4/20/82

UNITED STATES OF AMERICA
NUCLEAR REGULATORY COMMISSION

Before the Atomic Safety and Licensing Board

In the Matter of	)	
	)	
LOUISIANA POWER & LIGHT COMPANY	)	Docket No. 50-382
	)	
(Waterford Steam Electric Station, Unit No. 3)	)	

APPLICANT'S REBUTTAL TESTIMONY
OF GEORGE B. HUTCHISON ON
CONTENTION 8/9

Q1. Please state your name and address.

A1. My name is George B. Hutchison. My address is 677 Huntington Avenue, Boston, Massachusetts.

Q2. Briefly describe your current position and educational and vocational background.

A2. I am a Professor of Epidemiology at the Harvard University School of Public Health. I received an M.D. from Harvard Medical School in 1951 and a Master of Public Health degree from the Harvard School of Public Health in 1960. I was a member of the 1972 National Academy of Sciences Committee on the Biological Effects of Ionizing Radiation which produced the BEIR I Report. In addition, I am a Board Member of the National Council on Radiation Protection and Measurements. I have been involved in

the epidemiological study of cancer incidence, and in particular cancer incidence following irradiation, for many years. Since 1960 I have concentrated my efforts almost exclusively on radiation epidemiology. I am author or co-author of approximately forty scientific publications, roughly half of which relate to radiation epidemiology and half to other topics in cancer epidemiology. Further details are provided in my attached curriculum vitae.

Q3. Are you familiar with Dr. Irwin D. J. Bross?

A3. Yes.

Q4. Are you familiar with the following documents authored or co-authored by Dr. Bross:

(a) Bross, I.D.J., Driscoll, D.L., Paper presented at Symposium on Effects on Humans of Exposure to Low Levels of Ionizing Radiation, Yale University School of Medicine, May 14, 1981 (Joint Intervenors Exhibit 25);

(b) Bross, I.D.J., et al., "A Dosage Response Curve for the One Rad Range: Adult Risks From Diagnostic Radiation," American Journal of Public Health, Vol. 69, No. 2, Feb. 1979 (Joint Intervenors Exhibit 27)?

A4. Yes, I am familiar with both of these documents.

Q5. Provide briefly your comments on the Yale paper authored by Dr. Bross, Joint Intervenors Exhibit 25.

A5. This paper provides Dr. Bross's opinion that, based on his reviews of data on Portsmouth Naval Shipyard workers and to a lesser extent on his reviews of data on Hanford workers, the risk of low-level radiation is considerably greater than risk estimates derived by bodies such as BEIR. I disagree entirely

with Dr. Bross's views as expressed in this paper and below in my testimony provide my opinion on the data upon which Dr. Bross relies for this paper.

Q6. Provide your comments on the One Rad Range paper which appeared in AJPH in February, 1979, Joint Intervenors Exhibit 27.

A6. This 1979 paper by Bross and coworkers published a reanalysis of the Tri-State Survey data. On the basis of the reanalysis, Bross et al. concluded that they had demonstrated a leukemogenic effect in man by direct observations in the one rad range.

The fundamental concept underlying this Bross reanalysis is that the population consists of vulnerable and non-vulnerable subgroups characterized by strikingly different risks of leukemia. In addition, Bross et al. in this paper also link increased risk of heart disease with prior exposure to radiation. These authors postulated that the effect of radiation exposure is not the specific effect commonly presumed of initiating a malignant transformation but rather a general effect of creating a non-specific damage to genetic material and thereby rendering a portion of the population more vulnerable to leukemia and heart disease. Under this hypothesis, an investigator can study the frequencies of vulnerability (or of being "affected") as related to radiation exposure rather than studying the more rare event of diagnosis of cancer.

Bross et al. also postulated that members of the vulnerable group have a leukemia incidence which is 10 times the incidence in

the non-vulnerable group of the same age and sex. This particular multiple of 10 was determined in a preliminary examination of the data on men of age 65 and over with less than 5 rad exposure. Bross subsequently argued that the value of 10 could be accepted as a general relative risk for all ages and doses among males. (It is not analytically proper to extract a parameter from a given set of data and then use it as a fixed--not statistically determined--parameter in the later statistical analysis of the same data with respect to determining other parameters.) Under this assumption, if one can find the proportion of the population who are vulnerable ("affected"), F_i for a given radiation exposure level i, one can readily determine the leukemia risk for the same level:

$$L_i = (1-F_i) \cdot L_0 + F_i \times 10 \cdot L_0 = (1 + 9F_i) \cdot L_0$$

where L_i is the leukemia risk at the exposure level i, L_0 is the leukemia risk in the "unaffected" subpopulation, and 10 L_0 the postulated higher risk characteristic of the "affected" (vulnerable) population.

The overall risk of leukemia for all radiation levels is known from tumor registration data for any given age and sex group. The weighted average of the risks determined by the above formula for individual radiation levels must equal this overall leukemia risk:

$$L = \sum L_i \cdot p_i = L_0 \cdot \sum (1 + 9F_i) \cdot p_i$$

where L is mean population leukemia risk and p_i is the proportion of the population with radiation exposure level i. Bross et al.

gave the quantity L as 25.69 per 100,000 per year, as determined from tumor registry data.

