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A REVIEW OF THE NATURAL RESOURCES DEFENSE COUNCIL PETITION CONCERNING LIMITS FOR INSOLUBLE ALPHA EMITTERS

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J. W. Healy, C. R. Richmond, and E. C. Anderson

The interpretations of the potential effects of insoluble alpha-emitting particles in the lung, as described in the document supporting the Natural Resources Defense Council petition of February 14, 1974, are reviewed in light of present evidence. It is concluded that the theories upon which the proposal is based are not in accord with the evidence and that the theories do not correctly predict the outcome of experiments actually using such particles.

I. INTRODUCTION

On February 14, 1974, the Natural Resources Defense Council (NRDC) submitted a petition to the U. S. Atomic Energy Commission (AEC) and the Environmental Protection Agency (EPA) requesting that they amend their standards as said standards apply to insoluble particles of plutonium and other alpha-emitting "hot particles."[1] (The terminology of "hot particles" is that of the NRDC and refers to particles which contain more than 0.07 pCi of insoluble alpha emitters.) In support of their petition, the NRDC included a report by Drs. Arthur R. Tamplin and Thomas B. Cochran which provides the basis for the proposal.[2]

The question of the possible biological effects from radioactive particles which can irradiate small quantities of tissue to large physical doses has been of interest to the scientific community and radiation protection groups for many years. In several studies involving large extrapolations of available data, an enhanced tumor production from numbers of such particles has been predicted.[3,4] However, the tenuous nature of the evidence and the indirect methods of arriving at the answer have, in general, prevented these predictions from gaining acceptance in the biomedical community, and the standards have continued to be based upon other evidence.

In view of the current interest in this question and the somewhat unusual procedure of submitting the proposal through legal channels rather than through scientific review, it was felt that an examination of the allegations and conclusions would be useful in informing those concerned as to the validity of the bases. This report, therefore, reviews in some detail the basis for the NRDC proposal and briefly indicates the experimental information available on the question.

II. THE CONTENTION

While it is difficult to condense the arguments of an author without running the risk of changing his meaning or emphasis, we will briefly summarize in this section, for the orientation of the reader, our understanding of this contention. However, it is urged that reference be made to the original document[2] to obtain their full viewpoint. It is our impression that the following are the key technical items upon which the petition is based.

1. The responsible standards-setting organizations, the International Commission on Radiological Protection (ICRP) and the National Council on Radiation Protection (NCRP), have given no guidance on the question of localized radiation dose resulting from an alpha-emitting particle.

2. In Tamplin and Cochran's words, the Geesaman hypothesis indicates that "when a critical architectural unit of a tissue (e.g., a hair follicle) is irradiated at a sufficiently high dosage, the chance of it becoming cancerous is approximately 10^{-3} to 10^{-4}." The Geesaman hypothesis was published in 1968 in a Lawrence Radiation Laboratory report[5] (now Lawrence Livermore Laboratory) but was never published in the open literature. In this theory, Geesaman relied upon a theoretical

investigation of the dose distribution around a particle in the lung and estimated sizes above which cell death would result in no cancer. In an addendum,[6] he used data on the induction of tumors in rat skin and the relation of these to atrophied hair follices as a result of radiation. Perhaps his conclusions can best be stated by quoting from the conclusions section of the addendum.[6]

"Summing up, intense radiation exposure of mammalian skin and lung tissue commonly results in cancers. Tissue injury and disturbance are a primary consequence of intense radiation insult, and are observed in association with carcinogenesis. Albert has exhibited a simple proportionality between skin carcinoma and atrophied hair follicles. No general description of precarcinogenic injury exists, but in a crude sense the available observations are compatible with the idea of an injury-mediated carcinogenesis. Cancer is a frequent instability of tissue. Since tissue is more than an aggregate of cells, and has a structural and functional unity of its own, it would not be surprising if some disrupted local integrity, a disturbed ordering, comprises a primary pathway of carcinogenesis. The induction of sarcomas with inert discs of Mylar, cellophane, Teflon, and Millipore is indicative that such a mechanism exists. Presumably mitotic sterilization is an important factor in any carcinogenesis mediated by radiation-induced tissue injury. The functional relation of this factor to the carcinogenic response may be quite different from a linearity in the surviving mitotic fraction.

