that a major cause of heart attack is the rupture in a coronary artery of an atherosclerotic plaque's fibrous cap, whose rupture releases the plaque's thrombogenic lipid pool into the bloodstream.

● Our Unified Model proposes that a lipid–containing arterial plaque arises where mutations (acquired after conception) produce a clone of dysfunctional cells (mini–tumors) which do an incomplete job of clearing the lipids out of that patch of dysfunctional tissue and of protecting the arterial lumen from the accumulated lipids therein. This model is consistent not only with previously established risk factors for IHD, but it also explains why plaques occur only in discrete patches, surrounded by normal tissue.

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Attach - 2, Gofman

Message

Dr. Arthur C. Upton, former director of the National Cancer Institute, provided the statement below for the purpose of stimulating additional research and attention to ALARA measures. The message is reproduced with his permission, and may be reproduced ONLY in its entirety, verbatim. JWG.

From: acupton@eohsi.rutgers.edu (Arthur Upton MD)
Date: Mon, Nov 29, 1999, 2:51pm (PST+3)
To: gofman123@webtv.net
Subject: Medical Radiation and Disease Rates

Dear Dr. Gofman:
Thank you for kindly sending me a copy of your recent book entitled "Radiation from Medical Procedures in the Pathogenesis of Cancer and Ischemic Heart Disease". Your observations are impressive and are consistent with the linear-nonthreshold dose-response hypothesis for the genetic and carcinogenic effects of ionizing radiation, and they support the wisdom of the ALARA principle in radiation protection. At the same time, however, the associations you have so skillfully demonstrated cannot be taken as proof of causal relationships, owing to the possible influence of confounding variables. Just as the inverse relationship between lung cancer rates and county residential radon levels, as reported by Bernard Cohen, does not suffice to prove that low-level exposure to radon protects against lung cancer, neither do your observations suffice to establish medical radiation as a causal factor in the associations you have identified. Nevertheless, I find your observations intriguing, and your interpretation of them to be thoughful and constructively hypothesis-generating. I hope that your book stimulates the productive follow-up research that your findings clearly call for. Many thanks, again, for sharing your findings with me, and best wishes for continuing productivity in the new millennium. Arthur C. Upton

ALARA: As Low As Reasonably Achievable.

Arthur C. Upton, M.D. is a former Director of the National Cancer Institute (1977–1979). Beforehand and afterwards, he has been a member of various Committees which produce reports on the health effects of ionizing radiation, including:
   BEIR: The Committee on the Biological Effects of Ionizing Radiation (BEIR) of the National Research Council, National Academy of Sciences. 1972, 1980, Chair 1990.
   NCRP: National Council on Radiation Protection; Chairman of Scientific Committee 1–6, to evaluate the linear non-threshold dose–response model. The Committee posted its 284-page draft report online in October 1998.
   NIH: National Institutes of Health, Ad Hoc Working Group to Develop RadioEpidemiological Tables. 1985.
   ICRP: International Commission on Radiological Protection. 1977, 1985–1989.
   UNSCEAR: The United Nations Scientific Committee on the Effects of Atomic Radiation. 1977.

Hach-3, Gofman

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.

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U.S.A.

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.

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.

   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 (1st edition, 1995). LCCN 96-2453 (2nd edition, 1996).

SECTION ONE
Orientation, Materials, Methods

SECTION TWO
Cancer Mortality: Evidence that Medical Radiation Became a Principal Cause by 1

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

SECTION FOUR
Ischemic Heart Disease: Evidence that Medical Radiation Became an Important Cau

Section 4 continues ...

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

SECTION SIX
The Status of Hypotheses One and Two

APPENDICES

To denote emphasis, this monograph uses CAPITALIZED words (instead of italics).
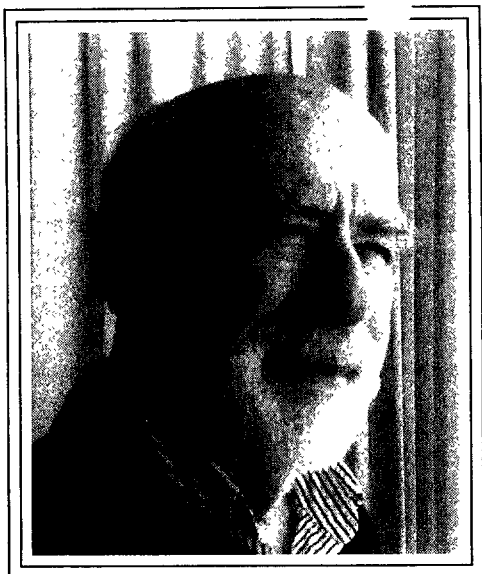
The Author's History
by Egan O'Connor

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.

