EIR-Bericht Nr. 434

Eidg. Institut für Reaktorforschung Würenlingen
Schweiz

Human Evidence on the Shape of the Dose-Response Curves for Radiation Carcinogenesis

W. Burkart

Würenlingen, September 1981

HUMAN EVIDENCE ON THE SHAPE OF THE DOSE-RESPONSE CURVES FOR RADIATION CARCINOGENESIS

WERNER BURKART
ABT. STRAHLENUEBERWACHUNG
EIDG. INSTITUT FUER REAKTORFORSCHUNG
CH-5303 WUERENLINGEN / SWITZERLAND

AND

NEW YORK UNIVERSITY MEDICAL CENTER
INSTITUTE OF ENVIRONMENTAL MEDICINE
550 FIRST AVENUE
NEW YORK, N.Y. 10016

MAY 12, 1981

ABSTRACT

The carcinogenic effects of high levels of ionizing radiation are better understood than those of any other environmental agent. However, the somatic risk from low doses is highly disputed. The uncertainties stem from the fact that a direct estimation of small risks requires impracticably large samples. Therefore, risk estimates for low doses have to be derived indirectly by extrapolation from high exposure data and are heavily dependent on assumptions about the form of the dose-response curve. Although radiobiological theories tested on *in vitro* systems predict a quadratic term in the dose-response equation which should, at least for sparsely ionizing radiation, dominate the shape of the curve, the epidemiological data available cannot exclude the possibility of a pure linear relationship. In some cases, apparent thresholds may result from latent periods inversely related to dose. Besides depending on the quality of the radiation, the shape seems also to differ with the type of cancer induced.

Studies on uranium miners, atomic bomb survivors and on irradiated patients are reviewed with emphasis on the shape of the dose-response. The credibility of the most publicized reports claiming a large cancer risk from low levels of radiation is assessed.

The feasibility of a new study in a area of high natural background is explored. Finally, the influence of the uncertainties concerning the effect of low level radiation on future exposure limits set by regulatory bodies is discussed.

TABLE OF CONTENTS

1. INTRODUCTION

In 1980, after one year of intense internal debate, the Committee on the Biological Effects of Ionizing Radiation of the U.S. National Academy of Sciences released the final version of its report "The Effects on Populations of Exposure to Low Levels of Ionizing Radiation: 1980" (1). Although this volume of 520 pages, popularly known as BEIR III to distinguish it from earlier reports and drafts, represents probably the most complete and concise collection of data and dose-response theories of the effects of ionizing radiation, it falls short of providing a basis for the U.S. Environmental Protection Agency, which commissioned the report, to confirm or adjust exposure limits for ionizing radiation. The unique feature of BEIR III is that it includes statements of dissenting members of the committee which on one side believe the dangers of radiation are still overstated and on the other side claim that the reason to give less weight to the more conservative linear hypothesis is the biased selection of data. Therefore, the report in itself shows in a dramatic way how uncertain the present risk estimates are.

The big problem in the estimation of the effects of exposure to radiation is that at the levels of radiation presently encountered in nuclear or X-ray professions and by the general public, the by far most important somatic effect of radiation, induction of cancer will always be hidden by a much higher spontaneous cancer incidence. Nevertheless, the long half-lives of some radionuclides and the fact that for some exposures the whole population is at risk make it still worth while to determine those radiation effects. However, this means that risk estimates cannot be calculated directly, but have to rely on extrapolation from effects at high exposures encountered by atomic bomb survivors, irradiated patients, early uranium miners and from experimental data.

This review tries to give an overview of the most important epidemiological studies and of the hypotheses underlying the risk estimates. Finally, additional studies on the so far poorly

investigated populations living in areas with high background radiation are proposed to narrow down today's wide range of estimates.

2. THE ORIGIN OF HUMAN CANCER

Cancer incidence rates vary from country to country. Third world countries have an excess of liver cancer, western nations suffer more of breast and colon cancer whereas Japan shows an excess of stomach cancer (2). Since immigrant populations tend to convert to the pattern of cancer that is characteristic of their homeland, cancer seems to be caused to a large extent by diets, life style and environment rather than by genetic factors. An important conclusion of this notion is that cancer should be at least partially a preventable disease. The question whether life style (smoking, diet) or environmental and occupational carcinogens, both man-made or natural in origin, contribute more to the present cancer incidence remains unsolved (3,4).

The molecular events leading eventually to the transformation of a single cell or a group of cells, which then would start to form a tumor, are largely unknown. Although lesions in the DNA seem to be involved in most neoplastic processes, there is good evidence that at least in teratocarcinomas the defect is not mutational in origin (5). Cancer involves probably a multistage process. In the two-stage theory of carcinogenesis, the first stage is initiation followed by the second-stage promotion, the uncontrolled proliferation of the initiated cells into a detectable cell mass. Unfortunately for epidemiology, the two stages may be separated by many years. It is evident that all these uncertainties have an adverse affect on the accuracy of risk extrapolations.

3. DOSE-RESPONSE MODELS FROM *IN VITRO* STUDIES WITH ANIMAL AND HUMAN CELLS

To make best use of the scant epidemiological data, dose-response models derived from experiments with animals, cell cultures of human and non-human origin and from theoretical considerations are fitted to the available data to predict the response at the low dose levels not covered by direct observations. Optimally, the values in the region of known dose-incidence relationship would allow to calculate the parameters of the general form 3-1 of the dose response equation and hence to predict incidence rates at low doses, not directly accessible to epidemiological studies. Unfortunately, the quite large standard deviations of the observed incidence values in populations exposed to high doses, seldom allow one to exclude all but one model, which then could be used for an estimation of effects.

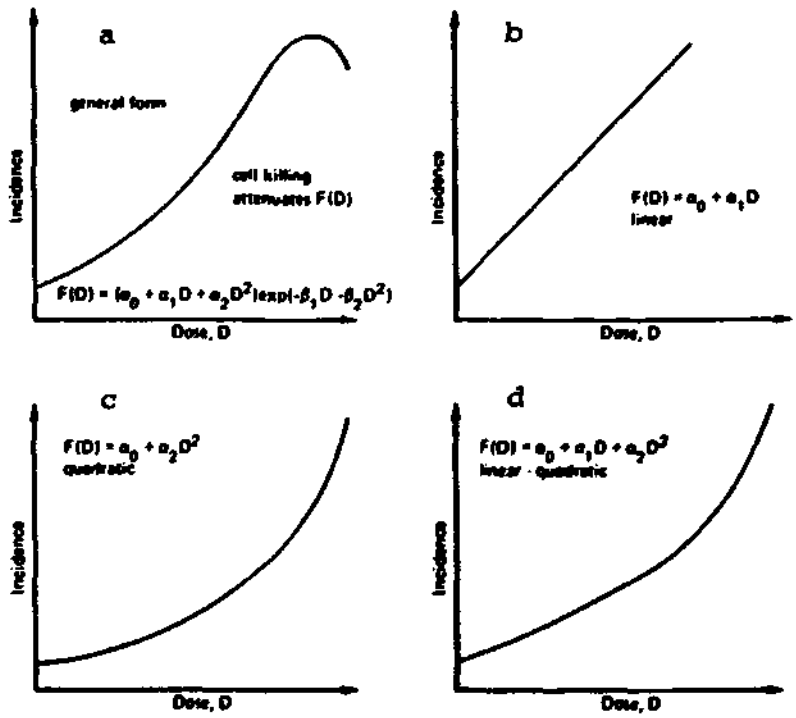

Fig. 1: Alternative dose-response curves (from 1a).