The values F_i, as determined from the analysis of Bross et al., are shown below. Bross et al. did not give the proportion of the population at each exposure level, p_i, but this parameter was later calculated for the Bross analysis by Boice and Land (see discussion below). L_0 is found from the above relation to be 14.23×10^{-5} per year.

Group i	Dose, rad	Per cent Affected, F_i	Proportion of Population in group, p_i	Leukemia Risk, $L_i \times 10^5$
1	Less than 1	4.12	.32	19.5
2	1-5	5.52	.30	21.3
3	5-10	5.35	.22	21.1
4	10-20	22.86	.13	43.7
5	20 or more	61.04	.03	92.6
All doses		8.95	1.00	25.69

From this tabulation one can study the effect of radiation by observing either the per cent affected, F_i, or the leukemia risk, $L_i = (1 + 9F_i)L_0$, a linear transformation of F_i. Bross et al. assumed that the quantity "percent affected" was particularly useful for analyzing this association and they suggested 3 possible outcomes to be distinguished by the data and to be interpreted as follows:

(1) F_i increases by a constant amount for every unit of increase in dose in the range from 0.1 to 10 rad. This would be consistent with usual linear assumptions relating to radiation leukemogenesis.

(2) F_i is zero at some low dose and at all lower doses. This would be consistent with a threshold effect, with "spontaneous" (non-radiogenic) leukemia incidence of L_0 in the low dose range where $F_i = 0$.

(3) F_i is consistent but positive at some low dose and all lower doses. These authors state that this outcome would imply that a radiation effect begins at even lower doses than those observed in this study (lowest dose is 0.17 rad and lowest group considered large enough to study includes doses 0.17 to 0.99 rad) and is constant in the dose range in which F_i is constant.

Bross et al. interpreted a similar table in their paper to be consistent only with the outcome (3), and on this basis they concluded that a radiation effect had been demonstrated by actual observations at low doses. As I will indicate below, this interpretation of the results of the analysis is erroneous.

Bross et al. have interpreted the relation between the proportion vulnerable (F_i, called by the authors percent affected) and the radiation dose to imply that there is an effect of radiation dose at doses below 1 rad. This interpretation rests on the fact that F_i is positive and constant (within limits of sampling variability) over the three dose groups, less than 1 rad, 1 to 5 rad, and 5 to 10 rad. The interpretation presumes that this proportion must be zero by its inherent nature at zero dose and ignores the contrary result, namely that the incidence is essentially constant at low dose, possibly implying a background

incidence not caused by radiation. There is, however, nothing in the analytic handling of the data to imply that the variable F_i would be zero for an unexposed population. It is evidently only because Bross et al. have imposed a semantic constraint on the quantity F, which they defined as "proportion affected by radiation exposure," that they concluded that the quantity was logically required to be zero at zero exposure. As a result, one must conclude that they have defined the desired result into the analysis and no scientific evidence confirms their conclusion because no non-exposed population has, in fact, been observed.

If F is called "proportion of population in vulnerable subgroup," one can investigate (1) the variation of this proportion with radiation dose, and (2) the proportion vulnerable in the absence of exposure. There is no theoretical reason to think that all vulnerability is due to radiation dose, though this would be the interpretation if the table associating F with dose suggested that F was approaching 0 at low doses or if actual observations of an unexposed population showed its leukemia incidence to be L_0.

Contrary to Dr. Bross's assertions, the proper and most natural interpretation of the data tabulated above would seem to be that for both percent affected, F, and leukemia risk, L, the curve extrapolates to a fixed finite incidence level at zero exposure. That is, there is a "spontaneous" level of leukemia incidence in the absence of radiation of about:

$$F = 5\%$$

or

$$L = 20 \text{ per } 100{,}000 \text{ per year.}$$

Within the limits of the data used, this spontaneous level occurs throughout the range of 0 to 10 rad, above which both percent affected and leukemia risk begin to rise with dose. The most logical interpretation of these results is that the "spontaneous" incidence is due to other causes and no radiation effect is evident below 10 rad.

In addition, since the statistic L is a linear function of F, the new statistic does not appear to offer any special advantage in investigating the most commonly asked questions about low dose effects, such as:

(1) Is the risk of radiation-induced leukemia in the low dose range equal to that estimated by linear interpolation between risks observed at high dose and zero?

(2) Is there a threshold level for radiation leukemogenesis?

The F statistic does, however, seem to give information on the question of heterogeneity of the population with respect to vulnerability to leukemia. This heterogeneity is often discussed as an issue to be considered in standard setting for permissible occupational or population dose limits. It is sometimes argued that if the general population includes a sub-set of unusual leukemia vulnerability, then "acceptable" exposure levels should

be set so as to offer no "unacceptable" risk to these subgroups. The findings resulting from the analysis of Bross et al. would seem to imply that there may be a subgroup constituting about 9% of the population who have a leukemia risk of 142 per 100,000 per year as compared with a general population (male, aged 65 and over) risk of 26 per 100,000 per year. This especially vulnerable group, however, would be found in populations with no radiation exposure. Size of the vulnerable group is not increased by radiation exposure until one reaches exposures at least in the 10 to 20 rad level, and the leukemia risk of the vulnerable subgroup is not affected by radiation exposure (an assumption of the model used by Bross et al.).

