RADIATION-INDUCTION OF HUMAN LUNG CANCER

(a) Defense of the Hiroshima-Nagasaki Data on Lung Cancer
Induction by Radiation, including reference to the Uranium Miners.

(b) An Hypothesis that Fluoroscopic Radiation is the Underlying Cause
of Excess Lung Cancer in Tuberculous Persons.

(c) A Proposal for Rapid Resolution of any Remaining Questions of
Radiation-Induction of Lung Cancer through 100 Fold Increase in
Immediately Available Irradiated Subjects Beyond the ABCC Group.

(d) Some Important Suggestions for Decreasing the High Risk of Lung
Cancer in Patients with Tuberculosis.

By

John W. Gofman and Arthur R. Tamplin

Division of Medical Physics (Berkeley)

and

Bio-Medical Research Division
Lawrence Radiation Laboratory (Livermore)
University of California

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(a) The Hiroshima-Nagasaki Data on Lung Cancer Induction by Radiation.

Wanebo and co-workers, utilizing several separate, but interdependent samples of the Hiroshima-Nagasaki Atom bomb survivors, reported a significant increase in lung cancer in those exposed to ionizing radiation (1). Summarizing their experiences they indicated:

(a) Based upon death certification in the large JNIH-ABCC* Life Span Study the observed to expected ratio for lung cancers was 1.9 times in those exposed to 90 or more rads.

(b) Based upon principal autopsy diagnoses, the observed to expected ratio of lung cancer was 2.15 times in those exposed to 90 rads or more.

(c) Based upon the ABCC-JNIH Adult Health Study the observed to expected ratio was 1.6 for those exposed to 90 rads or more.

Significance tests leave little reason to doubt the increase in lung cancer associated with radiation, as proposed by Wanebo and co-workers.

Yet, Miller recently expresssed doubt, and Storer has quoted Miller in these doubts - doubts we shall show here rest upon totally erroneous, indefensible scientific grounds. (2)(3).

Miller stated the the Japanese results are weakened by "the finding that the lung cancers were non-specific as to histologic type, rather than of the small cell type, as in U.S. uranium miners and in workers heavily exposed to mustard gas, a radiomimetic chemical"

Miller has, in our opinion, made a great error in his statement. This arises out of the data from the lung cancer story among the U.S. uranium miners. In those studies Saccomanno showed that small cell, undifferentiated cancers are 57% of all lung cancers in the uranium miners, whereas they are 20% or fewer of all lung cancers in non-miners (4). Out of these important observations, a

*JNIH-ABCC=Japanese National Institutes of Health-Atom Bomb Casualty Commission.

mythology has arisen, obviously perpetuated by Miller, that radiation induces a specific form of lung cancer, namely that which is histologically of the small cell, undifferentiated variety.

In a previous report of this series, we have demonstrated that this is a grossly erroneous interpretation of the lung cancer findings in the uranium miners (5). The Saccomanno observations, properly utilized, demonstrate that

(a) Radiation induces both bronchiogenic lung cancer and small cell, undifferentiated cancers of the lung.

(b) The reason for the preponderance of small cell cancers of the lung in the miners is that the domain of cells giving rise to such cancers receives more irradiation from the radon-daughters than the domain of cells giving rise to bronchiogenic cancers.

Therefore, since the basis for so-called specific lung cancer induced by radiation has been exploded, the grounds upon which Miller's criticism of the Japanese data rest simply no longer exist. We, therefore, believe it is appropriate to dismiss Miller's comments as not being justified in any way.

Storer's doubts rest largely upon Miller's comments concerning specificity of radiation-induced lung cancer, which is erroneous as shown above.

There does remain, with respect to the Japanese data, an effort to determine the doubling dose for lung cancer by ionizing radiation. This we shall address now. Unfortunately, not enough time has elapsed in the Japanese study so that the latency-period for lung cancer induction is fully over. Therefore, in studies completed by 1966, it is anticipated that the number of radiation-induced cases observed per year will be less than they would be when latency is fully over.

For purposes of conservatism, we shall underestimate the probable radiation effect, and assume that in the period of 1950-1966 (5 to 21 years after exposure), 2/3 of the rate of appearance of radiation-induced cancers would be observed compared with the rate to be observed at some later period when latency is over.