The following general equation covers all relations considered here between dose and cancer incidence:

$$I(D) = (\alpha_0+\alpha_1 D+\alpha_2 D^2)\ e^{-(\beta_1 D+\beta_2 D^2)} \qquad (3\text{-}1)$$

where D represents dose in rad and I(D) cancer incidence or mortality. The parameters α_0 - β_2 correspond to the following concepts (6,7):

α_0: control or spontaneous rate of the effect under study (i.e., cancer incidence in the absence of radiation);

α_1: linear term, cancer incidence proportional to dose, one-track event (Fig. 1b);

α_2: quadratic term, additional carcinogenic effect of multiple, closely-spaced ionizing events, two-track event (Fig. 1c);

$e^{-(\beta_1 D+\beta_2 D^2)}$: survival term, β_1 and β_2, are analogs of α_1 and α_2, but for cell killing instead of carcinogenesis. This term takes into account that at very high doses, i.e., α-emitting α particles in the lung (hot particles), most cells affected are killed and therefore can no longer undergo transformation (Fig. 1a).

As stated earlier, the epidemiological data rarely allows the rejection of all but one of the possible dose-response curves. Different theories based on findings from cell culture experiments like the target theory and the dual action theory (8,9) are also unable to predict values for α_1 and α_2. Figure 2 and Table 1 taken from Land (7) illustrate this frustrating

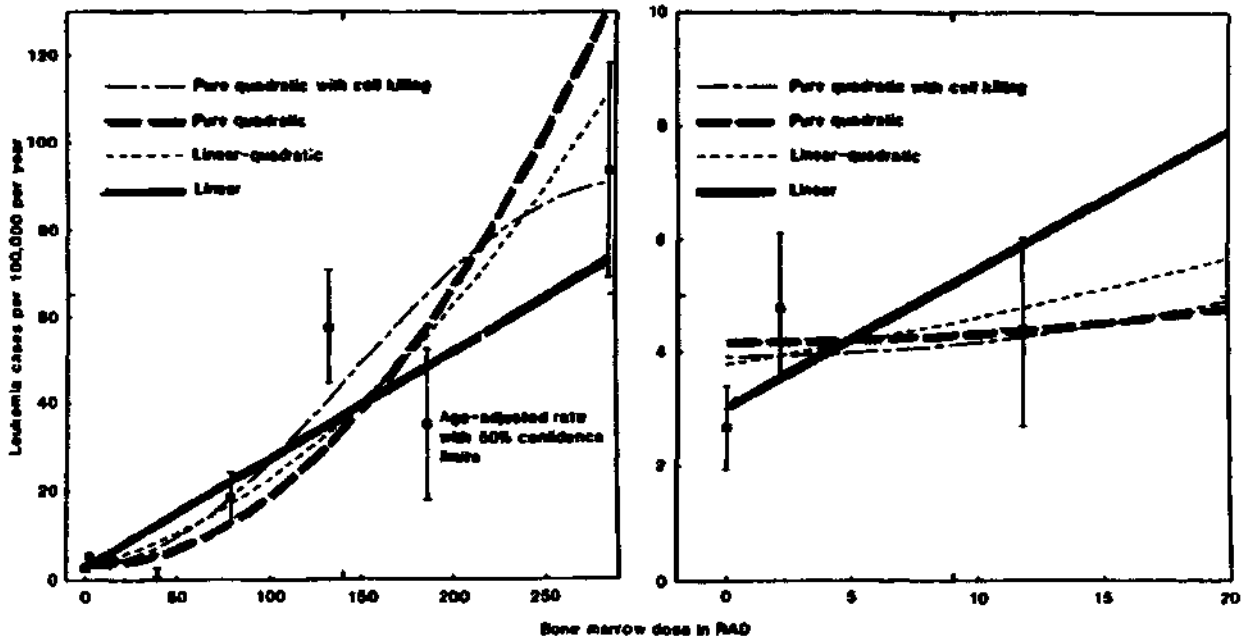

Fig. 2 Example: Dose-response analyses of leukemia incidence, 1950 to 1971, among Nagasaki A-bomb survivors. The right-hand panel is a detail of the left-hand panel. Age-adjusted rates are given with approximately 50 percent confidence limits. Fitted curves correspond to different dose-response models given in the text.

situation. Analysis of the leukemia incidence among Nagasaki A-bomb survivors gives, for the linear, linear-quadratic and the pure quadratic model with cell killing, similar results in an analysis for lack of fit (Table 1). That means all the equations

Table 1. Summary of curve-fitting analyses of age-adjusted leukemia incidence data.

	Model and equation	Parameter estimate ± S.D.*	Analysis for lack of fit		
			χ^2	d.f.†	P
———	Linear $I(D) = \alpha_0 + \alpha_1 D$	α_1 : 2.5 ± 0.6	6.9	6	.33
	Linear-quadratic $I(D) = \alpha_0 + \alpha_1 D + \alpha_2 D^2$	α_1 : 1.0 ± 1.2 α_2 : .010 ± .008	6.3	5	.28
	Linear with cell killing $I(D) = (\alpha_0 + \alpha_1 D) \exp(-\beta_1 D^2)$	α_1 : 2.5 ± 1.0 β_1 : 0 ± 8.4‡	6.9	5	.23
	Linear-quadratic with cell killing $I(D) = (\alpha_0 + \alpha_1 D + \alpha_2 D^2) \exp(-\beta_2 D^2)$	α_1 : 0 ± 1.8‡ α_2 : .026 ± .028 β_1 : 11. ± 11.	4.7	4	.32
———	Pure quadratic $I(D) = \alpha_0 + \alpha_2 D^2$	α_2 : .016 ± .004	7.7	6	.26
	Pure quadratic with cell killing $I(D) = (\alpha_0 + \alpha_2 D^2) \exp(-\beta_2 D^2)$	α_2 : .026 ± .010 β_1 : 11. ± 7.0	4.7	5	.45

*Estimate and standard deviation scaled by 10^2. †Degrees of freedom. ‡Boundary value estimate. Parameters constrained to be nonnegative. Standard deviation is approximately that of the negative estimate obtained by fitting the corresponding unconstrained model.

in the table fit the data equally well or poorly. However, the estimate of excess risk from the response to 1 rad ranges from 2.5 excess cases of cancer per million per year for the linear model to only .016 excess cancer cases for the pure quadratic model, a difference of a factor of 156. More valuable information from experimental studies are the findings that high LET radiation (resulting in tracks with the ionizing events close to each other) yields a linear response and that several genetic diseases in humans resulting in increased susceptibility to cancer have their cause in defects of the DNA repair system of the cell nucleus (10). Once the biochemistry of these diseases is fully understood, epidemiological data on affected patients will produce valuable information on the dose-response in healthy subjects.