The assumptions and the results of the model are exhibited by the following two tables, the first of which shows that the assumed relative and absolute risks are the same for susceptible and nonsusceptible groups for all range doses, and the total risk depends only on the percentages susceptible and nonsusceptible (and vice versa) as set forth in the second table.

Dose (rad)	Under 1	1-5	5-10	10-20	Over 20	Total
TABLE 1	Risk of leukemia x 10^{-5} per year					
Susceptible	142.3	142.3	142.3	142.3	142.3	142.3
Nonsusceptible	14.2	14.2	14.2	14.2	14.2	14.2
Total (weighted average)	19.5	21.3	21.1	43.5	92.3	25.71
TABLE 2	Population Distribution in Percent					
Susceptible	1.32	1.66	1.18	2.97	1.83	8.96
Nonsusceptible	30.68	28.34	20.82	10.03	1.17	91.04
Total	32.00	30.00	22.00	13.00	3.00	100.00

The above comments refer only to the interpretation of the findings of Bross et al. The validity of the analytic model itself has been criticized by Boice and Land,[1/] who find that the model does not produce estimates of usable precision. Boice and Land conducted a reanalysis by conventional methods of the Bross results. They note the semantic problem discussed above whereby the parameter F is described as "proportion affected by radiation exposure" despite the fact that its value is found to be significantly positive and essentially constant in the dose range from less than 1 to 10 rad. These authors also state that if it is recognized that this parameter is in fact a measure of "proportion in vulnerable sub-group," the data suggest that this proportion is positive at zero dose and therefore not an effect of radiation exposure at low doses.

Boice and Land made the following additional observations:

(a) The authors have incorrectly treated parameter estimates as known constants. This approach leads to a false impression of precision of the results.

(b) With the previously assumed known constants correctly analzyed as determined by the data, the model includes so many estimated parameters that resulting estimates do not have usable statistical precision.

(c) In particular, statistical significance of F_i values is not found when analysis is carried out treating relative risks (relative risks of leukemia and of heart disease in vulnerable group as compared with non-vulnerable group) as parameter values estimated from the data.

(d) The method of statistical analysis is presented as new but is not presented in sufficient detail for review as to methodologic validity. It has not been presented in a statistical journal for peer review.

1/ Boice, J.D. and Land, C.E.: Adult leukemia following diagnostic x-rays? Am. J. Pub. Health 69, 137-145 (1979).

(e) No dosimetry data are available. Dose values used in analysis are obtained by assuming constant doses per examination for all chest x-rays and for all abdominal x-rays.

(f) Review of relevant literature is incomplete, undercutting the validity of the interpretation.

(g) The Hanford data are incorrectly cited as supporting conclusions of the present study.

(h) No independent data have confirmed the findings of the 1979 Bross study.

(i) Potential biases in data collection are described but not accounted for.

(j) The authors have been careless in detail of data presentation.

(k) Conventional analysis yields no increasing association between leukemia and heart disease as dose increases. This result contradicts the concept of a joint vulnerability to leukemia and heart disease from irradiation at low doses.

Of these findings, by far the most important are a, b and c, which relate to the relation between the assumptions and the statistical precision of the results. In the Bross et al. paper, the ratio of risk of leukemia in the susceptible group to the risk in the unsusceptible group was taken as a fixed constant 10. The ratio of risks for heart disease was taken to be 3. Under these assumptions the F values (proportion of the population who are susceptible) were determined to be significantly different from zero. However, when the ratios of risks are allowed to float and be determined by the statistical fit to the data, computed 95% confidence limits on the F parameters are such that the values are not determined to be different from zero. When in addition the parameter estimating prevalence of heart disease is

allowed to float in similar manner, the confidence limits increase further and the conclusion that the results are different from zero is even less supported.

The findings of the Bross model in the highest dose level are questionable on substantive grounds as well. In the tabulation above, the risk at dose 20 or more rad is 92.3 per 100,000 per year as compared with 19.5 per 100,000 per year for the lowest exposure group. The dose range for the highest group is given as 20 to 68 rad, and Figure 3 of Bross et al. indicates a mean dose of about 40 rad. Thus the radiation attributable risk at a mean dose of 40 rad is 72.8 (that is 92.3 minus 19.5) per 100,000 per year. Studies at high dose levels, usually 100 rad and above, find risks of only 10 to 20 per 100,000 per year at 100 rad exposure. Thus the risk estimate of 72.8 derived from the results of Bross et al. at 40 rad is not only greater than the interpolated estimate (4 to 8) derived from high dose studies for 40 rad exposure but is even greater than the response actually observed previously in human beings at 100 rad. Previous studies of adult leukemia at diagnostic x-ray levels by Stewart et al. and by Gunz and Atkinson and previous analyses of the data of the Tri-State Study have suggested an effect only following very large numbers of diagnostic x-rays, and the results of these studies do not conflict with findings of other studies of cancer incidence due to high exposure levels.

In summary, Bross et al. have misinterpreted the findings of their own analysis; their analytic model does not offer a useful

addition to statistical methodology for radiation dose-response studies; their findings conflict with findings of well-established high dose studies and the interpretation differs from that given other studies at similar exposure levels; and they have conducted an erroneous statistical analysis, a correct version of which leads to results which are so statistically indeterminate as to be meaningless.

Q7. Have you reviewed Dr. Bross's testimony which he provided at this hearing on March 30 and 31, 1982?