The most rigorously studied group of Wanebo et al are 66 lung cancers in Hiroshima and Nagasaki, observed to occur between 1950-1966. Ideally we would like to have a larger series starting 10 or more years after the bombing, but that must await further ABCC studies.

In Wanebo et al (Reference 1, Table 4) are presented the following data for 66 cases of lung cancer, male plus female, together with an "expected" incidence for each dose category, assuming no effect of radiation.

1950-1966 (Hiroshima and Nagasaki). Total Cases Lung Cancer
Radiation-Dosage Category (Rads)

	200+	90-199	40-89	20-39	10-19	0-9	Unknown	Not in City
Observed	8	9	8	5	7	11	5	13
"Expected"	5.05	5.59	5.59	4.21	4.02	20.49	4.32	16.73

(5 cases out of 66 were in subjects whose dose was unknown)

We could do the analysis directly, but for convenience we shall estimate the population-at-risk for each dose category by what amounts to the inverse of the procedure used by Wanebo et al to arrive at the "expected" numbers of cases of lung cancer.

There are 66 total cancers occurring in ~15000 subjects (Wanebo states 15006 were examined in the first cycle). To arrive at "expected" numbers, what was done was to assume no effect of radiation, and then,

$$\frac{\text{Population in a dose category}}{15000} = \frac{\text{Expected}}{66}$$

Transposing, we have

$$\text{Population in dose category} = \frac{(\text{Expected})(15000)}{66}$$

In this way we arrive at the following approximate population-at-risk values for the various dose categories, and we are confident these must be extremely close to the true values.

Dose Category (Rads)	Population-at-Risk (for 15000 total)
200+	1148
90-199	1270
40-89	1270
20-39	957
10-19	914
0-9	4657
Not in City	3802
Unknown	982

Total   15000

(Actually, if the total size of the Adult Health study sample is $>$ 15000, or

$<$ 15000, the tabulated numbers are still totally usable, since all frequencies

would thereby be changed by a constant multiplier).

Now we can proceed to estimate doubling dose as follows:

I. Mean Dose Calculation

Above 40 Rads, we have

1148 subjects $\geq$ 200+ Rads (Use 300 Rads as median dose)
1270 subjects   90-199 Rads (Median dose = 145 rads)
1270 subjects   40-89 Rads (Median dose = 65 rads)

$$\text{Mean Dose} = \frac{(1148)(300)+(1270)(145)+(1270)(65)}{1148 + 1270 + 1270}$$

$$\text{Mean Dose} = \frac{344,400 + 184,150 + 82550}{3688} = \frac{611100}{3688}$$

Mean Dose = 165.7 Rads

Occurrence of Cancers

In the irradiated group, we have $8 + 9 + 8 = 25$ lung cancers in 3688 persons

at risk, or a rate of 67.8 cases per 10,000.

For the spontaneous incidence we can use those not-in-city at time of

bombing plus the 0-9 Rad group. (This gives an overall group with radiation

exposure of $\sim$ 5 Rads, which dose we can neglect compared with the mean of

165.7 Rads above).

So, "spontaneous" incidence $= 11 + 13 = 24$ cancers in $4657 + 3802$ persons,

or 24 cancers in 8459 persons at risk. This correponds to a rate of 28.4 per

10,000.

Excess cancers, radiation induced, = 67.8-28.4= 39.4 cases/10000 persons.
Now, to correct for the fact that these observations were made with many subjects
still in the latency period, we shall use the factor 3/2, described above.

Excess lung cancer, latency corrected, 3/2 x 39.4 = 59.1 cancers/10000.

Doubling Doses = $\frac{\text{Excess}}{\text{Spontaneous}}$ = $\frac{59.1}{28.4}$ = 2.08 doubling doses.

But 165.7 Rads corresponds to this excess,

So, 1 Doubling Dose = $\frac{165.7}{2.08}$ = 79.7 Rads

Note: Since we have been very conservative in correcting for latency in the
1950-1966 sample, our expectation is that the true doubling dose for radiation
induction of lung cancer must lie below 79.7 rads. This value is highly consistent
with all the other data we have previously presented, which indicated the
doubling doses for human radiation carcinogenesis to lie in the neighborhood of
100 rads, with a high probability it may even be a factor of two lower (8)(9).