4. EPIDEMIOLOGICAL STUDIES

4.1. General Considerations

There is ample epidemiological data and little disagreement about cancer risks from exposures to hundreds of rads. Most of the disagreement about low-dose risk estimates stems from the lack of knowledge on the shape of the dose-response curves from the high exposure values down to natural background radiation. It would be a big help to know which fraction of the spontaneous cancer rates is caused by background radiation. Since a multitude of known chemical carcinogens, both natural and man made, and endogenous factors contribute to the spontaneous cancer rate, the significance of background radiation on the naturally-occurring cancer incidence is unknown but generally believed to be quite small, i.e., in the range of a few percent. Evidence for this statement comes from the fact that relatively large differences in background radiation between different regions of the U.S. or Switzerland have no measurable effect on the spontaneous cancer rate. Thus, natural cancer incidence and background radiation do

not provide a convenient anchorage point at the lower end of the dose-response curve. Nevertheless, some very conservative linear extrapolations from high exposure data can be rejected because they predict a higher cancer rate from background radiation alone than the rate observed in the general public (11).

In the following sections, some of the most important epidemiological studies on radiation-induced carcinogenesis are reviewed.

4.2. Lung Cancer Incidence in Uranium Miners

Uranium miners are exposed to elevated levels of radon gas which is emitted from radium containing rock. By breathing the short-lived radon decay products which are bound to dust particles in the ore, they exposed the surface of the tracheobronchial and the pulmonary region to quite high levels of α-radiation. Information on exposure is commonly given in working level months (WLM). One WLM is defined as exposure for 170 hours (1 working month) to a concentration of 1 working level which is any combination of short-lived decay products of ^{222}Rn in complete equilibrium with its daughter equal 1 WL. One WLM results in a dose of about 1 rad or 10 rem to the basal cells of the tracheobronchial region (12). Risk estimates for exposures from 20 WLM (Canadian uranium miners) up to several thousand WLM in U.S. mines in the early forties were compiled. Figure 3 taken from a report by Cohen (11) shows the range of results reported. The line drawn by Archer (13) represents the most conservative interpretation of the data possible. It seems more reasonable to assume a linear relationship resulting in about 6.5 cases/year-WLM-million as it was done in the BEIR report (1). On the other hand, an estimate of zero risk for low levels of exposure cannot be excluded.

Although the number of miners followed up and the quite accurate dose assessments gave results over a large dose range which are highly significant, the uranium miner data has several shortcomings:

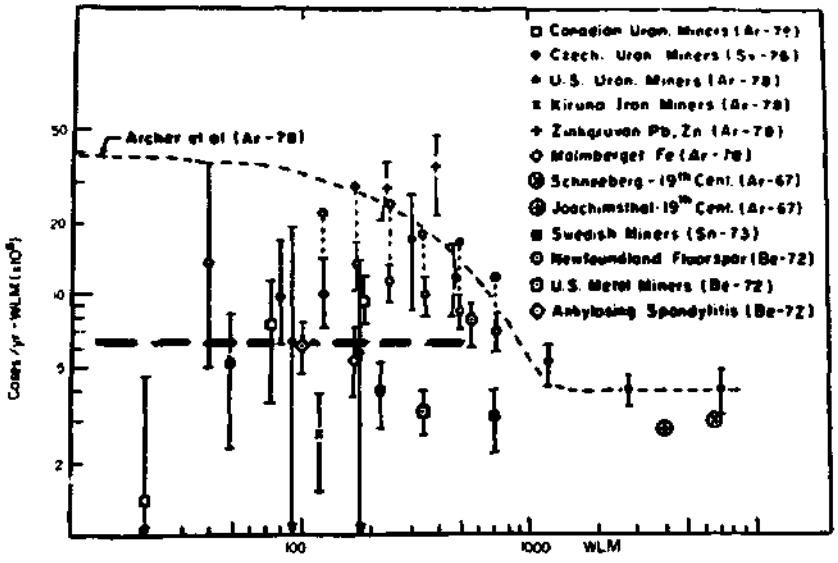

Fig. 3: Lung cancer mortality/year-WLM vs. radon exposure in WLM for various groups (modified from 11).

— At the beginning of operation in the 1940's, exposures were sometimes underreported.

— Often mine air contains additional carcinogens like heavy metals and organic fumes from drilling operations.

— Many uranium miners had a previous work-history in lung disease from occupations like hard-rock and coal mining.

— The aerosol characteristics in the mines are quite different from indoor air in homes.

The last point became quite important because the recent trend to conserve heating energy may result in a several-fold increase of exposure of the general public to environmental radon and its daughters (14). Measurements of present radon concentration in indoor air of 37 Bq/m³ (1 pCi/ℓ) yield an exposure of about

.25 WLM per year or 15 WLM per average lifetime. Widespread insulation of dwellings resulting in lower air exchange rates will result in a large buildup of radon indoors (15). Recent studies indicate an increase in radon levels by a factor of about 3 (16). Estimates of excess risk from present indoor radon concentrations predict about 11,000 lung cancer cases/year in the United States (16). Lifetime exposure in insulated buildings would be comparable to the exposure in modern uranium mines (Canadian and Czechoslovakian exposures in Figure 3).

Two features should facilitate the assessment of risk from low levels of radon:

1) Radon and its daughters emit high LET α-radiation. All experimental data available suggests that high LET radiation has a linear dose-response relationship.

2) The dose equivalent of about 25 mSv/year (2.5 rem/year) to the basal cells of the tracheobronchial region from environmental radon concentrations is by no means a low dose, hence the dose range distance to be covered only by extrapolation is small in this case. Nevertheless, exact predictions of the lung cancer risk from environmental radon are still lacking.