A7. I have read his testimony hastily, but have concentrated my review on selected portions only.

Q8. At various points in his testimony, Dr. Bross relies for his views on low level radiation risks and doubling doses on data on Hanford workers. Are you familiar with those data and analyses of it?

A8. Yes, I am familiar with a number of studies of data on the Hanford workers. In 1964, Dr. Thomas Mancuso and colleagues began a long-term study of employees of the Hanford Works in Richland, Washington, a large nuclear plant involved in the handling and manufacture of radioactive substances. Mancuso's group identified employment records of all workers in this plant from 1944 to 1964, and subsequently accumulated records of new employees after 1964. Mancuso and coworkers studied the mortality of all these workers during the years from beginning of employment until 1972. These employment records included year-by-year records of the radiation exposure of each worker, as measured by film badges required to be worn by all workers in any jobs at the Hanford Works which

might involve radiation exposure. Mancuso and colleagues published the first of a series of papers on this study in 1977.[2/]

The method of analysis in this study was a commonly used epidemiologic procedure known as proportional mortality analysis. The use of this procedure implies that the analysis is confined to the group of workers who have died, in the Hanford case a total of 3,520 men (a small number of women were also in the group, but the analysis is primarily limited to the men). In a proportional mortality analysis one does not compute actual risks of cancer incidence or cancer mortality (number of cancers divided by number of persons at risk at specified times), but rather the proportion of cancers among the total deaths. In the Hanford study, there were 670 cancer deaths among the 3,520 deaths. This number may then be compared with the proportion of deaths due to cancer in some comparison group.

Note that a high proportion of cancer in such a study does not logically require high cancer mortality. A high cancer proportion could be due either to high cancer mortality or to low mortality from all other diseases. The interpretation that the death rate for all causes of death was very sharply reduced is unlikely, however, and if it had occurred that fact would probably be known. Proportional mortality analysis is a common method of study for epidemiologists, and for rare diseases, for example, leukemia or a single site of cancer, a sharp increase in the

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2/ Mancuso, T.F., Stewart, A., and Kneale, G.: Radiation exposures of Hanford workers dying from cancer and other causes, Health Physics, 33:369-385 (November, 1977).

proportion of deaths from this disease implies a very high likelihood that cancer mortality was indeed higher.

The Hanford study investigators used as comparison groups various subgroups of the Hanford workers. If radiation exposure caused cancer, the proportion of deaths due to cancer should be higher in the heavily exposed group and lower in the less exposed group. The plan of analysis was based on the fact that, if cancer deaths were most common after heavy exposure, then heavy exposure would have to be more common in cancer deaths than in non-cancer deaths. One could then compute the average amount of radiation exposure in the cancer deaths and the average amount in the other deaths. If radiation caused cancer deaths, the mean exposure should be higher for the cancer deaths than for non-cancer. This indeed appeared to be the case in the Mancuso analysis. The mean dose in excess of background over the total occupational lifetime of the employees for all the exposed deceased in this study was 1.72 rad and for all the exposed cancer deaths 2.10, a statistically significant excess in the cancer group. For single cancer sites the mean dose was higher in the reticulo-endothelial system cancers, in the bone marrow cancers (multiple myeloma plus myeloid leukemia), in cancers of the pancreas, brain, kidney, lung, and colon, each compared with the group of all other deaths.

It will be convenient for further discussions to express these same results in two other ways. First, the excess cancer risk can be described in terms of a <u>doubling dose</u>. A doubling dose is simply a different way of expressing the rate of increase of

risk with dose. To determine a doubling dose, the cancer mortality is first ascertained for a population exposed to no occupational radiation (though this population will have been exposed to some level of "natural" or "background" radiation, as are all populations). One then measures the cancer mortality at a series of occupational exposures and finds how much occupational exposure is necessary to give a mortality twice that of the unexposed population.

In the Mancuso study, proportional mortalities were measured rather than actual mortalities, so the doubling dose was taken to be the dose at which the proportion of death due to cancer would be twice the proportion seen in an unexposed population. This is not necessarily equal to the dose that would correspond to a doubling of the absolute cancer risk. Although there were 3,520 deaths studied including 670 cancer deaths, these included only 442 cancer deaths in men who had had any radiation exposure and only 20 cancer deaths in men who had had more than 10 rad cumulated exposure during their total work experience. One could therefore not actually measure the proportional mortality at a dose large enough to cause a doubling.

It is mathematically possible to observe how the proportional mortality increases with dose at the low doses between .01 rad and 10 rad and to estimate from the slope of that dose-effect curve what dose would cause a doubling. There is, however, necessarily much doubt about the reliability of any estimate of doubling dose based on such a narrow range of dose observations. To

make this estimate, Mancuso et al. assumed that the proportional mortality increased approximately linearly with dose, and the doubling dose for cancer was estimated by extension of this line to be 12.2 rad.

Another way to describe this result is in terms of the relative risk of cancer in this exposed population as compared with the unexposed. Again assuming a linear relation, and substituting proportional mortality for actual mortality, if the relative risk is 2 (doubling) at 12.2 rad (the doubling dose), then the relative risk at 2.10 rad (the actual mean exposure for the exposed cancer patients) is 1.2, or a 20% increase in cancer risk.

In summary, the principal result may be given in 3 ways:

(a) Mean dose:

Cancer deaths 2.10 rad.
All deaths 1.72 rad.