Certainly, as additional time elapses, new cases from Japan will allow
further refinement of this doubling dose calculation. We can see no valid reason
either for Miller's or Storer's doubts about the Japanese data. They appear quite
firm, and are consistent with all other data concerning human radiation
carcinogenesis.

(b) <u>An Hypothesis That Fluoroscopic Radiation is the Underlying Cause of Excess
Lung Cancer in Tuberculous Persons</u>

Recently, Steinitz, in Israel, published a paper probably destined to
become a classic in the literature of epidemiology (10). It is entitled
"Pulmonary Tuberculosis and Carcinoma of the Lung . A survey from Two Population-
Based Registers". The conclusion of that paper is that patients with pulmonary
tuberculosis histories have 5 to 10 fold the expected risk of later cancer of
the lung - a risk increase comparable with that for heavy smoking of cigarettes.

We shall consider the Steinitz data and then show that

(a) The Steinitz observations are sound. The most probable quantitative explanation of the observed association of later lung cancer with tuberculosis therapy is the fluoroscopic radiation associated with collapse therapy of tuberculosis, such as pneumothorax.

(b) A world-wide study of the records of patients who have been hospitalized in the past for pulmonary tuberculosis should be made; particularly with respect to fluoroscopic radiation exposure and the subsequent development of lung cancer. The records are available now; it is a matter of studying them. If this is done, an epidemiological base would become available for the study of radiation-induced cancer of the chest region (lung and other) that is perhaps 100 times the size of the Hiroshima-Nagasaki exposed group.

(c) If our explanation for the Steinitz observations is correct, the need for drastic reduction in fluoroscopic exposure of tuberculosis patients will be evident, if they are to have their enormously excessive lung cancer risk lowered. Undoubtedly the recent lessened use of collapse therapy has already reduced fluoroscopic radiation exposure. To the extent that fluoroscopies are still used, and need to be used, modern techniques with dosage reduction become imperative as part of management of pulmonary tuberculosis patients.

The Steinitz Observations

Steinitz points out that in the very early literature, the general theme was expressed that pulmonary tuberculosis and lung cancer were almost mutually exclusive. Co-existence of the two diseases was, even up to recent decades, sufficiently rare, she notes, as to be worth literature reporting. Early it was considered that the rarity of co-existence of the two diseases was due to the fact that tuberculosis killed so many patients early in life that they didn't reach the age where bronchiogenic cancer of the lung became prominent as a

general cause of death.   But as Steinitz describes, many more recent reports
have noted a high frequency of lung cancer and tuberculosis in the same person,
and controversy has recently existed concerning tuberculosis as <u>an</u> etiologic
contributor to lung cancer.

Steinitz was prompted to carry out her epidemiologic study for the following
interesting reason. "Some two years after starting a cancer registry in 1960,
Israel noted that case records of male patients with pulmonary carcinoma contained
tuberculosis <u>approximately seven times</u> as frequently as those of stomach cancer
in the same age groups." The suspicion of an association of <u>lung</u> cancer with
prior tuberculosis was therefore high, and led to a detailed epidemiologic study
of essentially the entire Israeli population. As we shall see later an
association of lung cancer with prior tuberculosis and a <u>failure</u> of such
association for gastric cancer is <u>precisely</u> what would be expected if fluoroscopic
radiation had caused the excess lung cancers in persons with prior tuberculosis.

Two separate studies were conducted by Steinitz

(a) A comparison of malignant neoplasms, including pulmonary neoplasms in
the total Israeli population and in the population under
supervision for prior tuberculosis.

(b) The autopsy data on 1155 cases of carcinoma of the lung were
reviewed with respect to presence or absence of a history of
tuberculosis.

Both studies were completely consistent with each other, indicating a
5 to 10 fold higher risk of lungcancer in persons who had had tuberculosis
serious enough to require hospitalization therapy at some past period.

The Risk of Lung Cancer in Persons with Tuberculosis.

Several important inputs were required for the Steinitz data:

(a) The distribution of pulmonary tuberculosis cases in the
Israeli population.

