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MAJOR FALLACIES IN THE AEC STAFF COMMENTS ON THE GOFMAN-TAMPLIN PAPERS AND CONGRESSIONAL TESTIMONY

I. The Demonstrated Validity of the Doubling Dose Concept as Used by Gofman and Tamplin.

by

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INTRODUCTION

In a recent publication entitled "AEC Staff Comments on Papers and Congressional Testimony by Dr. John W. Gofman and Dr. Arthur R. Tamplin"(1), the following statement is made by AEC Staff.

"The concept of a doubling dose as applied to carcinogenesis by Gofman and Tamplin is here reviewed in detail and found to be without scientific validity".

This remarkable statement would be interesting if it were true. However, one could search the AEC Staff document for an infinite period and still not find the proof of this heralded finding that "the concept of a doubling dose.....is found to be without scientific validity". Indeed, so unsure of itself is the AEC Staff that on the very next page of their document they state,

"Whether they (Gofman and Tamplin) are justified in evaluating hazard by use of the 'doubling dose' is a matter of opinion".(1)

This is indeed strange. First the AEC Staff finds the concept without scientific validity, and then backs off and indicates the concept's validity to be "a matter of opinion". Surely, if the AEC Staff had found the concept to be without scientific validity, that should end the matter. How is there still room for "opinion" in a concept that the AEC Staff has already proved invalid on scientific grounds? Could it be that the AEC Staff is ambivalent on this matter, and thus says, "Yes, No, and Maybe" all at once?

Whatever may be the basis for the AEC Staff position of vacillation, we propose to show here the following:

1. Scientific evidence does exist which clearly supports the validity of the "doubling dose" concept even in two extreme tests.

2. The AEC Staff position is not only erroneous, but in the field of radiation standard setting, this position can result in serious irresponsibility with respect to the public health.

THE SUBSTANTIVE PROBLEM RE DOUBLING DOSES

The only real challenge to the doubling dose concept is for a specific type of extreme case. Let us describe such a case, since the ICRP Task Force has alluded to it, and the AEC Staff has seized upon it.(2)

Suppose we consider stomach cancer incidence, in response to radiation. The ICRP Task Force quotes incidence rates (including males and females) varying from 65 per 10^6 up to 706 per 10^6, among five different countries. The doubling dose concept would predict the following, if we use 1% increase in incidence rate per rad or 100 rads as the doubling dose:

For spontaneous incidence of 65 per 10^6/yr, the radiation-induced cases, for 100 rads, would be 65 per 10^6/yr.

For a spontaneous incidence of 706 per 10^6/yr, the radiation induced cases, for 100 rads, would be 706 per 10^6/yr.

On the other hand, if 100 rads induced a fixed number of cases (the ICRP Task Force assumption), say 65 per 10^6 per year, the radiation-induced cases would be 65 per 10^6 per year, in both situations. Obviously, there is a large difference between 65 additional cases and 706 additional cases. Which is correct?

In essence, this is a description of the central problem of co-carcinogenesis, namely synergism versus additive nature of co-carcinogenic

influences. Now, what the carcinogenic influences are in one country versus another that lead to differing spontaneous incidence rates of a particular cancer, or in one group of people versus another in the same country, remain largely unknown. So we have no way of knowing whether any two potential carcinogenic influences should be additive or multiplicative. Multiplicative would be one expression, though not the only possible one, of synergistic action. It fits the doubling dose approach.

Suppose three influences were known, each of which could triple the cancer incidence rate in a population. If all three operate additively, the rate would go up 3+3+3 = 9-fold. If all three operate synergistically in the multiplicative manner, the rate would go up 3x3x3 = 27-fold, an enormously different answer.

As responsible public health officials, and in the absence of knowledge of additivity versus synergism, what should be assumed concerning such carcinogenic influences and exposure of hundreds of millions of people to them? Clearly, in the field of public health, our responsibility is to minimize hazard of death, and, therefore, where knowledge is yet incomplete, the conservative position is the only one that is a responsible position. Any other position is nothing short of playing Russian Roulette with the lives of humans. We choose not to play such Russian Roulette. The AEC Staff should think carefully about its views on this matter.

