Our Findings: In Conflict with Existing Evidence?

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       If two sets of findings in science are inherently contradictory, then at least one set must be untrue (and possibly both sets are untrue). Among scientific truths, harmony is a requirement. So, the last stage of checking our own work for errors is to ask: Are our estimates of Fractional Causation by medical radiation, of mortality rates from Cancer and Ischemic Heart Disease, incompatible with any OTHER evidence which we and others properly regard as incontrovertible?

       This chapter tests some "general wisdom" and some incontrovertible facts, for potential conflicts with our own findings. Earlier chapters have already examined several aspects of the issue.

● Part 1. Do Our Findings Conflict with High Fractional Causations by Smoking and Diet?

       Part 1 addresses the question: Do our findings, of high Fractional Causations by medical radiation, conflict with estimates of high Fractional Causations by smoking and by unfavorable nutrition?

       A piece of "general wisdom" is that about 30% of cancer deaths are attributable to tobacco and another 35% are attributable to unfavorable nutrition (AICR 1997). In addition, there are estimates that at least 10% of cancer deaths are caused by occupational exposure to carcinogens in the workplace (Landrigan 1996, p.67, citing Landrigan 1989). Additional estimates attribute 5% to 10% of cancer deaths to inherited mutations.

       Even if the estimates above were incontrovertible, such estimates would be fully compatible with our findings that Fractional Causation by MEDICAL RADIATION exceeds 50%. Reminder: Explanation of the compatibility occurs in this monograph's Introduction (Part 5).

   1a. The Meaning of "Cause" When Cases Have More Than One Cause

       A statement, that two or more co-actors each contribute to the same fatal case of a disease, means that each contribution is necessary --- for if the death would have happened as it did in the ABSENCE of one, then that one did not really contribute anything to the outcome. The concept of necessary co-actors was stated very nicely by the authors of the famous 1964 "Surgeon General's Report" on smoking (SurgeonGen 1964, 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."

       Among current cancer biologists, the concept --- that more than one cause per case is generally required --- is widely embraced as part of the initiation-promotion, multi-step, multi-mutation models of carcinogenesis. Such co-action has been discussed in the Introduction (Parts 4 + 5), Chapter 6 (Part 6), and Chapter 49 (Part 2).

       We know of virtually no one, today, who thinks that each case of fatal Cancer has a single

cause. When estimates are made about the percentage of Cancer caused by smoking, or by unfavorable nutrition, or by medical radiation, such estimates do not imply that such causes act alone. Such estimates refer to the share of Cancer which would be absent (prevented) by the absence of that particular cause. Example:

Our work indicates that Fractional Causation of the cancer MortRate (male) in 1988 was about 74% by medical radiation. The work also indicates that Fractional Causation of the male MortRate from Ischemic Heart Disease in 1993 was about 63% by medical radiation. These findings refer to the percentages in which medical radiation was a necessary co-actor --- and thus, the percentages which would not have occurred in the absence of exposure to medical radiation.

1b. A Distinction between Our Cancer-Findings and our IHD-Findings

The findings summarized in Chapter 66 show that, during the Twentieth Century, medical radiation has become a necessary co-actor in a very large share of the mortality rate from Cancer (USA), and the findings very strongly indicate that the same is true for Ischemic Heart Disease. The distinction lies in the fact that medical radiation is already a PROVEN cause of Cancer, whereas the evidence in this book is the FIRST evidence that medical radiation is a cause also of Ischemic Heart Disease.

With respect to Cancer, our findings do not conflict at all with the "general wisdom" about the importance of tobacco, nutrition, workplace (and environmental) carcinogens, and of inherited mutations in cancer-causation. Regarding inherited mutations, we suspect that they have a predisposing role in probably the majority of cancer-deaths (Gofman 1994, Chapter 7, Part 2b). With respect to Ischemic Heart Disease, our findings do not conflict at all with the very important roles, already well established, for various non-xray co-actors in that disease, including elevated blood-levels of atherogenic lipoproteins, high blood-pressure, smoking, diabetes, and many others (Chapters 44, 45, 46).

● Part 2. If All Cancer-Types Share Xrays as a Key Cause, Why Not Share One MortRate Trend?

Part 2 addresses the question: If all kinds of Cancer share medical radiation as a key cause, why do they NOT share the same trend in their MortRates? (Part 2a describes the trends.) Why have MortRates increased for some types of Cancer and simultaneously decreased for others? We think that the question's correct answer is co-action --- multiple causes per fatal case --- as illustrated in Part 2b.

2a. Some Nearly "Incontrovertible" Facts: Figure 67-A

We consider the simultaneous rise and fall of MortRates, for different types of Cancer, to be "incontrovertible." We have called attention to this phenomenon, not only in Chapter 22 (Part 1c) and in Chapter 58, but also by featuring such changes in every Table "A" of Chapters 49 through 63.

Figure 67-A depicts the contrast in MortRate-trends among nine types of Cancer, for the period 1930-1988. For the MortRates which decline in those graphs, the explanation is almost certainly NOT a rising fraction of cured cases --- because the declining MortRates embrace years when there were very few effective treatments for Cancer. The 1930 MortRates in Figure 67-A necessarily omit a few states (Chapter 4, Part 1), but the 1930 age-adjusted rates may be reliable enough to say that the trend was DOWNWARD between 1930-1940 for the following three types of Cancers in Figure 67-A (and may have been downward long before 1930):

Females: Uterus (cervix + corpus), Stomach, Liver.
Males: Stomach, Liver.