(b) The distribution of heavy smoking in the Israeli population.

(c) The distribution of new primary lung cancer cases (1960-63).

(a) The distribution of pulmonary tuberculosis cases in Israel

Two independent sources of information were available to Steinitz

(a) the tuberculosis registry.

(b) the results of mass radiographic examination of 500000 Israelis
between 1952 and 1962.

Both led to consistent results. The prevalence data from mass radiography
are reproduced here (Table 6 Reference 10).

(Steinitz data)

Prevalence of Pulmonary Tuberculosis (all grades of diseases activity) in the
Jewish Population

By Age and Sex

(Based upon Mass Radiography 1952-1962)

	Number of Examinations	Prevalence of Pulmonary Tuberculosis
Males		Rate/1000 examined
All Ages	291,002	11.63
45-64 yrs.	51212	37.18
65 and over	10,211	40.83
Females		
All Ages	231,336	8.55
45 and over	44087	21.15

From these data, it is readily calculated that, for example, for men 45-64 years
of age, 37.18 per 1000

So for 51212 persons, tuberculosis $= \dfrac{51212}{1000} \times 37.18 = 1904.1$

Therefore, % of such males with tuberculosis

$$= \dfrac{1904.1}{51212} \times 100 = 3.72\%$$

In a similar manner the % prevalence of tuberculosis can be calculated for each
age group.

From independent data, Steinitz estimated the % prevalence of heavy

cigarette smokers (20 or more/day) in Israel.

New cases of primary lung cancer for the period 1960-63 in Israel were 837 distributed between males and females and into the different categories of age, sex, tuberculosis history, and cigarette smoking. A very few cases were both heavy smokers and tuberculosis. 9 such occurred in the men, 45-64 years of age, and 4 such occurred in the men over 65 years of age. Steinitz did the calculations of risk of lung cancer (see below) with these cases included and then excluded for both the smoking and the tuberculosis categories.

The results including risks of pulmonary carcinoma are reproduced from Steinitz (Table 7, Reference 10)

The results are striking, and significant.

Males (45-64 years), (with tuberculosis of all degrees of activity), show a rate of development of primary lung cancer 7.98 to 9.76 times as high as non-tuberculous persons. Indeed the risk of lung cancer, if tuberculous, is comparable to the risk for heavy cigarette smokers.

Females (45 or over) show a 10.8 fold higher rate of development of primary lung cancer, if tuberculous, when compared with the rest of the population.

Males (65 years or older) shows a 5.34 - 6.28 fold higher rate of development of primary lung cancer, if tuberculous, then do all others. Again, the risk of lung cancer, if tuberculous, was comparable to the risk for heavy smokers of cigarettes.

In a similar study, based upon review of autopsy data, Steinitz demonstrated that malignant neoplasm is excessive as a cause of death in patients with pulmonary tuberculosis and that the excess malignancy is totally accountable as pulmonary malignancy. She quotes Campbell (11) and Gebel (12) as having found similar results.

TABLE 7 REFERENCE 10

Estimate of Risk of Developing Primary Carcinoma of the Lung (ICD Code Number 162) for Patients with Pulmonary Tuberculosis and for Heavy Smokers, compared with That for the General Population (Jews) by Age and Sex.

	Distribution of Population According to Prevalence		New Cases of Lung Cancer		Period 1960-63 Risk Relative to General Population
	%	Number	Number	Rate per 100,000	
MALES					
Age 45-64	100.00	207424	252	518-634	7.98-9.76
Tuberculous persons	3.72	7722	49/9+	518-634	7.98-9.76
Heavy Smokers	8.72	17928	94	474-524	7.30-8.07
Other	87.56	181774	118	64.9	1.00
Age 65 and over	100.00	55179	160		
Tuberculous persons	4.08	2251	24+	1020-1199	5.34-6.28
Heavy Smokers	6.00	2210	42	1148-1269	6.01-6.64
Other	89.92	49618	95	191	1.00

+Cases both reported as heavy smokers and as tuberculous. Rates calculated with and without these cases in each group. Maximum rate includes these cases. Minimum rate excludes these cases.

This is the reason for the ranges given.