4.3. Atomic Bomb Survivors

The survivors of the atomic bombings of Hiroshima and Nagasaki constitute probably the most important source of information on the effect of ionizing radiation. In 1947, the Atomic Bomb Casualty Commission (ABCC) was organized for the purpose of detecting late radiation effects in the people of the two towns. After 28 years of operation, ABCC was reorganized in 1975 into a private foundation called the Radiation Effects Research Foundation (RERF) founded equally by Japan and the United States (17). Extensive clinical observation of newborn

children did not demonstrate any evidence of hereditary abnormalities attributable to prenatal exposure. Mental retardation and inpaired growth and development have been bound in some of those exposed *in utero*. By far the most important effects noted are an excess risk for several tumors (18). The reasons that make the bomb survivors an extremely useful tool for the study of late somatic effects (cancer) are as follows (1b):

— The samples available for study are generally the largest of their kind.

— An elaborate dosimetry program has yielded individual dose estimates for the major samples for the tissues of organs considered for carcinogenesis. However, some of these calculations for Hiroshima are disputed today (45,46).

— The Japanese family registration system guarantees virtually 100% mortality followup.

— The population was relatively unselected with respect to disease or working status.

On the other hand, the major disadvantages and limitations are (1b):

— The samples are still too small to detect presumably smaller risk in the low dose region.

— The radiation was delivered in a single exposure at a very high dose rate.

— The radiation was a mixture of neutrons and γ-rays.

— The radiation dose of a survivor depended on his location and shielding situation, i.e., there was no random assignment.

— Besides radiations, the bombs released large amounts of heat and blast.

— Each city was so devastated that living patterns were profoundly disrupted.

— The fact that tens of thousands were killed by the bombs raises the possibility that the survivors were fitter than those who died.

Table 2 lists the four most important fixed samples from

Table 2: Major fixed samples[a] studied at the Radiation Effects Research Foundation (from 1c)

Sample	Year Observations Began	Size
Life-span study (LSS) sample (extended)	1950	109,000
Adult health study (AHS) sample[b]	1958	20,000
In utero mortality sample	1945	2,800
In utero morbidity sample[c]	1950	1,600

[a] All samples include some representation of those who were not in the city at the time of the bombing, i.e., not directly exposed.
[b] A subsample of the life-span study sample.
[c] Progressively enlarged from 1950 to 1959.

the 284,000 survivors used to derive data on late somatic effects. In addition, special disease registries were set up for leukemia and much later (1957) general tumor registries supplemented 1970 with so-called "tissue registries" for neoplasma (19).

Absolute risk estimates expressed in excess cancers per million per year per rem generally agree very well with other human data. The only very marked exception is the absence of an excess cancer risk among those exposed *in utero*.

These findings are contrary to the significant risk (McMahon (20) and Stewart and Kneale (21)) found for prenatal exposure to X-rays. Information on the shape of the

dose reponse curve is suggestive at best. It seems that the carcinogenic effect of the Hiroshima bomb, which may have had much higher neutron contribution to the overall dose than the Nagasaki bomb, follows more or less a linear relationship whereas the Nagasaki experience concerning leukemia, lung and stomach cancer points more to a linear-quadratic or quadratic relationship. However, the Nagasaki data below 100 rad are too weak to make a final conclusion. Attempts to separate the effects of neutrons and γ-rays in the Hiroshima data were not very successful.

Although the Japanese data covers the low to moderate range of exposure much better than most other studies, a direct estimate of the excess risk at low doses and the shape of the dose-response curve is not possible. Regression analyses of the leukemia incidence and the mortality excluding leukemia both show no significant differences in goodness of fit between "linear-quadratic gamma, linear neutron" (LQ-L), "linear gamma, linear neutron" (L-L) and "quadratic gamma, linear neutron" (Q-L) models (1d, see also Fig. 1). Table 3 illustrates this point.

Table 3: Regression analyses of leukemia incidence, Hiroshima and Nagasaki, 1950-1971

	Coefficient ± se			Goodness of Fit	
Model (Equation)	α_1	α_2	β_1	χ^2, df	(p)
LQ-L (V-6)	0.99 ± 0.93	0.0085 ± 0.0056	27.5 ± 7.5	10.4, 11	(0.49)
L-L (V-7)	2.24 ± 0.60		25.4 ± 7.5	11.5, 12	(0.49)
Q-L (V-8)		0.014 ± 0.004	31.1 ± 6.9	12.3, 12	(0.42)

A new recalculation of the radiation fields experienced in Hiroshima claims that the generally accepted figures for neutron radiation are grossly overstated (47,48). Although this would mean a blow to Rossi's quadratic dose response theory for gamma-radiation, the adjustment needed if the new field calculation prove to be correct is a small fraction

of the factors brought forward in some precocious publications (45,46) since parallel with the drop in neutron dose, the gamma dose has been readjusted to higher values (49).

4.4. Data from Therapy in the Healing Arts

In highly developed countries diagnostic X-ray procedures contribute up to 80 mrads and 100 mrads/year per capita to the gonads and the bone marrow, respectively. However, epidemiological data on cancer incidence is mostly derived from the much larger doses used in treatment of diseases. Well controlled studies were published on the breast cancer incidence of patients treated for postpartum mastitis (inflammation of the breast after giving birth) (22), on late effects of radiation treatment for ankylosing spondylitis (inflammation of the vertebrae leading to stiffness (23), on skin and thyroid cancer risk after scalp irradiation for ringworm (fungal infection of the skin) (24), only to mention a few.

Table 4: Cancers induced by radiation (from Upton (44))

	Atom bomb radiation			Medical radiation										Occupational radiation			
Type of Cancer	Japanese atom bomb survivors	Marshall Islanders	Nuclear test participants	Ankylosing spondylitis (x-ray)	Ankylosing spondylitis (radium)	Benign pelvic disease	Benign breast disease	Multiple chest fluoroscopy	Tinea capitis (children)	Enlarged thymus (infants)	Thorotrast	Thyroid cancer (I-131)	In utero x-ray	Diagnostic x-ray	Radium dial painters	Radiologists	Uranium & other miners	Nuclear workers
Leukemia	***		*	***		**				**	***	*	***	*		***		*
Thyroid	***	**							**	***								
Female breast	***				*		***	***										
Lung	***			***							**						***	*
Bone				*	***										***			
Stomach	**			**														
Esophagus	**			**														
Bladder	**																	
Lymphoma (incl. mult. myeloma)	**			**							*				**			*
Brain									**			*			**			
Uterus						*												
Cervix	*																	
Liver	*										***							
Skin									**	**					***	**		
Salivary gland	*								**	**								
Kidney				*	*						*							
Pancreas																		*
Colon	*					**									*			
Small intestine						*												
Rectum						**												

* Strong associations are indicated by ***, meaningful but less striking associations by **, and suggestive but unconfirmed associations by *

4.4.1. Thyroid Tumors Following Thymus Irradiation

Both from the amount of data available and from the fact that the thyroid gland is the critical organ for radioiodide, the most dangerous short-term component of bomb fallout or accidentally-released activity from nuclear power plants, the thyroid gland merits special consideration. Dose effects can be studied over a large range. Therapeutic external radiation of the thyroid gland ranges in most series from approximately 100 to 1500 rads. Irradiation of other sites like the scalp results in samples with doses of few rads to the thyroid gland.