We note a common feature among these three types of Cancer, which appear to have had declining MortRates between 1930 (or earlier) and 1940: Infectious agents are regarded as extremely important causes. Cervical Cancer is causally associated with the Human Papilloma Virus (Chapter 14); Stomach Cancer, with the bacterium, Helicobacter pylori (Chapter 57); Liver Cancer (Hepatocellular Carcinoma), with infection by the Hepatitis Virus, usually type-B (WHO 1996, p.59).

2b. At Constant Xray Dosage: Opposite MortRate Trends

In any decade, the Observed Cancer MortRates are the result of co-action among carcinogens --- the presence of which has been rising for some co-actors, constant for other co-actors, and falling for other co-actors. Unlike xrays, which have access to every organ of the body, chemical and infectious carcinogens do not necessarily have "universal access", nor do they necessarily have equal activity within cells of different organs. Thus if exposure decreases to some non-xray co-actors for Liver Cancer, while exposure simultaneously increases to some other non-xray co-actors for Respiratory-System Cancers, the outcome (at constant exposure to xrays) is very likely to be MortRates which simultaneously decline for Liver Cancer and rise for Respiratory-System Cancers. And yet Fractional Causation, by medical radiation, can remain high for these two Cancers --- which have OPPOSITE trends in their MortRates.

How can this happen? An uncomplicated model can suffice here, although additional models also are consistent with our findings. (Chapter 49, Part 2b, provides two related illustrations.)

We can suppose that Liver Cancer requires the presence of two carcinogenic mutations in the same cell, and that by mid-century, medical radiation has become the source of one (sometimes both) of the mutations in most cases of Liver Cancer. Also, we can suppose that the U.S. population consists of 1,000,000 persons, and that they have a combined total 1,000 "liver-cells" which have acquired, or will acquire, one of the necessary mutations from MEDICAL XRAYS.

Lowering the cells' exposure, to non-xray mutagenic co-actors, reduces the fraction of those 1,000 cells which ever acquire both of the required mutations. Result: A falling MortRate from Liver Cancer. By contrast, increasing the cells' exposure, to non-xray mutagenic co-actors, increases the fraction of those 1,000 cells which ultimately acquire both of the required mutations. Result: A rising MortRate from Liver Cancer. Yet, in either case (a falling or a rising MortRate from Liver Cancer), medical radiation can be a necessary co-actor in most of the fatal cases of Liver Cancer which DO occur.

If one repeats the illustration for Respiratory-System Cancers, it is clear that livers and lungs, which may share the SAME history of medical radiation, can develop OPPOSITE trends in their Cancer MortRates.

● Part 3. Did Cancer MortRates RISE Enough after the Year 1900?

Part 3 addresses the question: Did Cancer MortRates RISE enough after the year 1900 to be consistent with our findings?

3a. The Solid Basis for an Affirmative Answer

The answer is, yes. Indeed, even a post-1900 decline in the age-adjusted National All-Cancer MortRate would be compatible with our findings of high Fractional Causation by medical radiation. Fractional Causation refers to the age-adjusted National Cancer MortRates which DID OCCUR in post-1900 decades, and is independent of whether the trend in post-1900 Cancer MortRates was rising, flat, or falling (a point made in Chapter 22, Part 1c).

Introduction of medical radiation in 1896 requires that the RADIATION-INDUCED SHARE of All-Cancer MortRates must rise from zero percent in 1896 to some positive fraction in subsequent decades --- fractions whose quantification has been the goal of our research. But introduction of medical radiation does not automatically require a net rise in post-1900 All-Cancer MortRates. After all, specific non-xray causes may have declined after 1900. So, the direction of post-1900 All-Cancer MortRates can not be predicted --- the direction can be learned only by observation.

3b. Age-Adjusted All-Cancer MortRates: Post-1900 Trends

The available records indicate that the age-adjusted All-Cancer MortRate rose dramatically in the USA between 1900 and 1940. For males and females combined, including all "races" without any exclusions, the age-adjusted rate rose from 79.6 per 100,000 population in the year 1900, to 120.3 per 100,000 in the year 1940 --- an upward change by a factor of 1.5 --- an increase by 50%.

Box 1 shows the sources of these data, and shows how the crude rate in 1900 (which was 64.0 per 100,000) converts to the age-adjusted rate in 1900 of 79.6 per 100,000. The "general wisdom," that age-adjusted Cancer MortRates increased by a large factor between 1900 and 1940, is probably solid (perhaps even "incontrovertible"). However, we have little faith that the specific factor of 1.5 is reliable.

One source of unreliability in the factor of 1.5 is the fact that the 1900 records include only the ten "registration states" (Chapter 4, Part 1), whereas the 1940 data include all 48 states. So this is a comparison of "apples with oranges." Would complete data from 1900 increase the factor of 1.5, or lower it? It will never be known. A second source of unreliability is present if there was greater under-reporting of Cancer in 1900 than in 1940. Approximately 38% of deaths which occurred in 1900 "had no cause listed," according to Patterson 1987 (p.80), who states also that it was acceptable to report "old age" as a cause of death. How many cancer deaths in 1900 were never reported as Cancer? This, too, will never be known. Even in 1940, there was a stigma associated with having a cancer death in the family, and the stigma --- absurd though it was --- may have been stronger in 1900. These considerations (and some others) make the upward change-factor of 1.5 unreliable for the age-adjusted National All-Cancer MortRates. As for Ischemic Heart Disease, there are no records back to 1900. However, for the reasons stated in Part 3a, the magnitude of the change-factors, for Cancer and IHD MortRates between 1900 and mid-century, is essentially irrelevant to the validity of our findings on Fractional Causation by medical radiation --- as is the magnitude of the change-factor between 1940 and 1990.