Overview, and Some Practical Implications of This Work

Part 1. Practical Implications of Hypotheses One and Two
Part 2. Differing Origins of the Two Hypotheses
Part 3. Some Rather Dazzling Results to Examine
Part 4. Why Our Findings Do Not Challenge the Importance of Other Causes of Cancer and IHD
Part 5. How to Reconcile High Fractional Causations by Xrays, Smoking, Diet

● 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.

>>>>>>>>>>

Radiation from Medical Procedures in the Pathogenesis of Cancer and
Ischemic Heart Disease:
Dose-Response Studies with Physicians per 100,000 Population.

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 of 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	All-Cancer MortRates 1940 (males) vs. PhysPop 1940 Regression Output:	
Pacific	159.72	122.9	Constant	11.5484
New England	161.55	135.5	Std Err of Y Est	5.4727
West North Central	123.14	110.9	R Squared	0.9508
Mid-Atlantic	169.76	140.9	No. of Observations	9
East North Central	133.36	119.6	Degrees of Freedom	7
Mountain	119.89	99.8		
West South Central	103.94	86.9	X Coefficient(s)	0.7557
East South Central	85.83	73.6	Std Err of Coef.	0.0650
South Atlantic	100.74	88.9	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 magnitude 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 over-all 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.

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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: Frac. Causation by Medical Radn	Col.D: R-squared	Col.E: X-Coefficient	Col.F: Ratio of XCoef/Std.Error
Ch49, 1940-88, All-Cancer: M	Big net rise. 115.0 --> 162.7	90% --> 74%	0.95 --> 0.93	0.76 --> 0.75	11.6 --> 10.1
Ch50, 1940-88, All-Cancer: F	Net decline. 126.1 --> 111.3	58% --> 50%	0.86 --> 0.87	0.53 --> 0.34	6.6 --> 6.9
Ch51, 1940-88, Resp'y Ca: M	Enormous rise. 11.0 --> 59.7	~100% --> 74%	0.87 --> 0.78	0.12 --> 0.27	6.8 --> 5.0
Ch52, 1940-88, Resp'y Ca: F	Enormous rise. 3.3 --> 24.5	97% --> 83%	0.96 --> 0.90	0.02 --> 0.13	13.4 --> 7.8
Ch53, 1940-88, Diff-Ca: M	Approx. flat. 104.0 --> 103.0	84% --> 72%	0.93 --> 0.92	0.64 --> 0.46	10.0 --> 8.7
Ch54, 1940-88, Diff-Ca: F	Big decline. 122.8 --> 86.8	57% --> 48%	0.85 --> 0.84	0.50 --> 0.25	6.3 --> 6.1
Ch55, 1940-90, Breast-Ca: F	Flat. 23.3 --> 23.1	~100% --> 83%	0.92 --> 0.89	0.19 --> 0.12	8.7 --> 6.7
Ch56, 1940-80, AllExcGen: F	Flat. 94.0 --> 94.8	75% --> 66%	0.87 --> 0.93	0.51 --> 0.43	6.8 --> 9.6
Ch57, 1940-88, Digest-Ca: M	Big decline. 60.4 --> 38.8	97% --> 82%	0.91 --> 0.87	0.43 --> 0.20	8.3 --> 7.0
Ch58, 1940-88, Digest-Ca: F	Big decline. 50.1 --> 23.5	80% --> 68%	0.76 --> 0.86	0.29 --> 0.10	4.6 --> 6.7
Ch59, 1940-80, Urinary-Ca: M	Approx. flat. 7.4 --> 8.2	~100% --> 83%	0.92 --> 0.61	0.08 --> 0.05	9.0 --> 3.3
Ch60, 1940-80, Urinary-Ca: F	Decline. 4.0 --> 3.0	86% --> 78%	0.94 --> 0.91	0.02 --> 0.02	10.4 --> 8.5
Ch61, 1940-90, Genital-Ca: M	Some rise. 15.2 --> 16.9	79% --> 47%	0.77 --> 0.79	0.09 --> 0.05	4.9 --> 5.2
Ch63, 1940-80, Buccal-Phar: M	Approx. flat. 5.1 --> 4.6	~100% --> 81%	0.72 --> 0.73	0.04 --> 0.03	4.3 --> 4.4
Ch64, 1950-93, IHD: M	Enormous fall. 256.4 --> 131.0	79% --> 63%	0.95 --> 0.73	1.49 --> 0.50	11.2 --> 4.3
Ch65, 1950-93, IHD: F	Enormous fall. 126.5 --> 64.7	97% --> 78%	0.87 --> 0.68	0.90 --> 0.30	6.8 --> 3.9