(b) Doubling dose:

12.2 rad.

(c) Relative risk at 2.10 rad:

1.2.

Other findings in the Mancuso study related to individual cancer sites. The excess risk was shown to be due to excess principally in 4 sites, reticuloendothelial system cancers (RES), bone marrow cancers, and cancers of the pancreas and lung. For these 4 sites mean dose and doubling dose are given and relative risk associated with the mean dose can be determined, as follows:

	RES	Bone Marrow	Pancreas	Lung
Mean dose, rad	2.99	6.44	3.99	2.49
Doubling dose, rad	2.5	0.8	7.4	6.1
Relative risk at mean dose	2.2	9.0	1.5	1.4

Certain errors in analysis of this study and certain findings that seem inconsistent with much other knowledge on radiation effects will be noted. First, the test of statistical significance used in the main analysis was noted by the authors to give p-values that were much too small, so that the significance of their results is over-stated.

Second, the authors noted that secondary associations with calendar year of exposure, interval between beginning employment and exposure, interval between exposure and death, age at exposure and age at death imply that these are probably confounding variables in these data. They did not, however, control for these confounding factors in their analysis to identify cancer sites sensitive to radiation.

Third, the presentation of doubling values of radiation for selected cancer sites is potentially misleading, since the doubling dose is essentially an alternative way of identifying sites with rates significantly increased in these data. The computed doubling dose for a given site bears an approximately inverse relationship to the statistical parameter used to test for significance. The observed doubling dose is partly due to a true association between dose and cancer risk and partly due to chance fluctuation. Therefore doubling doses should be given for all sites for which

significance was tested rather than simply for sites for which significance was found, namely those with unusually high significance and therefore automatically unusually low doubling doses. A certain number of low values would be expected by chance, and the implication of these is apparent only if all doubling doses are reported.

Fourth, the finding of no increase in leukemia mortality contradicts the finding in most other populations in which radiation carcinogenesis has been observed.

Finally, as will be discussed further below, the reported doubling doses for several sites are so small as to be inconsistent with the assumption of the linear dose-response model which the authors have used in their analysis. Therefore for these sites the linear model cannot be correct and the estimates of doubling dose derived from the model must be disregarded. These five points are discussed further in the following section.

The Mancuso results are very surprising in view of estimates of radiation effects as determined from the numerous higher dose studies. The first striking finding is that leukemia does not appear prominently in the results. Most earlier studies of external radiation find leukemia as the prominent malignancy, appearing after shorter intervals following exposure and in greater incidence than is seen with solid tumors. In this Hanford study, the cancers categorized as bone marrow cancers include myelocytic leukemia, the leukemia type most commonly reported as a radiation effect; but the Hanford excess in bone marrow tumors is almost entirely due to an

increase in multiple myeloma, not to the leukemia. For leukemia, higher dose studies have showed 2 to 10-fold increases at various doses.

The second unusual finding is the size of doubling doses. Doubling doses previously estimated for leukemia are about 50 rad and for the group of all cancer other than leukemia about 500 rad. For several of the more sensitive tumors estimates are in the range of 100 to 200 rad. In the Hanford study the estimate of doubling dose for bone marrow cancer, 0.8 rad, is less than 2% of the former estimate for leukemia, while the Hanford doubling dose for total cancer, 12.2 rad, is less than 3% of the former esimate.

The small observed doubling doses for individual sites in the Hanford study are also surprising for another reason. The authors used an estimate of "doubling dose" as a means of describing the (assumed linear) association of cancer mortality with radiation exposure. This method is essentially equivalent to determining the slope of a dose response curve but expressing it in terms of the dose required to double the spontaneous rate of cancer. The more sensitive a cancer is to induction by radiation, the smaller is the dose required to double the spontaneous rate. Spontaneous cancer rates, however, are always observed in human populations that are exposed to background radiation. Therefore if cancer, or any other disease, were caused in part by radiation doses as low as background levels, the spontaneous cancer rate would include these cases induced by background radiation. That is, the incidence

of cancer due to background radiation is part of the spontaneous incidence and would be the entire spontaneous incidence if all cancer were radiation-induced. The incidence due to background radiation cannot be greater than the spontaneous rate. But since the doubling dose, by definition, is a large enough dose to double the spontaneous cancer incidence, it must be at least as large as the background dose if the incidence increases linearly with dose.

The interpretation of data by means of doubling dose and a linear model fails when the observed doubling dose is lower than background exposure. Logically this must mean that the small doubling dose accounts for all the spontaneous cancer and the larger background level must produce even more than the spontaneous number of cancers, a contradiction. It must be concluded that the analytic theory used for computing doubling doses must be rejected when such small values are found. Since most populations naturally receive about 0.1 rad per year background radiation, then adult populations have accumulated about 3 rad or more, and estimates of doubling dose of less than 3 are logically rejected as impermissible solutions to the calculation model. I conclude that the estimates of 2.5 rad and 0.8 rad as doubling doses are in error and the other estimates are at very great variance with prior experience at higher doses.

Because of the surprising results reported in the Hanford study my coworkers and I obtained the detailed Hanford data and

reanalyzed them. This review led us to a revision of some of the Mancuso findings as follows.