Indeed, the synergism assumption is not even necessarily the most conservative position. If a particular population shows a higher than usual cancer incidence rate spontaneously, they may be inordinately sensitive to additional carcinogenic effects. Thus radiation may be even more carcinogenic in such a population than the doubling dose concept predicts. In other words, the effect could be even more than multiplicative. So, the doubling dose approach to this problem, while conservative, is by no means

the most conservative. But it is far better than Russian Roulette with human lives.

Thus far, our considerations have been generalized, as though no solid scientific evidence could help solve the problem. But very solid scientific evidence does exist on this question of co-carcinogenesis. It is indeed surprising to us that the AEC Staff launched an attack on synergism (which is what an attack on the doubling dose concept implies) without seriously considering the devastating human evidence directly pertinent to our question. The first important study involves radiation as a human carcinogen plus cigarette smoking as a co-carcinogen. And this study deals with the most important form of cancer in men in the USA, namely bronchogenic lung cancer. The second important study involves asbestos exposure as a human carcinogen and cigarette smoking as a co-carcinogen - again for the all-important lung cancer.

Both studies, on humans, are highly significant and in close agreement pointing very strongly toward synergism between co-carcinogens, and away from additivity. Thus, in the radiation case, the evidence to be discussed below militates strongly in favor of the doubling dose concept and its implication of synergism. The asbestos exposure study points clearly in the same direction.

1. The Lundin-Archer Studies of Uranium Miners

In a continuing brilliant set of epidemiological investigations, Archer, Lundin, Holaday, Wagoner, and their collaborators have enormously advanced our understanding of lung cancer in man, and especially with respect to radiation-induction of lung cancer. Recently, Lundin and collaborators, and Archer and Holaday together, have published their experiences concerning mortality of uranium miners through September 1967.[3] Among the numerous extremely valuable contributions of this publication is a very important

evaluation of the question of possible synergism between radiation and cigarette smoking among uranium miners.

For the period ending September 1967, these workers now have data on 62 cases of lung cancer having occurred among 3414 white uranium miners. They point out that it was technically feasible to define the uranium miners into two groups, smokers of cigarettes and non-smokers (this group including some who had smoked some cigarettes for less than 3 years). Utilizing the U.S. White Male rates for lung cancer together with standardized mortality ratios by smoking class, they were able to calculate the expected respiratory cancer deaths for the uranium miners, if radiation had had no effect. These expected values were then compared with the observed respiratory cancer deaths for smoking uranium miners and for non-smoking uranium miners. Since the radiation exposures are essentially the same for smokers and non-smokers, we have the direct comparison desired.

The Lundin-Archer data are reproduced here:

(Lundin-Archer data)

		Respiratory Cancer Deaths	
	Person-Years	Observed	Expected
Cigarette Smokers	26,392	60	15.5
Non-Smokers	9,047	2	0.5

Lundin and Archer concluded that radiation produces a 10-fold greater effect, in absolute terms, in cigarette smokers than in non-smokers, which is precisely what synergism, on the doubling dose concept, would predict!

Let us look at the data closely, for still further comment on the meaning of these very important findings.

In the non-smokers

2-0.5 = 1.5 excess cases of cancer.

$\frac{1.5}{0.5}$ = 3.0 doubling doses, radiation-induced.

In the smokers

60-15.5 = 44.5 excess cases of cancer.

$\frac{44.5}{15.5}$ = 2.87 doubling doses, radiation-induced.

Now 2.87 and 3.0 are so close together as to be regarded as identical. The 3.0 is, of course, based upon a small number of cases, so the statistics are not yet firm. But we shall show, even taking this into account, these data are far more in agreement with the doubling dose concept than with the fixed number of cases per unit radiation as suggested by the ICRP Task Force. Let us explore this in further detail.