The classification of the World Health Organization divides thyroid cancer into follicular, papillary, squamous cell, undifferentiated (anaplastic) and medullary types (25). Only the papillary and follicular types appear to be induced by radiation. At necropsy, up to 28% of patients were shown to have benign thyroid neoplasia. For all studies, it is very important to separate these minimal or occult microscopic thyroid cancers from the other cases.

At the University of Rochester, 2,872 people who were irradiated during the first year of life for enlargement of the thymus gland were compared with 5,055 siblings. The relative risk of the exposed groups to develop a thyroid tumor was nearly 100. Recently the tumor data from the 1971 survey were further analyzed to elucidate the form of the dose-reponse curve (26). Although the relatively small number of cases does not permit a final conclusion, the thyroid cancer incidence (adjusted by sex and interval since irradiation) in function of the dose suggests both a linear and dose-squared component. The benign tumor (adenoma) incidence, however, shows a different dose response best described with a strong linear trend and a small quadratic trend with a negative sign. Therefore, a linear regression of the data would, at low doses, overestimate the risk for thyroid

cancer by a factor of 2.3 whereas the risk for adenomas would be slightly underestimated. The considerably higher thyroid tumor incidence in female and Jewish subjects in this study shows the importance of sex and ethnic factors.

4.5. "High Response" Studies

Every once in a while in scientific journals and the news media, scientists claim to have detected even greater carcinogenic effects after exposure to low levels of ionizing radiation than expected from the linear hypothesis. Such evidence, indicating that the linear hypothesis commonly considered conservative underestimates effect would have tremendous implications on future regulations if the results could be substantiated. Although some of these studies show statistically significant increases of cancer risk, it has to be kept in mind that with quite large p values near .05, one out of 20 significance tests would show positive response only from the statistical fluctuations of a totally unaffected population. Since at least a dozen major different cancer sites and types can be studied in a multitude of ways and since positive results are clearly overreported compared to negative results in the very competitive U.S. scientific community, the publication of such results will probably go on. In most cases so far, the claims did not stand up to additional tests of significance or can be explained by confounding factors and bias.

4.5.1. The Hanford Study

This study is based on the 3,500 male deaths from the work-force of the Hanford Laboratory (Richland, WA, USA), searching for correlation of death and radiation exposure (26). The proportional-mortality analysis of death certificates revealed statistically significant associations between dose

and mortality from cancers of the lung, pancreas, and bone marrow (myeloid leukemia and multiple myeloma together). Cancer risk increases of 28% per rad for bone marrow cancers were found which contrast maskedly with the risk increase of 2% per rad for mortality from leukemia derived from A-bomb survivors and medically exposed populations (28). Adjusted analyses of the same data by other authors failed to find statistically significant associations between dose and mortality from all cancers as a group and from lung cancer (29,30). However, the risk estimates for multiple myeloma and pancreatic cancer remained extremely high. Comparison with background radiation and spontaneous rate of these cancers in the general public as well as the lack of increased risk for other cancers led to the interpretation of the Hanford study results as a small sample phenoma. Further studies on confounding factors like chemical carcinogens are needed to untangle this problem.

4.5.2. Leukemia Incidence at the Portsmouth Naval Shipyard

After one of his patients, a shipyard worker, died from leukemia, Najarian, a physician in Boston, started together with a newspaper team a proportionate mortality study of deceased workers of the Portsmouth Naval Shipyard where nuclear submarines are refuelled and repaired (31). The reporter from the "Boston Globe" separated out the former "radiation workers" from unexposed workers by asking their next of kin whether they remembered them wearing film badges. This strongly criticized methodology yielded 146 death certificates from "radiation workers" with six listing leukemia as cause of death versus 1.1 expected. When finally data became available on doses measured with film badges, it turned out that only three of the six leukemia victims had any radiation exposure. The remaining three had an average exposure of 13 mSv (1.3 rem) which is much less than the accumulated dose from background radiation and medical

sources. At this point, Najarian withdrew most of his claims. His paper is a classical example of an epidemiological study with a built-in bias. In the absence of exact information, a relative of somebody who died from leukemia will, when asked if the deceased probably worked with radiation, answer yes with a much higher probability than when the cause of death was not cancer.

4.5.3. Childhood Leukemia Down-Wind from the Nevada Test Site

In an analysis of childhood leukemia in Utah, the state was divided into areas of high and low fallout from the Nevada Test Site (32). There appears to be a large excess of death from childhood leukemia during the high fallout time period in the high fallout area. However, these findings lose most of their significance due to the following two facts:

1) The effect is not an excess over the U.S. average during the high fallout time period as it is a deficiency relative to the U.S. average before and after the high fallout time period.

2) Childhood cancers other than leukemia dropped sharply during the bomb test in the high fallout area. This drop has about the same statistical significance as the increase for leukemia (33). Therefore, the entire effect may simply be a statistical fluctuation.

4.5.4. Melanoma Incidence at Lawrence Livermore Laboratory

An extensively reviewed study shows that the incidence of malignant melanoma among white workers of the laboratory was three to four times the national average. Although an

advisory board found no flaws in the study and revealed that the increased incidence seems to have continued, the absence of an increase in cancers known to be induced by radiation and the low exposures involved point to other causes than ionizing radiation. The incidence of melanoma, a relatively rare form of cancer has been increasing very fast in recent years. In San Francisco, the number of cases rose from 5.8 to 11.2 per 100,000 between 1970 and 1975 (34). Fair-skinned professionals working indoors and having a high socio-economic status seem to be most sensitive. Studies are underway to compare a similar group of professionals lacking the radiation exposure with the sample at Livermore Laboratory.

4.5.5. Conclusions on "High Effect" Data

Although several of the studies mentioned merit a follow-up, so far none of the evidence brought up against the linear hypothesis seems to hold under scientific cross-examination. None of it has been accepted by professional committees such as BEIR or ICRP. The scientific value of these studies seems to be small compared to the publicity given to them by newspapers and television.

Extensive reviews of the above and additional studies can be found in the BEIR III report (1e) and in a paper by Cohen (33).