3c. National Cancer MortRates (Box 2): Trends from 1900 to 1990

For everyone's convenience, we present a comparison right here of the National All-Cancer MortRates (USA) for various decades. The intervening decades are shown in the bottom section of Box 2. These rates are for males and females combined, per 100,000 population, and the non-1940 rates are age-adjusted to the population's age-distribution in 1940. The entries, prior to 1940, do not include all the states (Chapter 4, Part 1). The year 1900 includes the fewest states (only ten).

1900 = 79.6   1920 = 104.9   1940 = 120.3   1960 = 129.1   1990 = 135.0

In contrast with the bottom section of Box 2, the upper section of Box 2 presents the age-SPECIFIC All-Cancer MortRates (USA) from the year 1900 through 1990. Because each row displays rates per 100,000 persons of the SAME age, these entries can be directly compared across time. Illustration: Per 100,000 persons who REACH age 60, the row for ages 55-64 gives directly comparable cancer death rates across nine decades. With respect to the early decades, the warnings given in Part 3b apply also to Box 2.

For cancer death below age 45, rates peaked around 1950, and then declined. For cancer death at about age 50, the peak was in 1970. For cancer death above age 54, the age-specific rates have been climbing ever since the year 1900. In the mid-1990s (not shown), a slight decline may have occurred. We hope that the decline endures --- but we note that the decline in 1970 for ages 85+ did NOT endure.

The rates in Box 2, like the rates in Box 1, are fully consistent with our findings about Fractional Causation by medical radiation (Part 3a).

● Part 4. Did Cancer and IHD MortRates Rise Enough after PhysPop's Post-1965 Rise?

Part 4 addresses the question: Did National MortRates from Cancer and Ischemic Heart Disease rise enough to be consistent with the spectacular post-1965 rise in PhysPop values?

There is very little doubt that PhysPop values rose dramatically in all Nine Census Divisions after 1965 (after the enactment of Medicare and related legislation). Readers can see this for themselves in Chapter 3, PhysPop Table 3-A and in the top half of Figure 3-A. Although the National Average PhysPop values in Table 3-A are not weighted by the populations of the Census Divisions, the National Averages there are good approximations. The National Average was 133.01 in 1965, and was 233.72 in 1990 --- an upward change-factor of 1.76.

Concurrently, the National All-Cancer MortRate (Table 6-B) rose, from 129.1 in 1960, to

135.0 in 1988 --- an upward change-factor of 1.05. The National Ischemic Heart Disease MortRate (Table 40-B) fell, from 190.0 in 1960, to 94.9 in 1993 --- a downward change-factor of 0.50.

Should these virtually incontrovertible facts raise any doubt about the importance of medical radiation in causation of both diseases? Not at all. Hypotheses 1+2 say that medical radiation is a required co-actor in most of the fatal cases which DO occur, but Hypotheses 1+2 certainly do NOT require cancer and IHD MortRates to rise by 1.76-fold if PhysPop rises by 1.76-fold. Why not?

● (1) Physpop is PROPORTIONAL to dose in rads from medical radiation, but PhysPop is not EQUAL to such dose. Even while annual PhyPop values rise by 1.76-fold , average annual per capita dose from medical radiation could actually decline, if dosage per procedure declines sufficiently, for instance. Indeed, although there is no way to prove it, we believe that an unquantifiable net decline HAS occurred since 1960 in average annual per capita dose from medical radiation (Chapter 2, Part 3g) --- and most people in medicine seem to make the same assumption. Whatever the change, it is reasonable to assume that the change-factor has been similar in all Nine Census Divisions.

● (2) Even if annual per capita xray dosage had grown by 1.76-fold between 1965 and 1990 (which almost certainly did not occur), still there would be no reason to expect a simultaneous 1.76-fold increase in the MortRates from Cancer and IHD. The very gradual delivery of radiation-induced Cancer, in a mixed-age population, means that the full effect of any new dose-level would not occur until at least 45 years later (Chapter 2, Part 8, and Chapter 5, Part 1). And even if a 1.76-fold elevated dose-level were maintained for at least 45 years beyond 1990, still one should not expect MortRates from Cancer and IHD to rise 1.76-fold by the year 2035 (1990 + 45 years) --- unless exposure to co-actors had been constant (Point 3, below).

● (3) The per-rad potency of ionizing radiation --- the X-coefficient --- is modulated by co-actors (Chapter 49, Part 2). If exposure to co-actors is not constant over time, the X-coefficient for dose (PhysPop) will not be the same in every decade. Abundant evidence, of change in exposure to non-xray co-actors over time, is another reason for NOT expecting PhysPop values and MortRates for Cancer and IHD to change by the same factor (1.76, for instance). Cigarettes provide a noteworthy example of change in a co-actor. When PhysPop values experienced their big increase after 1965 in the USA, cigarette consumption simultaneously experienced a big decline in the USA (Chapter 48, Part 2a). Hypertension is another important co-actor for Ischemic Heart Disease. Death-rates from Hypertension (age-adjusted to the 1940 reference year) fell from about 68 per 100,000 population in 1940 to about 4 per 100,000 in 1990 --- as approximated from Figure 40-B. This dramatic decline almost certainly reflects a reduction also in the average severity of non-fatal cases of Hypertension. With respect to Cancer, Figure 67-A reflects big changes in levels of some unspecified co-actors (discussion in Part 2, above).