In the Lundin-Archer data they show 26,392 person-years of exposure to uranium mining in the smokers and 9047 person-years exposure to uranium mining in the non-smokers. Therefore, according to the opponents of the doubling dose concept, if there are 1.5 excess cases (2-0.5) in the non-smokers, we would expect

$$\left(\frac{26892}{9047}\right) \times 1.5 = (2.92)(1.5) = 4.4 \text{ excess cancers in the smokers.}$$

But we have 44.5 excess cancers observed due to radiation in the cigarette-smoking. So the opponents of the doubling dose concept are off by a factor of 10. These data are enormously supportive of the doubling dose concept in two populations that differ spontaneously 10-fold in risk of lung cancer, namely cigarette-smoking uranium miners and non-smoking uranium miners. The failure to use the doubling dose concept has led here to an absurdity, predicting 4.4 excess cancers from radiation and observing 44.5 cases!

Let us go further and answer in advance those who point out that the total number of lung cancers in non-smokers is 2, and since this is a small number, the data may not be firm. This will only lead such skeptics into a worse quagmire.

The 0.5 value for expected cancers in non-smokers is sound, since it is based upon estimates from Haenszel for large numbers of cases.[4] It remains to consider the observed 2 cancers in the non-smokers. Because the number, 2, is small, it might truly be smaller or somewhat larger. It can't get much smaller - certainly it should truly be no lower than 0.5, which is the expected value. Let us suppose it is 0.5, for argument. This, however, would mean no radiation effect for non-smokers. Now let us consider our population of cigarette-smoking miners with approximately a 10-fold higher lung cancer incidence rate due to smoking. Here the observations are very firm, showing 44.5 excess cancers due to radiation. If we use 0 cancers, as above, as the radiation-excess for non-smokers, we would have to say radiation is infinitely worse in the cigarette smokers than in the non-smokers. So assuming 0 excess cancers in the non-smokers is not too reasonable. Suppose we assume the observed 2 cases should truly be 1 case. Then the excess in the non-smokers, due to radiation, would be 1.0-0.5 = 0.5 cases. Now, using the ICRP Task Force estimate, we should assign (2.92) (0.5) = 1.46 cases as the radiation effect in smokers. But we observe 44.5 cases, or $\frac{44.5}{1.46}$ = 30.5 times as many! Clearly, the failure of ICRP to use the doubling-dose concept here would lead to an absurdity. The doubling dose concept would predict ~ 31 versus 44.5 observed.

Lastly, let us consider the small number, 2, were too low. Suppose it really might even be 4. Then radiation-induced excess cancers in non-smoking miners would be 4-0.5, or 3.5 cases. Since the ICRP Task Force suggests a fixed number of cases for a given amount of radiation, we would expect (2.92)(3.5) = 10.2 excess cancers in the cigarette-smoking uranium miners. But 10.2 is so far away from 44.5, as to consider the discrepancy results from an absurd assumption.

Thus, no matter how the small number, 2, would change in a larger series, we see that the ICRP Task Force's suggestion is very unreasonable for the uranium miner data of Lundin and Archer. The doubling dose concept predicts results in perfect harmony with the observations - and does so in precisely the kind of situation that the ICRP Task Force and AEC Staff are skeptical! The doubling dose concept may not be perfect, but it must be much closer to the truth than the ICRP Task Force approach.

Lundin and Archer point out that co-carcinogenesis between asbestos exposure and cigarette smoking provide data analogous to their own on co-carcinogenesis between radiation and cigarette smoking. Let us now examine the asbestos studies.

2. The Selikoff-Hammond-Churg Data on Asbestos Carcinogenesis

Selikoff and co-workers recently published extensive data on co-carcinogenesis between asbestos exposure and cigarette smoking in the induction of primary lung cancer and other cancers.(5) We shall restrict our considerations to bronchogenic lung cancer, for which their data are most extensive. There is no doubt that their on-going studies will later provide highly important data for other forms of human cancer, as well as for bronchogenic lung cancer.