5. CAN EPIDEMIOLOGICAL STUDIES SOLVE THE ENIGMA OF THE EFFECT OF LOW LEVELS OF RADIATION?

The difficulty to quantify the effect of radiation at high and intermediate exposure on the different segments of the human populations and the lack of direct access to the low exposure region is the cause of a lot of frustration in health physics circles. Although the disappointment with

the statements in the BEIR III report, or the lack of a generally-accepted statement, culminated in articles like "Futility of Epidemiological Studies of Radiation Effects" (35), the valuable information derived from the studies described in Section 4 indicates that the contributions from epidemiology will add to our understanding of radiation effects. The variability of the human population together with the relatively high spontaneous cancer incidence will render impossible the direct assessment of risk from background, medical and occupational exposures in the range of 1 mSv/year (100 mrem/year). However, carefully controlled new studies and the follow-up and interpretation of old studies should extend our knowledge of late somatic effects to lower exposure levels. The larger the known part of the dose-reponse curve grows, the higher becomes the probability to reject at least the most extreme dose-response models like pure quadratic or pure linear. This would allow to narrow down the range of estimates at low doses considerably.

6. STUDY PROPOSAL

There is one largely neglected field for studies which offer some potential to extend our knowledge of radiation-induced carcinogenesis. In a coastal area of Neendakara, Kerala, South India, the soil contains large amounts of monazite, a thorium-containing mineral, which results in a background radiation of 15-30 mGy/year (1.5-3 rad/year) (36). Reports on mutational effects like an increase in prevalence of Down's Syndrome in this region are disputed (36,37,38). An extended study on late somatic effect, i.e., carcinogenesis would have the following advantages:

— Well defined doses from ionizing radiation of known quality.

— Most organs receive low LET γ-radiation. The dose to the lung, however, will be determined by the decay products of ^{220}Rn from thorium and be mostly high LET α-radiation. Overall, the exposure pattern is quite similar to that of members of industrialized societies experiencing increased whole body γ-radiation plus α-radiation to the tracheobronchial and pulmonary region of the lung due to indoor radon.

— The exposed population is unselected and sufficiently large (tens of thousands of people).

— Control populations having the same socio-economic status and ethnic background exist nearby (Purakkade-Punna-pura villages) with a background radiation of approximately 1 mGy/year (100 mrad/year).

It is proposed that a cohort type study be initiated with the population of the high background radiation area as the population at risk. A first goal would be to determine how the incidence of some cancers known to be induced by radiation like neoplasms of the lung, breast, thyroid and leukemia compares to estimates of incidence derived from cancer rates at high exposures by linear extrapolation. If the linear assumption holds, a calculation using the following crude assumptions predicts effects which should become statistically significant after a reasonable time period.

Assumptions	Populations	
	Exposed	Control
sample size	50,000	100,000
exposure rate (a)	2 rad/year (20 mGy/year)	0.1 rad/year (1 mGy/year)
average life span	60 years	
average cumulative exposure (30xa)	60 rads (600 mGy/year)	3 rads (30 mGy/year)
latency	10 years	
average effective cumulative exposure (20xa)	40 rads (400 mGy)	2 rads (20 mGy)
duration of study	10 years	
effective rad-person-years	20,000,000	2,000,000
estimated excess cancer incidence per million-year-rad, 11-30 years after exposure, all sites-leukemia, age and sex-weighted average (Table 5)	18	
excess cancer cases	360	36
expected from spontaneous cancer rate (1f) (in the real study, this value would be derived from the control population)	1,365 ◄———	2,730

If the above assumptions are correct, a test of significance would yield the following result:

$$\chi_1^2 = \frac{(|O-E|-\frac{1}{2})^2}{E} = \frac{(1725-1365-.5)^2}{1365} = 94.7 \quad p << .001$$

A 30-year study with the same sample size would produce:

$$\chi_1^2 = \frac{(5175-4095-.5)^2}{4095} = 284.6 \qquad p << .001$$

Although a linear dose-response relationship for all cancer sites should show up nicely after 10 years, the outlook for a more probable linear-quadratic dose response is bleaker. If the linear hypothesis overestimates the effect at an exposure of 40 rad only by a factor of 5, the excess cancer cases would drop to 72 and 216 for 10 and 30 years of study, respectively. The χ_1^2 values would fall to 3.75 and 11.34. That means that the study could easily fail to record an effect after 10 years. Besides the statistical limitations, also the following points would have to be considered carefully before the start of the study:

— A recent exchange of letters in Nature (37,38) indicates that the average dose in the high background area is considerably lower than the 1.5-3 rad/year reported earlier (36).

— The life expectancy in India is about 20 years less than in highly-developed countries. Since a majority of tissues only develops tumors at a considerable rate after the age of 40, this fact could become very critical. Any latency effects would have similarly enhanced negative influence

Table 5. Estimated Excess Cancer Incidence (Excluding Leukemia and Bone Cancer) per Million Persons per Year per Rad, 11-30 Yr after Exposure, by Site, Sex, and Age at Exposure (from 1).

Site	Age at Exposure, yr					Age-Weighted Average[a]
	0–9	10–19	20–34	35–49	50+	
Males						
Thyroid[b,c]	2.20	2.20	2.20	2.20	2.20	2.20
Lung[d,e]	0.00	0.54	2.45	5.10	6.79	3.64
Esophagus[e,f]	0.07	0.07	0.13	0.21	0.56	0.26
Stomach[e,f]	0.40	0.40	0.77	1.27	3.35	1.53
Intestine[e,f]	0.26	0.26	0.52	0.84	2.23	1.02
Liver[e,f]	0.70	0.70	0.70	0.70	0.70	0.70
Pancreas[e,f]	0.24	0.24	0.45	0.75	1.97	0.90
Urinary[e,g]	0.04	0.23	0.50	0.92	1.62	0.81
Lymphoma[e,e]	0.27	0.27	0.27	0.27	0.27	0.27
Other[h]	0.62	0.38	1.12	1.40	2.90	1.52
All sites[i]	4.80	5.29	9.11	13.66	22.59	12.85
Females						
Thyroid[b,c]	5.80	5.80	5.80	5.80	5.80	5.80
Breast[j]	0.00	7.38	6.60	6.60	6.60	5.82
Lung[d,e]	0.00	0.54	2.45	5.10	6.79	3.94
Esophagus[e,f]	0.07	0.07	0.13	0.21	0.56	0.28
Stomach[e,f]	0.40	0.40	0.77	1.27	3.35	1.68
Intestine[e,f]	0.26	0.26	0.52	0.84	2.23	1.12
Liver[e,f]	0.70	0.70	0.70	0.70	0.70	0.70
Pancreas[e,f]	0.24	0.24	0.45	0.75	1.97	0.99
Urinary[e,g]	0.04	0.23	0.50	0.92	1.62	0.88
Lymphoma[e,e]	0.27	0.27	0.27	0.27	0.27	0.27
Other[h]	0.62	0.38	1.12	1.40	2.90	1.44
All sites[i]	8.40	16.19	19.31	23.86	32.79	23.10

[a] Average of the age-specific coefficients, weighted according to the age distribution, by sex, of the 1969-1971 U.S. life-table population.

[b] Estimate of 4 excess cases per million persons per year per rad adjusted by the observed male:female relative-risk ratio of 0.38 for atomic-bomb survivors.