● (4) There is a fourth reason, for NOT expecting PhysPop values and MortRates (from Cancer, IHD) necessarily to change by the same factor in the same direction. It is the expectation that better underlying health and better treatments can prevent a growing share of radiation-induced cases from becoming fatal.

● **Part 5. Are the Findings on Cancer Compatible with Existing Data on Xray Dose?**

Part 5 addresses the question: Are the new findings, that medical radiation accounts for a very large share of all cancer deaths in the USA, compatible with existing data on dosage from medical radiation?

5a. A Solution to the Permanent Uncertainty about Dosage in Rads

We expect that this new work will face the following claim from some people: Doses from medical radiation have never been high enough to cause such a Roentgen Tragedy. Such assertions, about past and current dosage, would not be based on any "well established" evidence --- as readers of Chapter 2 (Part 3) already know.

Of course, we do not expect such claims from anyone who has READ this work. Readers will understand that Fractional Causation in this work is not tied to specific dose-levels in rads. It is tied to the RELATIVE size of per capita medical doses in the Nine Census Divisions, as indicated by the relative number of physicians per 100,000 population.

And this tie, to the RELATIVE magnitude of per capita doses, is one of the important scientific strengths of our method. Our analysis has tested (and validated) Hypothesis-1 without resorting to any questionable estimates, in medical RADS, of average annual per capita doses from medical radiation. Estimates in rads could easily be wrong by factors like 3 to 10.

A related strength of our method is that it employs no estimates of risk per medical rad. While the evidence is incontrovertible that medical xrays induce cancer, the NUMBER of cases induced per medical rad is far from being a settled issue (Chapter 2, Part 7c) --- which is inevitable when the doses are so very uncertain in most of the studies which produce the risk-per-rad estimates.

Instead of depending on controversial estimates of doses and of risk per unit dose, we have let the RELATIVE sizes of medical doses, in the Nine Census Divisions, directly reveal the magnitude of Fractional Causation of cancer death-rates by medical radiation.

5b. Breast Cancer: Two Analyses Tied to Estimated Doses and Risk/Rad

By contrast with this book, our previous monograph (Gofman 1995/96) examines the induction of only Breast Cancer by medical radiation. In Gofman 1995/96, we undertook a scholarly effort to estimate average annual per capita breast-dose received in the USA by females of various ages, during forty relevant years (1920 - 1960). We determined an estimate of such dose, and then multiplied dose by the number of Breast Cancers (per 10,000 females) expected per rad of breast-irradiation --- based largely on our earlier work (Gofman 1990). The resulting number of radiation-induced Breast Cancers, divided by the total annual incidence of 182,000 Breast Cancers (USA, in 1995), yielded a Fractional Causation by medical radiation of 75% of current annual Breast Cancer incidence.

Reviewing our book in the Journal of the American Medical Association, the American Cancer Society's Clark W. Heath, Jr., began as follows (Heath 1995, p.657): "Although breast tissue is particularly sensitive to the carcinogenic effects of ionizing radiation, especially at young ages, it is likely that less than 5% of all Breast Cancer in the United States can be attributed to radiation and less than 1% to medical uses of radiation (Evans 1986)." There is a 75-fold difference in these two estimates (Evans compared with Gofman).

The Input on Estimated Dose to Breasts

The 1986 Evans' estimate, conspicuously embraced by Heath, was based on an average lifetime dose to the breasts of 2.1 rad "from diagnostic radiographs" (Evans 1986, p.812) of the 1970-1980 variety, whose types and frequency were assessed primarily from the 1977 records of Blue Cross, Medicare, and Medicaid patients in Maine (McNeil 1985), and whose presumed doses per exam were calculated with phantoms and Monto Carlo simulations. Breast irradiation received during interventional fluoroscopic procedures was omitted entirely. Estimated doses received during diagnostic fluoroscopy were included, but in the related paper (McNeil 1985, p.55), fluoroscopic doses were acknowledged to be uncertain due to "marked variations in fluoroscopy times and technique."

In making their estimate of Fractional Causation, Evans and co-workers used the 1980 Mortality Rates from Breast Cancer (Evans 1986, p.812). Breast irradiation occurring in 1977 had very little impact on the 1980 MortRates from Breast Cancer. For Breast-Cancer deaths in 1980, the average annual breast-dose during the 1920-1960 period is certainly much more relevant, but Evans and co-workers did not evaluate such doses.

By contrast, our careful study of practices in the 1920-1960 period yielded 27.9 rads as the relevant lifetime average breast-dose from diagnostic, interventional, and non-cancer therapeutic radiologic procedures (Gofman 1995/96, p.267, Col.T).

The Input on Estimated Risk of Breast Cancer per Rad

It is clear that dose-estimates account for about a 13.3-fold difference (Evans compared with Gofman), in estimates of Fractional Causation of recent Breast Cancer by medical radiation. Because 13.3 times 5.64 = 75, a disparity of only about 5.64-fold in estimated risk of Breast Cancer, PER RAD, would account for the 75-fold difference in estimated Fractional Causation.

When Evans et al chose the risk/rad estimates they used, they correctly acknowledged (Evans

1986, p.811): "The limitations of the available data and the reliance on unverified assumptions introduce uncertainty into any estimates of risk." We, too, explicitly emphasized the inherent uncertainties about risk per rad (Gofman 1995/96, p.273, 276, 281, 285). Indeed, available evidence explicitly on xray-induced Breast Cancer yields a 6-fold range in estimated risk per rad (BEIR 1990, p.255). The Evans paper uses risk/rad estimates which exclude the 6-fold higher values from the Nova Scotia evidence (Evans 1986, p.811), and employs risk models prepared by Gilbert for the Nuclear Regulatory Commission (Evans 1986, p.810; see specifically Gilbert 1985).