Their studies are based upon essentially complete followup of 370 asbestos-insulation workers observed between January 1, 1963 and April 30, 1967. Cigarette smoking histories were obtained by these investigators for the entire group. In the followup period, 24 deaths due to bronchogenic carcinoma occurred in the 370 asbestos workers. The distribution of cases of lung cancer by smoking category is presented below. (From Table 5 of Reference 5)

Table 5 (Reference 5)

Observed and Expected Bronchogenic Carcinoma Deaths by Smoking Habits for 370 Asbestos Workers

Smoking Habits	No. of Subjects	Observed Deaths	Expected Deaths	
Never Smoked Regularly	87	0	0.05	0.18
History of pipe, cigar smoking only		0	0.13	
History of regular cigarette smoking	283	24	2.98	
Total		24	3.16	

Let us now examine these data using the ICRP Task Force doctrine of "additivity", rather than the doubling dose concept. In the non-smokers of cigarettes group no cases were observed. According to ICRP Task Force, the same average exposure to asbestos should lead to 0 excess cases in the cigarette smokers who are exposed to asbestos. But the observed data show $24-2.98 \simeq 21$ excess cases. Now the difference between 0 and 21 is mammoth, indicating the absurdity of the "additivity" principle (no synergism) of ICRP Task Force.

But let us say that we are dealing with small numbers, and hence the observed 0 cases in the non-smokers could truly be 1, or 2, or even 3. We have to start straining our credibility to go beyond 3 and still observe 0 cases. So we will try 3 cases. Now, there are 87 persons who never smoked cigarettes regularly, with an expected lung cancer incidence = 0.18 cases. Having stretched our credibility, we assumed 3 observed instead of 0 which was observed. So the excess, due to asbestos exposure would be 3-0.18 = 2.82 cases in 87 men. If the ICRP Task Force view were correct, asbestos exposure in 283 cigarette smokers should produce $\left(\frac{283}{87}\right)(2.82) = (3.46)(2.82) = 9.75$ excess cancers. But the excess cancers observed = $24-2.98 \simeq 21$ cases. Clearly the ICRP Task Force approach is far wide of the mark, and this is even after we stretched the 0 cases in the non-smokers to 3, to account for the possible effect of small-number statistics.

In contrast, the observations of the asbestos workers are completely in harmony with the doubling dose concept. If 21 excess cancers are observed in the asbestos-exposed cigarette smokers, $\frac{21}{2.98} = 7.05$ doubling doses. Therefore, in the combined non-smokers of cigarettes (including cigar + pipe smokers), we expect $(7.05)(0.18) = 1.26$ cases, due to asbestos exposure. The total expected would be $1.26 + 0.18 = 1.44$ cases. The observed was 0 cases, and these are consistent, for the small numbers. Thus, with 1.44 expected, 0, 1, 2, or 3 occurring would not be at all unusual on a random basis. If anything, the observation of less than the 1.44 expected would indicate the doubling dose concept is conservative in its predictions for the effect of asbestos exposure on cigarette smoking, not radical.

In view of these two major and well-executed studies showing the doubling dose concept in harmony with observation when two sub-populations differing 10-fold in "spontaneous" risk are exposed to a co-carcinogen (radiation in one case, asbestos exposure in the other), and in view of the marked disagreement the ICRP Task Force position leads to, perhaps that Task Force and AEC Staff may wish to reconsider their position, now so very shaky.

3. Are There Any Cases of Co-Carcinogenesis in Humans Where the Doubling Dose Concept (Synergism) Doesn't Apply?

We have just presented data from two beautifully executed studies of co-carcinogenesis, one for radiation and cigarette smoking, the other for asbestos exposure and cigarette smoking. Both are clearly and unequivocally in harmony, at a minimum, with the doubling dose concept and synergism. Both are violently and grossly inconsistent with the additivity principle espoused by the ICRP Task Force. We are at a complete loss to understand how the ICRP Task Force in 1969 flatly "assumes no synergism".(2)

We would gladly admit that, in principle, situations may indeed exist where synergism between co-carcinogens may not operate. To assume in a particular case it doesn't operate is sheer public health irresponsibility, especially where two major studies on humans clearly show it does!