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.

		R-Squared	X-Coef.	XCoef/Std Err	Relationship, MortRates w. PhysPops by CensusDiv.
Ch23: All Causes Combined	Male	0.1299	Neg.	−1.02	Inverse, but not sig.
	Fem	0.2823	Neg.	−1.66	Inverse, and marginal.
Ch24: All NonCancer Combined	Male	0.2841	Neg.	−1.67	Inverse, and marginal.
	Fem	0.4362	Neg.	−2.33	Inverse, and significant.
Ch25: All NonCancer NonIHD	Male	0.7933	Neg.	−5.18	Inverse, and very sig.
	Fem	0.7037	Neg.	−4.08	Inverse, and very sig.
Ch26: Appendicitis	Male	0.0179	Neg.	−0.36	None.
	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 deaths during 1940 from xray-induced 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.
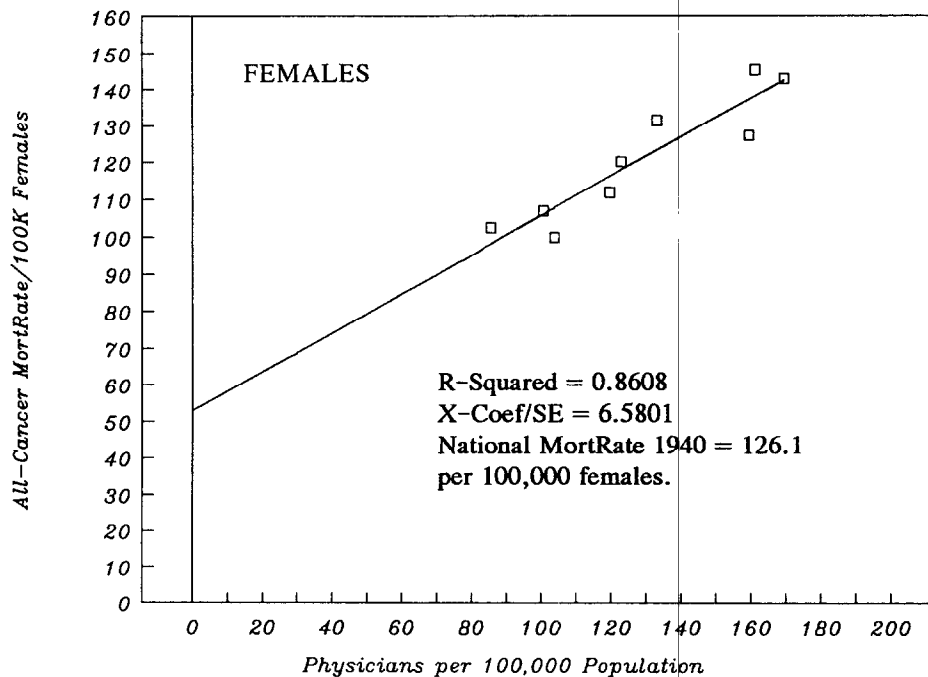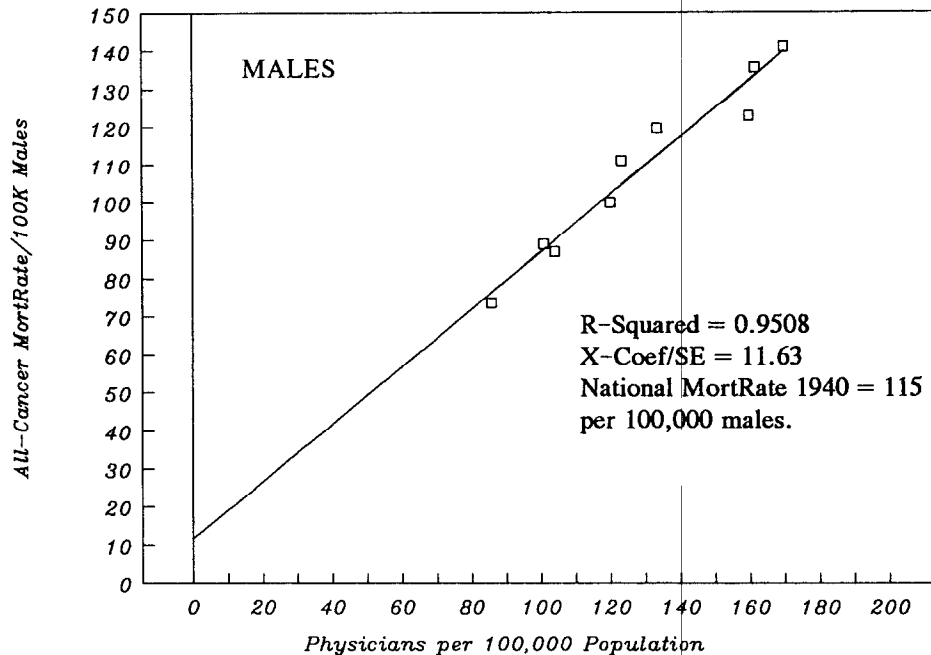
Area	Procedure	Entrance-Dose Reduction-Factor	Reference
All Types	Elimination of medically unnecessary procedures	1.2	Cohen 1985.
	Introduction of Quality Assurance programme (general)	2*	Cohen 1985.
Radiography	Decrease in rejected films through Quality Assurance programme	1.1	Gallini 1985. Properzio 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 CaWO4 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.
Computed tomography, head	Gantry angulation to exclude eye from primary beam	2 to 4 ***	Isherwood 1978.
Mammography	Intensifying screens	2 to 5	NCRP 1986. Shrivastava 1980.
	Optimal compression	1.3 – 1.5	NCRP 1986.
	Filtration	3	Hammerstein 1979.