No Conflict between Our Findings and Well-Established Facts

A difference in estimates of Fractional Causation, traceable to openly acknowledged uncertainties, clearly does not amount to a conflict between any of our findings and well-established, scientifically-solid facts. There is no mystery why estimates of Fractional Causation will continue to vary so dramatically, if analysts continue to depend exclusively on two key inputs whose values are so uncertain. By contrast, the method used in this book is independent of uncertain estimates of dose and of risk per dose-unit --- as emphasized in Part 5a.

5c. Two Routes --- but Arrival at a Single Answer

Because of claims like Clark Heath's (Part 5b), it is interesting to compare our results for Breast Cancer in the 1995/96 monograph, with the results for Breast Cancer in this monograph --- where the results are derived from a method and from data which are completely independent from the earlier analysis.

Gofman 1995/96:   75% of Breast-Cancer Cases in 1995 induced by medical radiation.
This analysis: 83% of Breast-Cancer Deaths in 1988 induced by medical radiation.

Naturally, we are pleased that both sets of findings are compatible --- indeed, nearly identical. But if someone asks which estimate we trust the most, the answer will be that we regard the results produced in this monograph as the more reliable --- due to the superior method.

Indeed, for several reasons, we doubt that there will ever be a MORE reliable test of Hypothesis-1 than the testing in this book. The first reason is that this testing avoids the pitfalls described in Part 5a. The second reason is that our testing "enrolled" the entire U.S. population in nine dose-cohorts (the Census Divisions) --- and a large prospective study is more likely to be correct than a small one, all other things being equal. The third reason, already discussed in Chapter 3 (Part 1c), is that this testing has been done by a straightforward, replicable method using utterly neutral data --- data collected long ago for other purposes and thus free from any conceivable bias with respect to Hypothesis-1.

● Part 6. Is the New Finding about IHD in Conflict with the A-Bomb Study?

Part 6 addresses the question: Is our finding, that medical radiation even at low and moderate doses is an important cause of Ischemic Heart Disease, in conflict with any well-established findings from the Atomic-Bomb Survivor Study?

There appears to be no conflict. We say "appears" because we have not analyzed the Japanese IHD data ourselves, using the "constant-cohort, dual dosimetry" method described in Chapter 2 (Part 5c). Between what OTHERS have recently reported from the A-Bomb Study regarding Ischemic Heart Disease, and what we report from our PhysPop studies in this monograph, there is no conflict.

6a. Positive Dose-Response in People below Age 40 during the Bombings

What do analysts at RERF report? Yukiko Shimizu, Hiroo Kato, William Schull, and Donald Hoel present the findings on Coronary Heart Disease (Ischemic Heart Disease) within the Life-Span Study, in a 1992 paper (Shimizu 1992, Table 6, p.255). The IHD results in their Table 6 are limited to the 1966-1985 time-period, and to IHD deaths among participants who were under age 40 at the time of bombing in 1945. The doses are entrance doses, not internal organ-doses (Shimizu, p.250), and they are bomb-rads, not medical rads. To convert bomb-rads to medical rads, the bomb-rads need multiplication by a factor of about 0.375 (details in Chapter 2, Part 7d). The total deaths from

Coronary Heart Disease in the study-sample are 363 deaths, distributed as follows (from Shimizu 1992, Table 6, p.255):

IHD deaths = 136.	Dose = 0.	Relative risk = 1.0.
IHD deaths = 190.	Entrance dose = 1-49 rads.	Relative risk = 1.35.
IHD deaths = 19.	Entrance dose = 50-99 rads.	Relative risk = 1.25.
IHD deaths = 8.	Entrance dose = 100-199 rads.	Relative risk = 0.92.
IHD deaths = 6.	Entrance dose = 200-299 rads.	Relative risk = 2.57.
IHD deaths = 4.	Entrance dose = 300-600 rads.	Relative risk = 2.38.

Although Shimizu's Table 6 does not show the number of participants in each dose-group, Shimizu's calculation of relative risk is, of course, the observed number of IHD deaths per 100 participants in an exposed group, divided by the observed number of IHD deaths per 100 participants in the zero-dose group.

We note the anomalous relative risk value of 0.92 in the middle of a positive dose-response trend. Biologically, the anomaly is improbable, while statistically, it is rather probable --- since it arises from only 8 cases.

6b. An Interesting Comment on CardioVascular Disease by Shimizu et al

The 1992 Shimizu paper also reports (Shimizu 1992, p.254): "Mortality from circulatory disease [cardio-vascular disease] in the years 1950-1985 shows a significant association with dose." Commenting later in their paper on this finding, Shimizu and co-workers seem to entertain the possibility that radiation-induced genetic mutations play a role in atherosclerosis. In their comment, below, they allude to the work of Arthur Penn (our Chapter 44, Part 9c) and to the concepts of stochastic and non-stochastic phenomenon. If a radiation-induced health disorder has a stochastic basis, its probability of OCCURRING in an exposed population is a function of dose; if it has a non-stochastic basis, the SEVERITY of radiation-induced cases will be a function of dose. Here is their comment, in full (Shimizu 1992, p.260):

"It is not unreasonable to assume that the effects of radiation on cancer induction (which is presumed to be a stochastic phenomenon) and on noncancer mortality differ, and that the latter may follow a nonstochastic process with a threshold dose. However, given the recent evidence of a transforming gene in the DNA from an atheromatous plaque (Penn 1986), the increase in cardiovascular disease is a particularly intriguing finding, and may suggest, if the association is real, that the effect of ionizing radiation on atherosclerosis should be treated as a stochastic phenomenon. Further data will be especially interesting in this regard."