Possibly the ICRP Task Force and the AEC Staff may be thinking about the observations of Jablon concerning stomach cancer in Hiroshima-Nagasaki atom bomb survivors.(6) We shall now consider that study, for it is assuredly a genuine red herring in the entire issue of human radiation carcinogenesis. Jablon examined "cancer of the digestive organs and peritoneum" as a cause of mortality during the 1950-1960 period in Japanese survivors of the atomic bombing. As any student of human radiation carcinogenesis knows, the real peak in incidence of radiation-induced cancers other than leukemia is between 15 and 30 years after exposure, and this peak differs for different cancers and for different dosages. Now, since the atomic bombing occurred in 1945, the data collected by Jablon for stomach cancer are for the period 5 to 15 years post-radiation. Since extremely few of the radiation-induced cancers can be expected at all in the first 10 years post-exposure, we can estimate that the largest part of the period of observation in the Jablon studies is not only irrelevant, it is positively deceiving. For the larger the part of the observation period during which the radiation-induced cancers can not occur, the more the radiation cases are diluted by spontaneous cases, and the more the entire effect is obscured. Assuredly, Jablon and co-workers had not the least intention of obscuring anything. They simply were reporting the data then available. But the real data one needs to see for Hiroshima-Nagasaki must be those where the largest part of the observation period is beyond 1955, and those data are not yet available in published form so far as we know.

In a personal communication to R. Batzel, B. Shore, E. Fleming and one of us (J. W. Gofman), Dr. John Totter reported to this group in 1969 that the stomach cancer data in Japan now clearly show a significant association with radiation. To ascertain whether synergism and the doubling dose concept fit this group (with a higher-than-usual spontaneous stomach cancer incidence), we simply must have the recent data from Japan. So far our efforts to obtain these particular ABCC data have been fruitless. We do hope they will be published soon. In the meantime, any comfort to be obtained either by the ICRP Task Force or AEC Staff should, above all, not rest upon the irrelevant studies of stomach cancer in Japan for the period 1950-1960, since it is so obviously diluted by a large period where radiation-induction wouldn't have been at all appreciable.

CONCLUSIONS

1. The Doubling Dose Concept (a manifestation of synergism) for Radiation-Carcinogenesis in humans has proved sound in a major study by Lundin and Archer where a sub-population of low risk (non-smokers) and a sub-population of high risk (10 times as high) (cigarette smokers) are compared with respect to lung cancer induction by radiation. Furthermore, in a totally separate human co-carcinogenesis study, the doubling dose type of concept of synergism has proved sound where a sub-population of low risk (non-smokers) and a sub-population of high risk (cigarette smokers) are compared with respect to lung cancer induction by asbestos exposure.

The ICRP Task Force additivity approach, namely, a fixed number of cases per rad of radiation, leads to absurd results in the radiation study, and its equivalent approach leads to absurd results in the asbestos exposure study. We suggest the Task Force beat a retreat, or produce some evidence supporting their dismissal of synergism.

The AEC Staff, following the ICRP Task Force, has produced some empty words in saying "the concept of a doubling dose as applied to carcinogenesis by Gofman and Tamplin is reviewed here in detail and found to be without scientific validity".

To use a favorite quotation of ours that the AEC Staff seems to enjoy, "We have produced here hard, incontrovertible data - facts, not opinions".

We invite some facts, some hard, incontrovertible data either from AEC Staff or the ICRP Task Force they quote so freely.

Even if someday a specific case of additivity is demonstrated, the already-existing major cases of synergism provide an enormous bulwark for the public health soundness of the synergism, or doubling dose, concept in any new unknown situation.

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