			FEMALES		
Age 45 and over	100.0	257200	83		
Tuberculous persons	2.12	5453	15	275	10.8
Heavy Smokers	1.97	5067	5	98	3.84
Other	95.91	246680	63	25.5	1.00

Fluoroscopic Radiation as the Basis for the Excessive Rate of Occurrence of Pulmonary Cancer in Persons with Tuberculosis.

Steinitz' data show some 5-10 fold higher rate of primary lung cancer in Israelis with pulmonary tuberculosis, active or otherwise. Her earlier studies indicated no such excess for gastric cancer in persons with a history of tuberculosis.

How are these results to be explained? One suggestion has been that the presence of pulmonary tuberculosis causes changes in lung or bronchial cells that might predispose to carcinoma. It can be pointed out that from other studies, the site of carcinoma is often grossly different from the site of tuberculosis. This argues against the above explanation (13). But there are far more potent arguments.

We shall, for purposes of argument, REJECT TOTALLY THAT LUNG CHANGES DUE TO TUBERCULOSIS ARE RESPONSIBLE FOR A HIGH RISK OF SUBSEQUENT LUNG CANCER.

Instead, we propose that fluoroscopic radiation in the course of tuberculosis therapy is the etiologic factor responsible for the excessive lung cancer in such persons.

Why do we propose this hypothesis?

In a previous report of this series we analyzed the Mackenzie study of breast cancer in women with tuberculosis (14). His data showed that women with prior tuberculosis treated by pneumothorax collapse therapy had a 24 fold higher incidence of subsequent breast cancer than did women in the same sanitorium with tuberculosis but without such pneumothorax therapy.

From Mackenzie's data we estimated that the ∼150 fluoroscopies associated with pneumothorax probably resulted in a delivery of between 900 - 2100 rads to the chest for the women treated with pneumothorax.

Now, the Mackenzie data are for a sanitorium in Nova Scotia. One cannot prove that the Israelis, wherever they were when treated for tuberculosis, would have received precisely the same fluoroscopic radiation dose. On the other hand,

for lung cancer showing up in 1960-63 (Steinitz data) and a 15 year latent period, the Israelis treated most likely received therapy comparable to other areas in the 1940's and early 1950's. Pneumothorax was widely practised then, with its accompanying numerous fluoroscopies. Since for present purposes, only an approximation is needed, we shall consider the _expectations_ anywhere in the world if tuberculosis therapy were like that of the sanitorium reported by Mackenzie.

He had

877 total patients treated

271 received prolonged pneumothorax
607 did not

Let us calculate average dose to _all_ patients, realizing that only the pneumothorax cases received appreciable irradiation, using our two estimated limits, 900 rads and 2100 rads.

At 900 rads
Mean Dose = $\frac{(271)(900)+(607)(0)}{877} = \frac{243900+0}{877} = $ 278.1 rads

At 2100 Rads
Mean Dose = $\frac{(271)(2100)+(607)(0)}{877} = \frac{569100}{877} = $ 648.9 Rads

Let us use, for argument, the central value between these two values, or 464 rads for the average patient in Mackenzie's sanitorium group. Now let us consider the implications in _any_ sanitorium where similar practises prevailed.

We have shown earlier in this report that ⌐ 80 Rads is a reasonable value for the doubling dose for lung cancer in the Japanese data. From other studies, we shall not be surprised if the final value turns out to be 50 rads.

Let us explore 100 rads as doubling dose:

For a group receiving 464 rads, this is 4.64 doubling doses. Therefore the total rate for future expected lung cancer is

1.0 for the spontaneous incidence
4.64 for the radiation induced excess
5.64 is the _factor_ of total increase in lung cancer expected.

Let us explore 50 rads as doubling dose for lung cancer

$$\frac{464}{50} = 9.3 \text{ doubling doses}$$

Therefore the total rate of future expected lung cancers is

       1.0 for the spontaneous incidence
       <u>9.3</u> for the radiation-induced excess
       10.3 is the <u>factor</u> of total increase in lung cancer expected.