Our own findings in this monograph, which arise from enormous databases (males and females separately), demonstrate a powerful dose-response between medical radiation and mortality from Ischemic Heart Disease. Such findings provide the first very strong epidemiologic evidence that ionizing radiation has a causal role in Ischemic Heart Disease. Moreover, the role of medical radiation is large, not small. In the USA, Fractional Causation indicates that medical radiation has been and continues to be an extremely important cause of fatal cases of Ischemic Heart Disease.

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Box 1 of Chapter 67

Century Begins: Year-1900 Age-Specific and Age-Adjusted All-Cancer MortRates (USA).

● This box (for the year 1900) is directly comparable to Box 4 of Chapter 4 (for the year 1990).

● Col.A entries are the observed age-specific 1900 All-Cancer MortRates per 100,000 [100K] population of each age-band, for both sexes combined. The data cover only the ten "Death-Registration States" (Chapter 4, Part 1). Source: Linder 1947, Table 14, p.250. The crude rate in 1900, before adjustment to the 1940 reference year, is 64.0 per 100,000 population (Linder 1947, Table 14, p.250).

● Col.B is the weighting factor, from the "Standard Million Population, 1940" (see Chapter 4, Box 1, "Fraction of Total").

● Col.C is the product of Col.A times Col.B. The SUM of Col.C is the 1900 age-adjusted MortRate, adjusted to the 1940 reference year: 79.5788 per 100,000 population. This age-adjusted rate, of 80 per 100,000 population, is confirmed in Grove 1968, Figure 21, p.87.

● Col.D divides each entry in Col.C by 79.5788, and thus determines the fraction of the 1900 Age-Adjusted Rate (79.5788 per 100,000) contributed by each age-band. The sum of the fractions for age 45 and older = 0.86550, or 86.5% .

Age-Band	Col.A AgeSpecific Rate/100K	Col.B Weighting Factor	Col.C = A times B	Col.D = Col.C / 79.5788
Under 1 yr	3.2	0.015343	0.04910	0.00062
1-4	2.9	0.064718	0.18768	0.00236
5-14	1.8	0.170355	0.30664	0.00385
15-24	3.2	0.181678	0.58137	0.00731
25-34	14.0	0.162065	2.26891	0.02851
35-44	52.5	0.139237	7.30994	0.09186
45-54	139.1	0.117811	16.38749	0.20593
55-64	260.9	0.080294	20.94861	0.26324
65-74	421.0	0.048426	20.38726	0.25619
75-84	544.7	0.017304	9.42536	0.11844
85 and up	623.2	0.002770	1.72640	0.02169
CANCER Sums		1.000000	79.5788	1.0000

For All-Cancer MortRates per 100,000 population (USA), this box presents age-SPECIFIC rates in its upper section, and age-ADJUSTED rates in its lower section, for males and females combined. Prior to 1933, not all states reported. Entries for 1900 are based on the fewest states (only ten).

Sources are (1) Vital Statistics Rates in the United States 1900-1940 (Linder 1947 in our Reference List, p.250, Table 14, "Death Rates" for "Cancer and Other Malignant Tumors, 45-55") and (2) Health: United States 1995 (PHS 1995 in our Reference List, p.132, Table 39, "Death Rates for Malignant Neoplasms").

Because entries in the upper section are age-specific rates, per 100,000 population of each age-band, different decades can be directly compared without age-adjusting.

Age	1900	1910	1920	1930	1940	1950	1960	1970	1980	1990
Under 1 year	3.2	3.1	3.2	3.1	4.4	8.7	7.2	4.7	3.2	2.3
Ages 1-4	2.9	3.3	3.1	4.1	4.8	11.7	10.9	7.5	4.5	3.5
Ages 5-14	1.8	1.5	1.6	2.0	3.0	6.7	6.8	6.0	4.3	3.1
Ages 15-24	3.2	3.5	3.8	4.2	5.4	8.6	8.3	8.3	6.3	4.9
Ages 25-34	14.0	14.1	14.7	16.7	17.3	20.0	19.5	16.5	13.7	12.6
Ages 35-44	52.5	55.6	56.0	58.9	61.1	62.7	59.7	59.5	48.6	43.3
Ages 45-54	139.1	156.7	155.1	159.6	168.8	175.1	177.0	182.5	180.0	158.9
Ages 55-64	260.9	322.4	341.2	355.6	369.6	392.9	396.8	423.0	436.1	449.6
Ages 65-74	421.0	541.7	607.7	677.1	695.2	692.5	713.9	751.2	817.9	872.3
Ages 75-84	544.7	749.9	900.0	1,019.7	1,161.0	1,153.3	1,127.4	1,169.2	1,232.3	1,348.5
Ages 85+	623.2	810.9	1,017.5	1,196.3	1,319.0	1,451.0	1,450.0	1,320.7	1,594.6	1,752.9

Entries in the three rows below are the age-adjusted National Cancer Mortality Rates per 100,000 population. Cancer-deaths at all ages are included in these age-adjusted rates. Because each entry is adjusted to the same "standard population" (1940), the entries in this row are directly comparable with each other --- despite changes over the century in infant mortality, average lifespan, etc. The male-female difference after 1940 results largely from the males' much higher rate of Respiratory-System Cancers.

