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JAN 16 2003

C. W. Jameson, Ph.D.
Head, Report on Carcinogens
National Toxicology Program

Dear Dr. Jameson:

Jan. 9, 2002

In September 2001, I submitted comments on the nomination of x-rays as an established human carcinogen (RoC #11). One of your courteous e-mails in September 2001 stated that "The NTP will accept public comment at any time during the RoC review process for any nomination."

Therefore, with respect to x-rays and RoC #11, I am submitting a 5-page follow-up to my original submission. The follow-up (co-authored by Egan O'Connor) is entitled "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)."

As you will see, none of the critiques to date have identified any reason to reject or to modify the 1999 study.

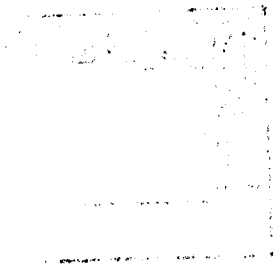
Will you see that this additional submission is transmitted to the persons who received the September 2001 submission and monograph? I would be grateful to hear from you about its disposition.

With all good wishes,

John W. Gofman

John W. Gofman, M.D., Ph.D.

P.S. For your convenience, I am enclosing several extra sets of the current 5-page submission. Because the font-size of the text and reference list is only 8-point, Egan O'Connor suggests that the NTP may need spare copies in order to prepare it for remaining legible in pdf format. That's something I know nothing about.



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

John W. Gofman, M.D., Ph.D., Professor Emeritus of Molecular & Cell Biology, Univ. of Calif. Berkeley
Egan O'Connor, Exec. Director, Committee for Nuclear Responsibility, Inc. (CNR), Publisher.

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• 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.

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And: http://www.x-raysandhealth.org
"X-rays and Health" is a CNR project.

• 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 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

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.

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?

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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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