* The role of proper training in radiation protection is extremely important. Dose reduction-factors in this regard may be large; however, they are difficult to quantify. ** Factor for gonads. *** Factor for eyes.

Figure 1-A.

All-Cancers-Combined: Dose-Response between PhysPop and MortRates.
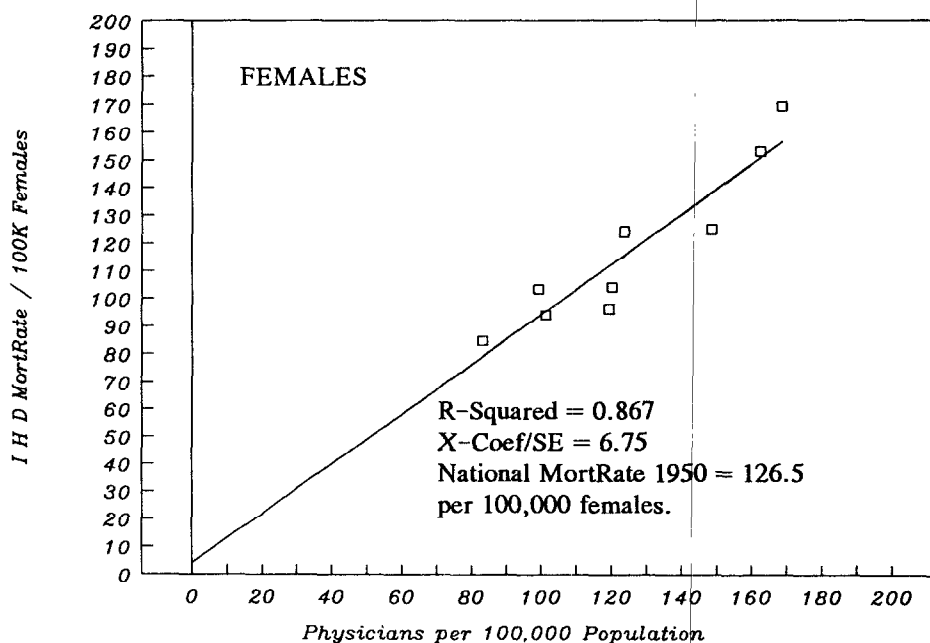
Please refer to Parts 5a-5d of this chapter. In each graph, the line of best fit results from regressing the 1940 All-Cancer Mortality Rates (male, female) on the 1940 PhysPop values. PhysPop (physicians per 100,000 population) is a surrogate for accumulated dose from medical radiation. The nine boxy symbols denote the observed values in the Nine Census Divisions. Full details are in Chapters 6 and 7.