First, we considered the problem that other associated variables might lead to an apparent association between an exposure and disease in non-experimental studies. Two variables were known to be highly related to the radiation dose and cancer incidence. These were the age at death and the calendar year of death. Mancuso and his colleagues had shown how these two variables were associated, but their analysis had not accounted for this association. This problem is particularly important for carcinoma of the lung because the mortality from this tumor increased rapidly during the years of the Mancuso study. Most other cancers increased relatively little or decreased in this period of time, so that the proportion of deaths due to lung cancer was even more variable than the absolute rate of mortality.

Mancuso and coworkers used proportional mortality data from 1960 to estimate the distribution of deaths expected for various causes of death in all the study years. Since lung cancer is much more common in older persons, many of the lung cancer deaths in this population would be expected to occur in the later calendar years, up to 1972, and for these years the proportion of lung cancers among all deaths observed in 1960 would be a great underestimate. We adjusted for this relation in our analysis, and, when this was done, the association of lung cancer with radiation exposure reported by Mancuso *et al.* was no longer found.

Second, we investigated the mathematical procedure used for testing statistical significance. Here again Mancuso et al. had noted a problem with their method but had not made a correction for it. When we made the appropriate correction, only the results for cancer of the pancreas and multiple myeloma were still found to be statistically significant. That is, the other radiation-cancer associations could be reasonably interpreted as chance findings in a limited body of data.

We did confirm the significance of the results for cancer of the pancreas and multiple myeloma. We also found doubling doses similar to those found previously by Mancuso et al. for cancer of the pancreas, namely 5.1 rad. We obtained the result that the doubling dose for multiple myeloma predicted by the mathematical model used by Mancuso et al. would be 1.5 rad, and we rejected this value as an impermissible solution of the model. That is, these data do not permit the calculation of a logically acceptable doubling dose from this mathematical model. There is also substantial reason from other experience and data to question the observed doubling dose of 5.1 rad for pancreas cancer.

We find the Hanford data alone do lead to the conclusion of a statistically very significant association between cancer of pancreas mortality and the radiation doses measured for this population. However, the association for cancer of the pancreas hinges on 5 of the 32 exposed cases having cumulative doses over 10 rad as compared with 1.4 expected cases. There is no evidence of a graded tumor response with increasing dose. Instead there is simply

an abrupt increase in the ratio of observed to expected incidence among those with doses exceeding 10 rad. Under the circumstances, the observed doubling dose for pancreatic cancer must be viewed with considerable caution.

In 1978 Kneale et al. (the same authors as those in the 1977 report) presented an extension and reanalysis of the Hanford study, including a total of 743 cancer deaths in men (vs. 670 in the 1977 report).[3/] The following table sets forth a summary of the new results:

	Bone Marrow	Pancreas, Stomach, Colon	Lung	High Sensitivity	All Cancers
Mean dose, rad	4.2	2.4	2.6	2.5	2.0
Doubling dose, rad (D)	3.6	15.6	13.7	13.9	33.7
Confidence limits of D	1.7 10.3	7.3 55.0	7.3 28.7	8.4 21.2	15.3 79.7
Relative risk at mean dose	2.2	1.2	1.2	1.2	1.1
Number of cases	25	165	215	456	743

The grouping of cancer sites is somewhat different from that used in 1977 and includes a category "high sensitivity" cancers, a group of sites identified in a 1969 report of the International Commission on Radiologic Protection as sites well established as radiosensitive to cancer induction (bone marrow, thyroid, lymphomas, pharynx, lung, pancreas, colon). For three of these site groups data are given

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3/ Kneale, G.W., Stewart, A.M., and Mancuso, T.F.: Re-analysis of data relating to the Hanford study of the cancer risks of radiation workers. Proceedings of Symposium on Late Biologic Effects of Ionizing Radiation Held by the International Atomic Energy Agency, Vienna, March 1978, pp. 386-412. (1978)

in both Hanford studies, namely bone marrow, lung, and all cancers. The new doubling doses are more than twice the previous values, and the 95% statistical confidence limits exclude the three prior estimates. This latter finding implies that the earlier estimates were invalid. The corresponding new relative risks are 2.2 (bone marrow), 1.2 (lung), and 1.2 (all cancers). For two other sites (doubling doses not given before), the new relative risks are 1.2. Thus most of the relative risks are in the range which has been described earlier as beyond the resolution of non-experimental epidemiologic studies. That is, one cannot be assured by any sample size that relative risks in this range represent causal associations as opposed to secondary associations due to inadequately controlled or unknown correlated factors. The large relative risk of 2.2, or more than a doubling of risk, for bone marrow cancer is not in this uninterpretable range. It is, however, based on the smallest number of cases, 25, and the upper end of the confidence interval for the doubling dose for this group of diseases is 10.3 rad, corresponding to a relative risk at the mean dose of 1.4, which is in the uninterpretable range. Thus there remains substantial doubt as to whether these data reflect a causal association even for bone marrow cancer.

It is important to note that increasing the number of cancers from 670 to 743 in the extension of the study had a profound effect on the overall result. Although the new cases are too few for separate analysis, it must be concluded that they differed sharply from the original series, and probably showed little if any

increased risk associated with radiation. Extension of the present study or the development of new studies involving other groups with occupational radiation exposure will clarify the high relative risk of 2.2, now reported for the bone marrow cancers. It is doubtful that any non-experimental study at these low doses of the other cancer sites, with relative risk of 1.1 or 1.2, will clarify those findings. A more profitable approach would be to study populations with exposure doses in the poorly studied dose range of 50 to 150 rad. Only here can non-experimental studies distinguish causal associations from effects of associated variables weakly correlated with radiation dose and with cancer risk.