"While regrettably unquantitative, the hypothesis of an injury-mediated carcinogenesis is suggestively descriptive. If the respiratory zone of the lung contains a structure analogous to the rat hair follicle, and if a radioactive particulate deposited in the respiratory zone has the capacity to disrupt one or more of these structures and create a precancerous lesion, then cancer risks of the order of 10^{-3} and 10^{-4} per particle can be expected for burdens much less than 10^{8} particles."

Again, however, the reader is urged to review the original document to obtain the full argument.

3. In deriving present limits for alpha emitters in the lung, Tamplin and Cochran indicate that no factor was included to account for the non-uniform distribution of radiation in the lung as is done in the ICRP and NCRP formulation of bone dosimetry. It was pointed out that such a distribution factor could be defined by:

$$DF = \frac{\text{number of cancers (non-uniform distribution)}}{\text{number of cancers (uniform distribution)}}$$

"Since direct experimental evidence are not available....,"[2] they chose to attempt a definition of this factor from the Geesaman hypothesis including the quantitative derivation of probability of cancer induction derived from rat skin hair follicles.

4. As regards human data, they discuss the case of a skin lesion from plutonium embedded in the epidermis; a purported case of synovial sarcoma due to contamination during handling of a carboy; the Los Alamos cases which date back to the Manhattan Project and are dismissed as not having received particles of sufficient activity; and a group of exposed Rocky Flats workers which are, again, dismissed on the grounds that the time since exposure has not been long enough for cancer to develop. In the first case, the statement of the pathologist that "their similarity to known precancerous epidermal cytological changes, of course, raised the question of the ultimate fate of such a lesion....."[7] seems to be interpreted as proof that cancer would have developed. In the second case, a series of circumstantial inferences is quoted to "prove" that the cancer was due to plutonium.

5. Since the Geesaman hypothesis,[6] as given in his earlier reports, seems to have no dependence of effect on radiation dose or amount of activity per particle but states that the effect is due to the number of particles, Tamplin and Cochran modify this hypothesis by establishing a critical particle size below which the effect will not be noted (i.e., a threshold?). Their basis is given by the following quotations:[2]

"Not all particles would be expected to result in these high cancer probabilities. As the particle size or specific activity per particle is reduced so is the dosage to the surrounding tissue. Indeed, at sufficiently small particle size or specific activity, one would expect the radiation insult to behave similar to uniform irradiation. The study of Albert on induction of cancer in rat skin indicates a precipitous change in the dose response curve as the dosage exceeds 1,000 rem.[55] ..... This suggests

that a particular level of tissue damage must occur before this unique carcinogenic response occurs. The experiments of Laskin *et al.* indicate a significant carcinogenic response in the lung at 1400 rem, suggesting a comparable sensitivity of lung tissue.[56] Geesaman indicates that the tissue repair time in the lung is of the order of one year.[57] It therefore seems appropriate, but not necessarily conservative, to accept as guidance that this enhanced cancer risk occurs when particles irradiate the surrounding lung tissue at a dose rate of 1000 rem/yr or more. .....using Geesaman's lung model, a particle with an alpha activity between 0.02 pCi and 0.14 pCi is required to give a dose of 1000 rem/yr to irradiated lung tissue. For purposes of establishing a maximum permissible lung particle burden we will use 0.07 pCi from long half-lived (greater than one year) isotopes as the limiting alpha activity to qualify as a hot particle."

Reference 55 in the above quotation is to Albert *et al.*;[8] reference 56 to Laskin *et al.*;[9] and reference 57 to Geesaman.[5]

6. From their definition of a "hot particle," Tamplin and Cochran derived values for occupational exposure by comparing the risk of lung cancer from dose rates of 15 rems/yr to the lung to assumed risks from particles of 1/1000, 1/2000, and 1/10 000 per particle. They then recommended as ".....a somewhat arbitrary compromise and ..... not the most conservative value....."[2] the use of a risk of 1/2000 per hot particle in determining the maximum permissible lung burden for insoluble alpha-emitting radionuclides in hot particles. From this they arrived at a value of 2 particles or 0.14 pCi for a reduction in the maximum permissible lung burden by a factor of 115 000.