MALES

R-Squared = 0.9508
X-Coef/SE = 11.63
National MortRate 1940 = 115
per 100,000 males.

All-Cancer MortRate/100K Males

Physicians per 100,000 Population

FEMALES

R-Squared = 0.8608
X-Coef/SE = 6.5801
National MortRate 1940 = 126.1
per 100,000 females.

All-Cancer MortRate/100K Females

Physicians per 100,000 Population

Related text = Parts 5a - 5d.

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Figure 1-B.
Ischemic Heart Disease: Dose-Response between PhysPop and MortRates.
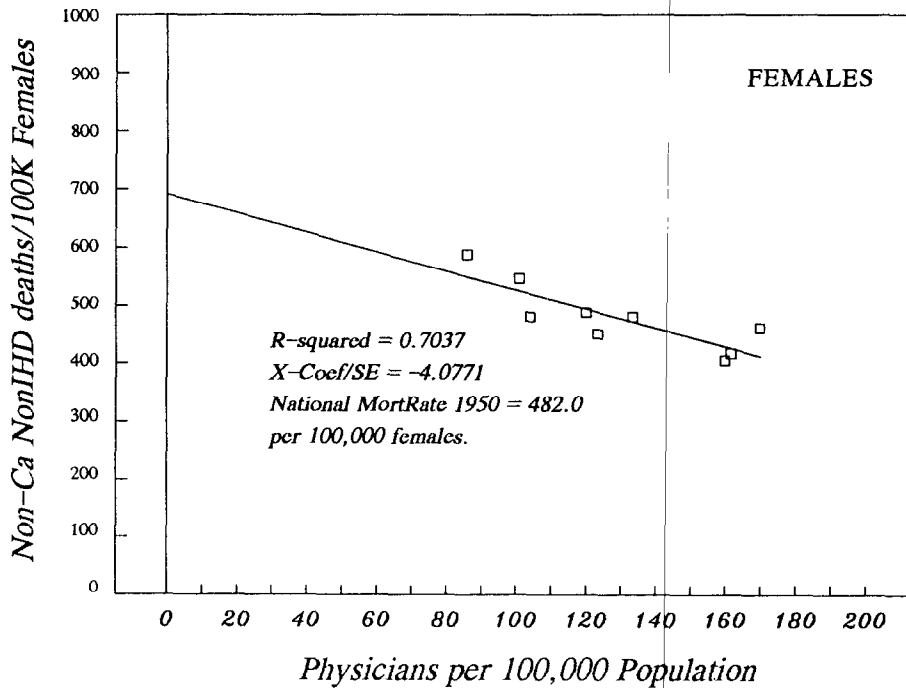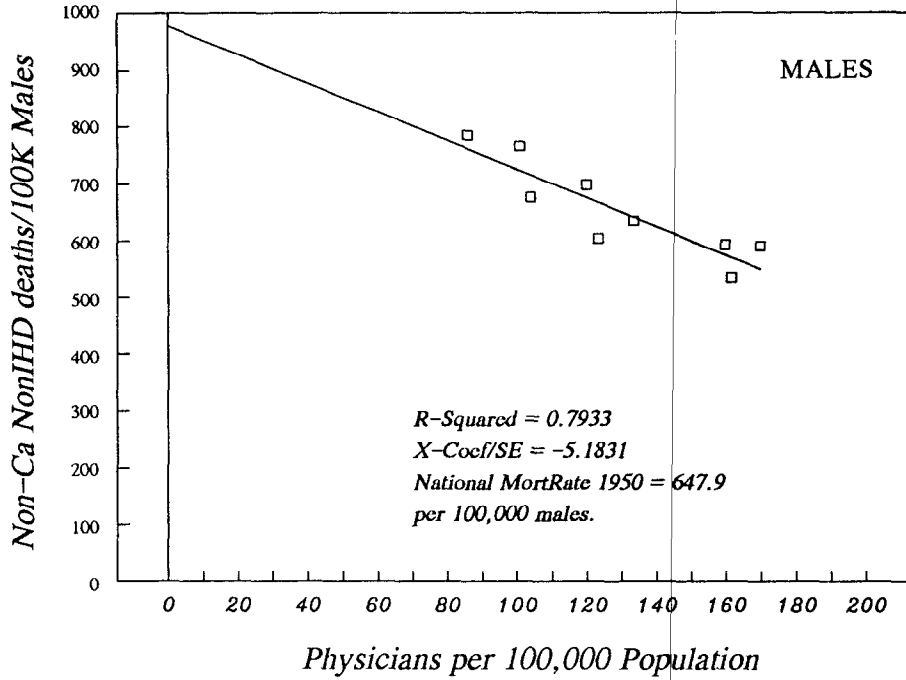
Please refer to Part 5f of this chapter. In the upper graph, the line of best fit results from regressing the age-adjusted male 1950 Mortality Rates from Ischemic Heart Disease on the 1940 PhysPop values. PhysPop (physicians per 100,000 population) is a surrogate for accumulated dose from medical radiation. 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.