In 1979 Gilbert and Marks did a more satisfactory analysis of these data in that they used the data on all the Hanford workers rather than data confined to the deceased workers.[4/] This allows the experience of these workers to be determined without the restrictions imposed by the proportional mortality form of analysis. It was found in this analysis that the increased risk of lung cancer previously reported was not confirmed. The principal positive findings of our proportionate mortality reanalysis were found in the Gilbert and Marks more standard risk analysis, namely an increased risk of multiple myeloma and cancer of the pancreas. It was their interpretation that these increases could not be causally associated with the radiation doses experienced by these populations. The conclusion was similar to our conclusion from our reanalysis and tends to confirm the position I have described.

4/ Gilbert, E.S., Marks, S. An analysis of the mortality of workers in a nuclear facility. Rad. Res. 79:122-148. 1979.

Q9. Directing your attention to Dr. Bross's answer to Question 19 in his prefiled testimony, do you agree with Dr. Bross that the BEIR work is unacceptable and that new statistical studies at lower levels of radiation provide a more appropriate basis for determining risks of ionizing radiation in the 0-5 mrem range of dose?

A9. No, I am aware of no studies that support Dr. Bross's thesis and I regard the BEIR work as supported by scientific data and the scientific literature.

Q10. Directing your attention to pages 1391 and 1637-1652 of the transcript of Dr. Bross's testimony, where Dr. Bross refers to the "radiation protection community," do you agree with the views expressed by Dr. Bross concerning this group's dedication to the proposition that low-level radiation is harmless regardless of scientific evidence and that views which are contrary to that proposition are improperly suppressed in the literature?

A10. It is difficult for me to respond to this question, since I must assume that Dr. Bross includes me among members of the "radiation protection community." There is a very large number of scientists involved in issues of radiation effects, and I am closely acquainted with many of them. They generally fit the widely perceived mold of dedicated investigators carrying out research studies in their various specialty areas in search of scientific findings. An individual cannot seriously do such work if he has blocked his perspectives in such a way as to exclude possible outcomes of his investigations. For the most part the work of these investigators is supported only after rather extensive review of research plans, both as to the reasonableness of the proposed work and as to the possibility of verifying steps of the work.

In three particular instances relevant to the present discussions this sort of review has, in fact, been carried out at

great length because of differences of interpretations among investigators. These are the studies of the children and adults with leukemia included in the Tri-State Study, the Hanford Atomic Plant workers, and the Portsmouth Naval Shipyard workers. While differences of interpretation as to results persist in all the studies, it is difficult to conceive that any conclusions have been blocked by a deliberate effort to deceive. The varying opinions have all appeared in appropriate scientific publications, and the basic data have been analyzed and reanalyzed by two or more investigators in each instance. Concealment can hardly occur in this setting.

It is similarly hard for me to conceive of a system that would effectively block publication of scientific work because of undesired findings. The review process involves so large a number of independent scientists on review panels for so many different publications that effective systematic distortion could result only from an incredibly enormous organized effort.

One particular instance which seems to me to counter Dr. Bross's position is the publication of Dr. Bross's own paper on Dosage Response Curve in the American Journal of Public Health (AJPH 69:130. 1979). In this instance the editor published this paper despite rejection in the standard review process, as noted in the Editor's Note associated with that article.

Dr. Bross has for some years adopted a position on radiation hazards which is considered extreme by all investigators in this area with whom I am acquainted. Nevertheless, his many publications

significance was tested rather than simply for sites for which significance was found, namely those with unusually high significance and therefore automatically unusually low doubling doses. A certain number of low values would be expected by chance, and the implication of these is apparent only if all doubling doses are reported.

Fourth, the finding of no increase in leukemia mortality contradicts the finding in most other populations in which radiation carcinogenesis has been observed.

Finally, as will be discussed further below, the reported doubling doses for several sites are so small as to be inconsistent with the assumption of the linear dose-response model which the authors have used in their analysis. Therefore for these sites the linear model cannot be correct and the estimates of doubling dose derived from the model must be disregarded. These five points are further discussed below.

The Mancuso results are very surprising in view of estimates of radiation effects as determined from the numerous higher dose studies. The first striking finding is that leukemia does not appear prominently in the results. Most earlier studies of external radiation find leukemia as the prominent malignancy, appearing after shorter intervals following exposure and in greater incidence than is seen with solid tumors. In this Hanford study, the cancers categorized as bone marrow cancers include myelocytic leukemia, the leukemia type most commonly reported as a radiation effect, but the Hanford excess in bone marrow tumors is almost entirely due to an

have appeared and his position has been widely publicized. If there has been an effort to suppress, it has clearly failed badly in this case.

Q11. At pages 1604-1637 of the transcript of Dr. Bross's testimony, a number of excerpts from critiques of Dr. Bross's work are referenced. To the extent you are familiar with these critiques or those who provided the critiques, please provide your opinion of the critiques and their authors.