	1900	1910	1920	1930	1940	1950	1960	1970	1980	1990
Both Sexes	79.6	97.0	104.9	113.4	120.3	127.7	129.1	129.8	131.9	135.0
Males	--	--	--	--	115.0	132.8	145.7	155.1	164.5	162.7
Females	--	--	--	--	126.1	123.2	114.9	111.7	108.5	111.3

Figure 67-A

Related text = Part 2a.
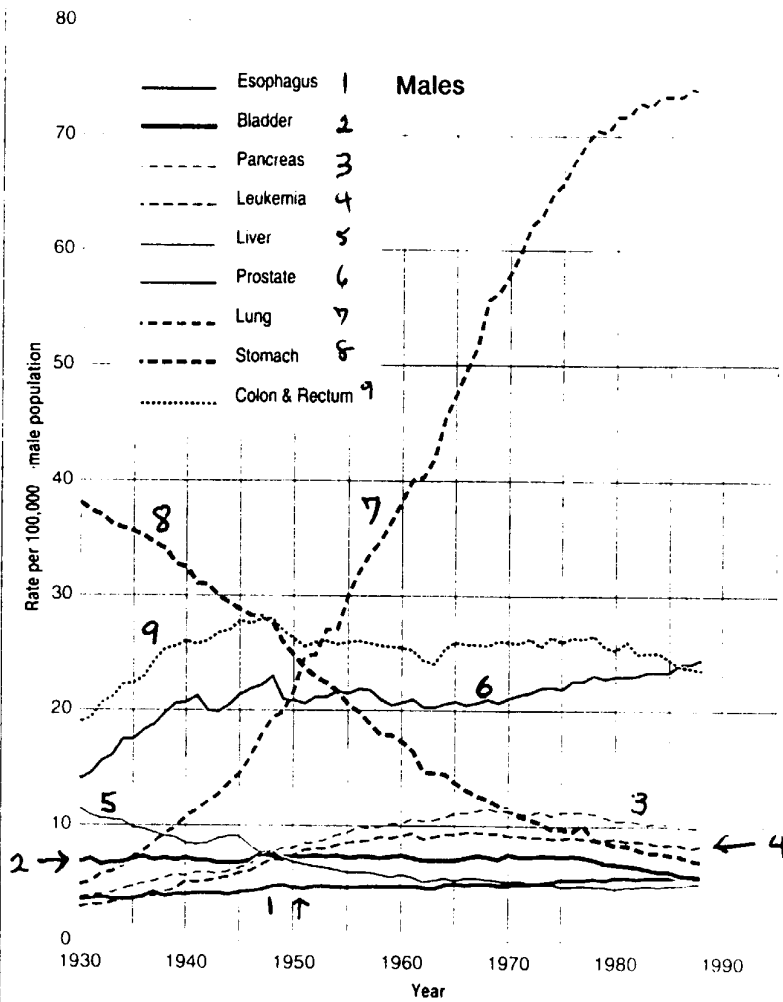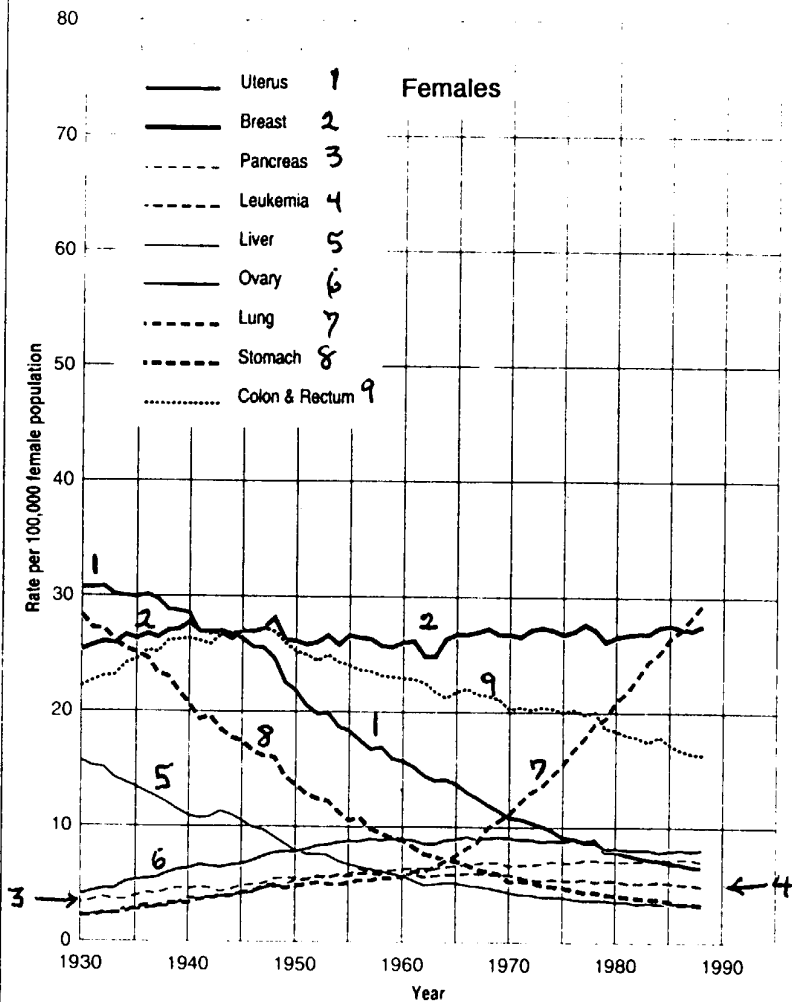
The two graphs above depict "Age-Adjusted Cancer Death Rates for Selected Sites, United States, 1930–1988." Except for our by-hand addition of the numerical labels, both graphs are reproduced from the January–February 1992 issue of the American Cancer Society's publication, CA – A Cancer Journal for Clinicians, Vol.42, No.1: pp.28–29. The age-adjustment by the ACS is to the age distribution of the 1970 U.S. Census. Sources of data: U.S. National Ctr. for Health Statistics and U.S. Bureau of the Census. (Reminder from Chap.4: Not every state reported Cancer MortRates in 1930.)