This range of 5.6 to 10.3 fold increase in expected lung cancer rate is so similar to the observed increase in Israel as to lead us to one conclusion - Most probably the radiation dosage in fluoroscopies associated with tuberculosis therapy in the Israel group was probably closely similar to that in Mackenzie's Nova Scotia cases.

We suggest that if Steinitz investigated the fluoroscopy - pneumothorax incidence in her cases, she will, in all probability, confirm our suspicions of radiation-induction of her excess lung cancers, qualitatively and quantitatively.

The much lesser, if any, excess of gastric cancers in tuberculosis subjects is precisely as expected - if the X-rays don't strike an organ, no excess cancer occurs.

(c) <u>A Proposal for a 100 Fold Increase in Immediately Available Information Concerning Radiation-Induction of Lung Cancers.</u>

Only very gradually do the new cases add to the lung cancer statistics in Hiroshima-Nagasaki. Through the vistas opened by Steinitz' remarkable epidemiologic study and our analyses here presented, there are immediately available at least 100 times as many lung cancers for analysis, and possibly several thousand times as many.

World-wide, in well-run tuberculosis hospitals where records <u>are</u> kept, there must have been millions of patients treated for tuberculosis, say between 1930-1950, during which time pneumothorax collapse therapy, with its associated fluoroscopies, was widely practised (as it was in Nova Scotia). If a study is made of the records

in such hospitals, together with follow-up data on the occurrence of primary lung cancer, there should be many thousands of lung cancers available for analysis. It must be emphasized that for persons hospitalized in 1930-1950, the latency period for radiation-induced cancers is past, so that cases must already have occurred - and it is simply a matter of record search to ascertain how many cases occurred in each category of fluoroscopic exposure. As Steinitz pointed out, a fraction of the lung cancers will be lost because it is all too easy to assume that pulmonary disease in persons with a prior history of tuberculosis is tuberculosis. But this should be an equal loss for previously fluoroscoped persons and those not receiving radiation, and hence should not affect the outcome.

We URGE the Epidemiology Section of National Cancer Institute, the WHO, and every tuberculosis sanitorium in the world to do this record study. Properly done, it will resolve the lung cancer radiation-induction problem, including the overall dose response curve far earlier and far better than waiting for the ABCC studies to mature further.

Additionally, we predict the following if such a study is done

(a) Leukemia will be found to be increased in the fluoroscopically irradiated tuberculous subjects.

(b) Mediastinal tumors, e.g. lymphomas, will also be found increased-separate from lung cancers.

(c) Both bronchogenic and small cell undifferentiated cancers will be found increased.

(d) Possibly even bone sarcomas will be shown increased, if the studies are pooled.

(e) If other sites of cancer are checked at the same time in these studies, the further the organ from the chest, the lower will be any evidence of radiation induction of cancer.

Such studies may well already be underway. If so, we urge their expansion broadly!

(d) <u>Some Important Suggestions for Decreasing the High Risk of Lung Cancer in
Persons with Tuberculosis.</u>

The 5 to 10 fold higher rate of pulmonary cancer found by Steinitz in
persons with a record of tuberculosis is shocking and terribly important. We
have presented evidence to make us believe these cancers were provoked by
fluoroscopic irradiation. Confirmation should not be long delayed, since only
record search is required.

In recent years, pneumothorax with its associated fluoroscopies has waned
greatly as a form of tuberculosis therapy. This is excellent, for radiation-
induced lung cancers should decrease as a result.

However, fluoroscopy with or without pneumothorax, is undoubtedly still a
highly frequent procedure in the management of pulmonary tuberculosis. Obviously
where the best therapy of the patient with tuberculosis requires fluoroscopies,
they should be done. But, as emphasized by Morgan, techniques are available for
grossly reducing the radiation-exposure with such fluoroscopies (15). Every effort
to achieve this must be carried through in the treatment of tuberculosis, if we are
right.

Steinitz, expressing her horror of the lung cancer risk in the subjects with
tuberculosis, pleads for more effort to <u>prevent</u> tuberculosis. Of course we agree
with Steinitz that prevention of tuberculosis is good. But we suspect the real
horror comes from the radiation in the course of therapy, rather than from the
tuberculosis per se.

Steinitz deserves the world's appreciation for her monumental epidemiologic
contribution to a vital subject.

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