A11. I am familiar with a number of the reports mentioned by Dr. Bross as critiques of several of his papers. These include comments by Boice and Land, comments by Oppenheim, comments by Rothman, and comments by the Editor, American Journal of Public Health, all relating to Dr. Bross's Tri-State Studies, childhood and adult. I am acquainted with the brief comment of the BEIR Committee on Dr. Bross's work in general. I was a member of the Committee of NCRP that prepared Report 64, which included a comment on Dr. Bross's work. In the case of specific individuals named above, I am closely acquainted with Boice (my student), Land and Rothman (my colleagues).

I am in general agreement with these critiques, and I find the Land and Boice critique a particularly careful and helpful document. My own evaluation of the Tri-State Study is similar to theirs and perhaps borrows on their argument.

Q12. What is your familiarity, if any, with the Portsmouth Naval Shipyard Study of radiation effects on workers?

A12. I have been closely associated with the studies of the Portsmouth Naval Shipyard workers from the beginning of the investigations.

Q13. Briefly describe the results of those studies to date and the current status of ongoing, related work.

A13. Drs. Najarian and Colton brought this material to me shortly after Dr. Najarian had observed a case of leukemia with history of shipyard work. This patient was seen by Dr. Najarian in his clinical work at the Veterans Administration Hospital in Boston. Because of the restricted data available to Dr. Najarian at that time, I suggested the method of proportionate mortality analysis, as the only practical way of interpreting these data. I advised Drs. Najarian and Colton against publication of the preliminary analysis because of its poor reliability, the bases of which have been extensively discussed. The paper was nevertheless published and was extensively, and I believe appropriately, criticized. Subsequent analysis by the Centers for Disease Control - National Institute of Occupational Safety and Health, based on the complete available exposure data, demonstrated the principal finding of the Najarian-Colton paper to be in error, and further study is continuing to indicate how so large an error could result from the study procedure used. The new result was that the many-fold leukemia excess found in the limited data set was not seen in the full data.

There remained a point estimate of an increased leukemia rate, of a magnitude that might well be expected as a result of some unexplored confounding factor, such as exposure to some industrial carcinogen. This estimate did not reach formal statistical significance. A new discussion arose as to the level of

statistical significance, and this issue has not been settled. Although this question remains, it has very limited relevance to the principal issue of radiation hazard. Whether of borderline significance, as Dr. Colton believes, or completely non-significant, as the CDC-NIOSH group reports, the association is small and easily understood as a result of a confounding factor.

Dr. Bross has introduced a new question into the Portsmouth Naval Shipyard study, namely that of a radiation related risk of lung cancer. Lung cancer had not been discussed separately in the CDC-NIOSH report, but that report noted, "We found no positive dosage response relationships between ionizing radiation and mortality for any cause reported." In a separate analysis of the Portsmouth Study, Dr. Bross noted a positive association between lung cancer mortality and radiation exposure in the limited set of lung cancer deaths occurring more than 15 years after exposure, a total of 19 lung cancer deaths. This positive result was found in a review of a large number of cancer sites studied, each observed at a variety of latent periods. A controversy remains, as yet unsettled, as to the interpretation of this finding. The positions of the CDC-NIOSH investigators and of Dr. Bross differ in their interpretations as to whether this is (1) a confirmed finding related to a prior hypothesis, or (2) an isolated positive result in a large mass of relations surveyed. From the point of view of Dr. Bross, this was a major cancer site in males and one identified as radiogenic at high doses in other literature, therefore one of a very few priority sites to study. From the point of

view of CDC-NIOSH, the lung cancer association turned up as an incidental finding and as such requires confirmation in a further data set. In the present data set, furthermore, it is being examined in case-control study design in an attempt to determine the role of asbestos exposure in the shipyard workers as a separate and confounding exposure.

CURRICULUM VITAE

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Personal:	Born October 18, 1922, at Lexington, Kentucky Citizen of the United States Single	
Education:	Harvard College	A. B. (Mathematics, Magna cum laude) (1943)
	Harvard Graduate School of Arts and Sciences	Biochemistry (1947)
	Harvard Medical School	M. D. (1951)
	Harvard School of Public Health	M. P. H. (1960)

Professional Appointments:

1951-52	Intern in Medicine	Massachusetts Memorial Hospitals, Boston, Massachusetts
1952-55	Fellow in Medicine	Lahey Clinic, Boston, Mass.
1955-56	Assistant Medical Director	Medical Department of Equitable Life Assurance Society of the United States
1956-57	Assistant Medical Director	Division of Research and Statistics, Health Insurance Plan of Greater New York
1957-59	Public Health Physician, Director of Research Activities	New York City Health Department
1960-61	Assistant Professor of Epidemiology	Harvard University, School of Public Health
1961-66	Associate Professor of Epidemiology	Harvard University, School of Public Health
1966-72	Epidemiologist	Department of Radiotherapy Michael Reese Hospital Chicago, Illinois
1970-72	Associate Professor Radiology	University of Chicago, Pritzker School of Medicine
1972-	Professor, Epidemiology	Harvard University, School of Public Health

Other Professional Activities:

Consultant on numerous advisory committees of National Institutes of Health and National Academy of Sciences, and consultant to several studies of Department of Energy.

Professional Organizations:

American Public Health Association (Fellow)
New York Academy of Medicine
New York Academy of Science
American Statistical Association
Delta Omega

Publications:

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