Trends in SEER Incidence Rates

Percent Change, 1973-94

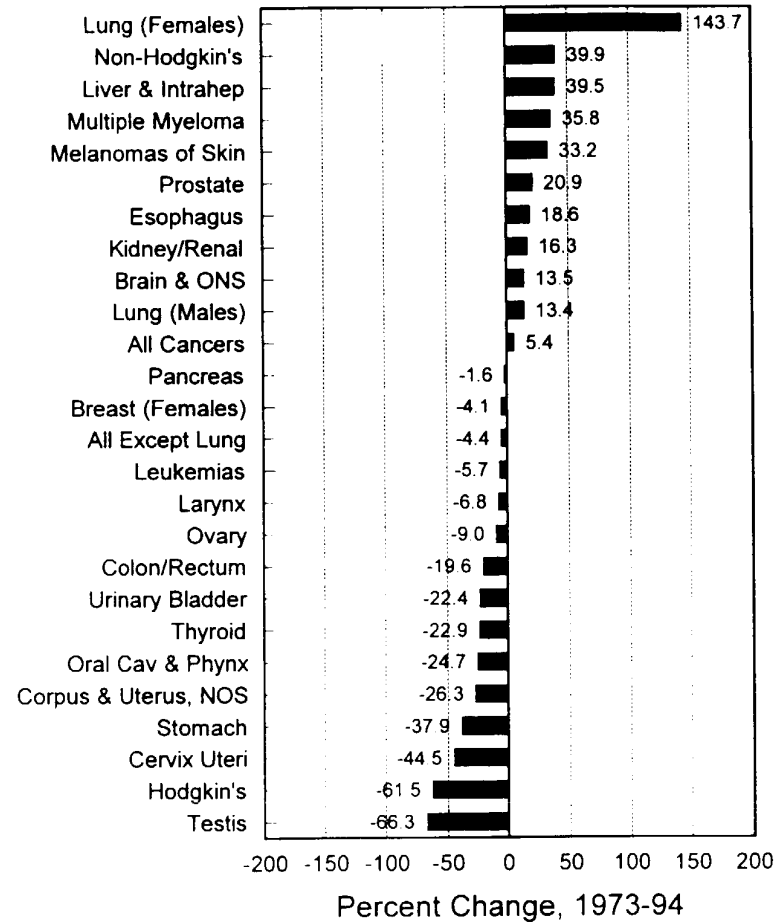| Cancer Site	Percent Change
Prostate	141.8
Lung (Females)	121.8
Melanomas of Skin	113.0
Non-Hodgkin's	80.6
Liver & Intrahep	61.0
Testis	50.6
Kidney/Renal	42.9
Thyroid	31.6
All Cancers	23.4
Breast (Females)	23.0
All Except Lung	22.2
Brain & ONS	18.5
Multiple Myeloma	14.4
Urinary Bladder	11.6
Esophagus	11.2
Lung (Males)	3.0
Ovary	0.5
Colon/Rectum	-5.2
Oral Cav & Phynx	-6.5
Leukemias	-9.3
Pancreas	-10.5
Larynx	-11.4
Hodgkin's	-15.5
Corpus & Uterus, NOS	-27.9
Stomach	-28.8
Cervix Uteri	-40.6

Trends in U.S. Cancer Mortality Rates

Percent Change, 1973-94

Cancer Site	Percent Change
Lung (Females)	143.7
Non-Hodgkin's	39.9
Liver & Intrahep	39.5
Multiple Myeloma	35.8
Melanomas of Skin	33.2
Prostate	20.9
Esophagus	18.6
Kidney/Renal	16.3
Brain & ONS	13.5
Lung (Males)	13.4
All Cancers	5.4
Pancreas	-1.6
Breast (Females)	-4.1
All Except Lung	-4.4
Leukemias	-5.7
Larynx	-6.8
Ovary	-9.0
Colon/Rectum	-19.6
Urinary Bladder	-22.4
Thyroid	-22.9
Oral Cav & Phynx	-24.7
Corpus & Uterus, NOS	-26.3
Stomach	-37.9
Cervix Uteri	-44.5
Hodgkin's	-61.5
Testis	-66.3

1973-1994

The two bar-graphs above depict "Trends in SEER Incidence and U.S. Mortality Rates by Primary Cancer Site, 1973-1994." They are reproduced from Figure I-4 at page 45 of SEER Cancer Statistics Review, 1973-1994 (SEER 1994 in our Reference List). SEER abbreviates Surveillance, Epidemiology, and End Results. SEER is a program, initiated in 1973 under the National Cancer Institute, to evaluate cancer incidence-trends in the USA. The trends in Incidence Rates are based on five states and four to six metropolitan areas (SEER 1994, p.1). Trends in the Mortality Rates are based on the entire USA.

Figure 67–B

Related text = Part 2.