MALES

R-Squared = 0.948
X-Coef/SE = 11.25
National MortRate 1950 = 256.4
per 100,000 males.

I H D MortRate, per 100K Males

Physicians per 100,000 Population

FEMALES

R-Squared = 0.867
X-Coef/SE = 6.75
National MortRate 1950 = 126.5
per 100,000 females.

I H D MortRate / 100K Females

Physicians per 100,000 Population
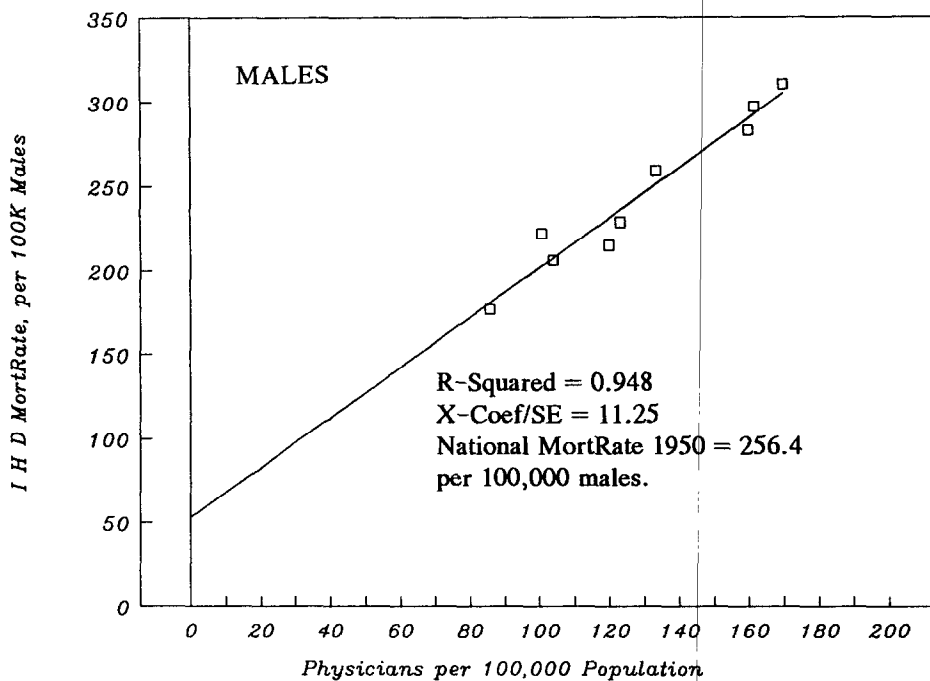
Figure 1-C.
NonCancer NonIHD Deaths: Dose-Response between PhysPop and MortRates.

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 in Chapter 25.

R-Squared = 0.7933
X-Coef/SE = -5.1831
National MortRate 1950 = 647.9
per 100,000 males.

Non-Ca NonIHD deaths/100K Males

Physicians per 100,000 Population

R-squared = 0.7037
X-Coef/SE = -4.0771
National MortRate 1950 = 482.0
per 100,000 females.

Non-Ca NonIHD deaths/100K Females

Physicians per 100,000 Population

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 pioneering 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 subject."

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.

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