[c] Risk assumed not to depend on age at exposure.

[d] Estimates are based on the expression, (attained age − 35) × 0.2, with a risk of 0 to attained age 35, latent periods of 15 yr for ages 20–34 at irradiation, and 10 thereafter, except that a risk of 7.0 is used for those irradiated at age 65 or older.

[e] Risk assumed not to depend on sex.

[f] Age variation assumed proportional to linear estimates of atomic-bomb survivors for all gastrointestinal cancers.

[g] Age variation assumed proportional to smoothed risk estimates for cancers of urinary organs among atomic-bomb survivors.

[h] Although cancers of other sites—especially pharynx, larynx, salivary glands, and brain—are thought to be produced by low-dose, low-LET radiation, good estimates of absolute risk are not available. An arbitrary average of 1.0 excess cancer per million persons (of the age and sex distribution of atomic-bomb survivors) per year per rad is assumed. Age-specific coefficients are proportional to those for deaths from all malignant neoplasms, except leukemia, in the atomic-bomb survivors of both sexes combined.

[i] The total, for "all sites," is one possible measure of the effect (excluding leukemia and bone cancer) of whole-body radiation with all tissues receiving 1 rad.

[j] The value for ages 10–19 has been reduced to allow for dilution of effect arising from inclusion of pre-age-20 yr of exposure when latent period is set at 10 yr for all ages.

with shorter life span. However, the expected lower spontaneous cancer rate could counterbalance these effects at least partially.

— Diagnostic centers for 150,000 people would have to be set up to gather the data needed from exposed and control populations.

— Although the change in disease pattern associated with the build-up of a full medical serive would affect both exposed and control populations alike, it adds additional variations with a potential to confound the findings.

Nevertheless, the proposed study would have a much bigger potential to improve our knowledge of effects of low level radiation than a large study undertaken in an area with moderately elevated background radiation in China (39). The exposed population of 73,000 people is receiving 300 mrad/year (3 mGy/year) or about three times the amount of the control population. No effects on the prevalence of chromosome aberrations or the incidence of cancer was found.

7. EXISTING EXPOSURE LIMITS

Most western countries have exposure limits for occupationally-exposed people and the general public derived from ICRP data. The present limits are 5 rem/year (50 mSv/year) and .5 rem/year (5 mSv/year), respectively, for whole-body radiation and higher values for some critical organs like the thyroid gland which can accumulate high dose equivalents in the absence of a substantial dose to the whole body. New concepts which satisfy scientists better are currently introduced (40) but will have no important effects on derived limits of radioactivity in air, food or water and external radiation.

Although the higher limits for occupational exposure are accepted by the majority of the public as an acceptable risk even if a pure linear dose-response relationship is assumed, the lower limits of 500 mrem/year for members of the public do not enjoy this status. At least in Switzerland, the public awareness of possible effects of radiation led to a situation where only temporary exposures of a small fraction of the public outside the healing arts in the range of 500 rem/year would lead to militant actions by political groups.

Since the contribution from nuclear power is below 1 mrem/year and will not rise above this level in this century (1g), the source of radiation most attacked in public will not be affected if limits of exposure would be lowered drastically. Use of X-rays and fluorography in medical checkups, however, would have to be used in a more restrictive way if the limits would be reduced, i.e., by a factor of ten. On the other hand, all therapeutic and a large part of the diagnostic procedures are used in healing where the limits do not apply.

Since the present data available cannot exclude that the dose-response follows a linear relationship and radiobiological theories do not suggest threshold values below which exposure would have no effect, K.Z. Morgan states: "The risks of developing cancer because of exposure to low doses of ionizing radiation are much greater than once thought" (41). By comparing the man-made sources, he points out that a reduction of only 1% in unnecessary diagnostic exposures in the United States would reduce the population dose of radiation more than the elimination of the nuclear power industry to the year 2000.

Since the exposure limits are no more considered safe levels excluding any radiation effects, a critical evaluation would have to include cost-benefit analyses and a comparison of life-saving efforts of regulatory organs

in the field of chemical carcinogenesis and individual transportation, a task beyond the scope of this article. The complex problem is discussed in depth by Cohen (42) and Gori (43). Both stress the need for a less emotional approach and a more efficient use of the scarce resources available to protect us and our environment from man-made pollutants.

8. CONCLUSIONS

— There is no and — for the near future — will be no direct human evidence on the shape of the dose-response curve at low exposures and hence on the effect of low level radiation.

— Preliminary human data suggest that depending on the quality of radiation (high versus low LET) and the cancer type under study, the shape of the dose-response varies.

— Experimental data both from animal and human *in vitro* systems indicate that the assumption of a linear dose-response relationship can be considered a conservative upper limit for low LET radiation. For high LET radiation, a linear dose-response model seems appropriate.

— There is no evidence from radiobiological theories for a threshold dose below which no effects occur. However, an increase in the latent period with lower exposures may result in an apparent threshold due to competition from other causes of death. Dose dependent changes in the latent period could also influence the shape of the dose-response curve if the relative risk model applies to a cancer type displaying only a short period of excess risk.

I would like to thank Dr. Roy Shore, NYU Medical Center, Institute of Envorinmental Medicine, for reviewing the manuscript.

REFERENCES

1. BEIR III, Committee on the Biological Effects of Ionizing Radiations, National Research Council, 1980, The Effects on Populations of Exposure to Low Levels of Ionizing Radiation: 1980, National Academy Press, Washington, D.C.

1a. Ibid., pp. 11-27.

1b. Ibid., pp. 150-157.

1c. Ibid., p. 151.

1d. Ibid., pp. 180-191.

1e. Ibid., pp. 455-471.

1f. Ibid., p. 145.

1g. Ibid., pp. 66-67.

2. Cairns, John, 1981, The origin of human cancers, Nature 289: 353-357.

3. Two views of the causes of cancers, 1981, Nature 289: 431-432.

4. Epstein, S.S. and J.B. Swartz, 1981, Fallacies of lifestyle cancer theories, Nature 289: 127-130.

5. Illmensee, K. and L.C. Stevens, 1979, Teratomas and chimeras, Scientific American 240: 121-132.

6. Upton, A.C., 1977, Radiobiological effects of low doses. Implications for radiological protection, Radiat. Res. 71: 51-74.

7. Land, Charles E., 1980, Estimating cancer risks from low doses of ionizing radiation, Science 209: 1197-1203.

8. Kellerer, A.M. and H.H. Rossi, 1972, The theory of dual radiation action. Curr. Top., Radiat. Res. Q.8: 85-158.

9. Kellerer, A.M. and H.H. Rossi, 1978, A generalized formulation of dual radiation action, Radiat. Res. 75: 471-488.

10. Bridges, B.A. and D.G. Harnden, 1981, Untangling ataxia-telangiectasia, Nature 289:

11. Cohen, A.F. and B.L. Cohen, 1980, Tests of the linearity assumption in the dose-effect relationship for radiation-induced cancer, Health Phys. 38: 53-69.

12. McPherson, R.B., 1980, Environmental radon and radon dosimetry in the respiratory tract, Health Phys. 39: 929-936.

13. Archer, V.E., E.P. Radford, O. Axelson, and H. Jorgensen, 1974, Frequency of different histological types of bronchiogenic carcinoma as related to radiation exposure, Cancer 34: 2056.

14. Evans, R.D., J.H. Harley, W. Jacobi, A.S. McLean, W.A. Mills, and C.G. Stewart, 1981, Estimate of risk from environmental exposure to radon-222 and its decay products, Nature 290: 98-100.

15. Hollowell, C.D., M.L. Boegel, J.G. Ingersoll, and W.G. Nazaroff, 1979, Radon-222 in energy efficient buildings, Trans. Am. Nucl. Soc. 33: 148.

16. Cohen, Bernard L., 1980, Health effects of radon from insulation of buildings, Health Phys. 39: 937-941.

17. Finch, S. and H.B. Hamilton, 1976, Atomic bomb radiation studies in Japan, Science 192, No. 4242.

18. Okada, S., H.B. Hamilton, N. Egami, S. Okajima, W.J. Russell, and K. Takeshita, 1975, A review of thirty years study of Hiroshima and Nagasaki atomic bomb survivors, J. Radiat. Res. (Tokyo) 16 (Suppl.): 1-164.

19. Ichimaru, M., T. Ishimaru, and J.L. Belsky, 1978, Incidence of leukemia in atomic bomb survivors belonging to a fixed cohort in Hiroshima and Nagasaki, 1950-71. Radiation dose, years after exposure, age at exposure, and type of leukemia, J. Radiat. Res. (Tokyo) 19: 262-282.

20. MacMahon, B., 1962, Prenatal x-ray exposure and childhood cancer, J. Natl. Cancer Inst. 28: 1173-1191,

21. Stewart, A. and G.W. Kneale, 1970, Radiation dose effects in relation to obstetric x-rays and childhood cancers, Lancet 1: 1185-1188.

22. Shore, E., L.H. Hempelmann, E. Kowaluk, P.S. Mansur, B.S. Pasternack, R.E. Albert, and G.E. Haughie, 1977, Breast neoplasma in women treated with x-rays for acute postpartum mastitis, J. Natl Cancer Inst. 59: 813-822.

23. Smith, P.G. and R. Doll, 1978, Age- and time-dependent changes in the rates of radiation-induced cancers in patients with ankylosing spondylitis following a single course of x-ray treatment, pp. 205-214. In Late Biological Effects of Ionizing Radiation. Vienna: International Atomic Energy Agency.

24. Shore, R.E., R.E. Albert, and B.S. Pasternack, 1976, Follow-up study of patients treated by x-ray epilation for tinea capitis, Arch. Environ. Health 31: 17-28.

25. DeGroot, L.J., L.A. Frohman, E.L. Kaplan, and S.R. Refetoff, Eds., 1977, Radiation-Associated Thyroid Carcinoma, New York: Grune & Stratton, 539 pp.

26. Shore, R.E., E.D. Woodard, B.S. Pasternack, and L.H. Hempelmann, 1980, Radiation and host factors in human thyroid tumors following thymus irradiation, Health Phys. 38: 451-465.

27. Mancuso, T.F., A. Stewart, and G. Kneale, 1977, Radiation exposures of Hanford workers dying from cancer and other causes, Health Phys. 33: 369-385.

28. National Research Council, Advisory Committee on the Biological Effects of Ionizing Radiations, 1972, The Effects on Populations of Exposure to Low Levels of Ionizing Radiation, Washington, D.C., National Academy of Sciences.

29. Gilbert, E.S. and S. Marks, 1979, Cancer mortality in Hanford workers, Radiat. Res. 79: 122-148.

30. Hutchison, G.B., B. MacMahon, S. Jablon, and C.E. Land, 1979, Review of report by Mancuso, Stewart, and Kneale of radiation exposure of Hanford workers, Health Phys. 37: 207-220.

31. Najarian, T. and T. Colton, 1978, Mortality from leukemia and cancer in shipyard nuclear workers, Lancet 1: 1018-1020.

32. Lyon, J.L., M.R. Klauber, J.W. Gardner, and K.S. Udall, 1979, New England J. Med. 300: 397.

33. Cohen, Bernard L., 1980, The cancer risk from low-level radiation, Health Phys. 39: 659-677.

34. Dickson, David, 1980, Melanoma increase in radiation labs?, Nature 28.

35. Briscoe, G.J., 1980, Futility of epidemiological studies of radiation effects, Health Phys. 38: 863.

36. Kochupillai, N., I.C. Verma, M.S. Grewal, and V. Ramalingaswami, 1976, Down's syndrome and related abnormalities in an area of high background radiation in coastal Kerala, Nature 262: 60-61.

37. Sundaram, K., 1977, Down's syndrome in Kerala, Nature 267: 728.

38. Verma, I.C., N. Kochupillai, M.S. Grewal, K. Ramachandran, and V. Ramalingaswami, 1977, Down's syndrome in Kerala, Nature 267: 729.

39. Luxin, Wei, 1980, Health survey in high background radiation areas in China, Science 209: 877-880.

40. International Commission on Radiological Protection, 1978, Limits for Intake of Radionuclides by Workers, A Report by Committee 2 (Pergamon Press, Oxford, New York, Frankfurt).

41. Morgan, Karl Z., 1979, How dangerous is low-level radiation?, New Scientist, pp. 18-21.

42. Cohen, Bernard L., 1980, Society's valuation of life saving in radiation protection and other contexts, Health Phys. 38: 33-51.

43. Gori, Gio Batta, 1980, The regulation of carcinogenic hazards, Science 208: 256-261.

44. Upton, A., 1981, Radiation hazards, In: Cancer, Achievements, Challenges, Prospects for the 1980's, Vol. 1 (Eds., J. Buchemel and H. Oettger), Grun and Stratton.

45. Marshall, E., 1981, New A-bomb studies alter radiation estimates, Science 212: 900-903.

46. Marshall, E., 1981, New A-bomb data shown to radiation experts, Science 212, 1364-1365.

47. Loewe, W. and Mendelsohn, E., Revised dose estimates at Hiroshima and Nagasaki, Health Phys. 41, in press.

48. Straume, T. and DOBSON R.L., 1981, Implications of new Hiroshima and Nagasaki dose estimates: Cancer risks and Neutron RBE, Health Phys. 42, in press.

49. Loewe, W.E. and Mendelsohn, E., 1981, Radiation estimates, Science 213, 6-8