For individual members of the public, a value of 0.2 hot particle, while recognizing the disparity in risk occasioned by a fractional number of particles per person, is recommended along with a value of 0.07 hot particle as the average lung burden for members of the public. Limiting values for soil contamination and accidents are also derived by similar considerations.

III. PARTICLES AND RADIATION DOSE

The origin of the NRDC proposal lies in the very non-uniform radiation dose to the tissue surrounding a radioactive particle. For this reason, we will initially provide some description of the nature of this non-uniformity and the application of the concept of radiation dose to biological problems.

A. The Radiation Dose around a Particle

The unique feature of a particulate source of radioactive material (particularly for an alpha emitter because of the short range of the alpha particle) is the rapid change in dose or dose rate as one moves away from the particle and the relatively small amount of tissue exposed to the dose. If one ignores the details of the Bragg curve, the dose in a uniform density tissue at reasonable distances from the particle follows the inverse square law for alpha particles. For the lung, the presence of the alveoli and air passages results in varying degrees of absorption, depending on the actual mass of tissue encountered, so that the inverse square relation is distorted by the varying absorption and the dose pattern may be non-symmetrical. Geesaman[5] has approximated this dose pattern by assuming a cubical lattice representing the air spaces in the human, while Anderson and Dean[10] have used micrographs and computer programs to calculate the pattern for the hamster.

The effect on the calculated dose of varying the volume over which energy deposition is averaged is shown in Fig. 1. (This is not the radial dose distribution, which extends only from the particle surface to the maximum alpha range and for which the

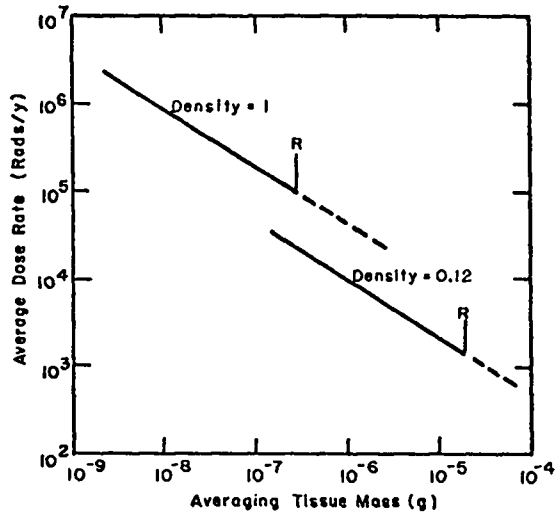

Fig. 1. Calculated dose rate averaged over different distances from a 0.28-pCi particle vs the tissue mass involved in averaging. R represents the range of the particle.

abscissa would be distance.) The calculations are for a particle of 0.28 pCi of ^{239}Pu in tissues of two different densities. It is assumed that the energy loss per unit path length is constant so that the alpha particle deposits energy uniformly along its path. The range in unit density tissue is taken as 40 μm,[11] with the range for other tissues scaled to the tissue density. The doses given are annual doses averaged over the volume of tissue given. The curve indicated as density = 1 is calculated for unit density tissue, and the curve for density = 0.12 is for a uniform tissue having a density of 0.12, corresponding to the average bulk density of Geesaman's lung model at half inflation.[5] No correction was made for the self-absorption in the particle, although this should be negligible for these small PuO_2 particles in comparison to the errors caused by other assumptions. The annual doses are given both in rads which can be converted to rems by the conventionally used quality factor of 10.[12] It must be emphasized that this conversion to rems is particularly uncertain for this case, since there are no data which can be used to assess the relative effects of alpha radiation and the reference radiation in this particular geometry of irradiation.

Figure 1 is intended to indicate the wide variation in dose which can be calculated by different assumptions of averaging volume. Even here we have minimized the dose to individual cells by plotting the average over the volume to the fraction of the range considered. The dose to an individual cell at differing distances varies even more than this average.

We have not considered in this calculation the photon dose from x rays or infrequent gamma rays from either ^{238}Pu or ^{239}Pu, since the focus of the discussion is on alpha-particle effects. It should be noted, however, that these photons are more penetrating and will result in lower doses at distances beyond the range of the alpha particles.

B. Limitations on the Usefulness of Radiation Dose

Calculations such as those given in the preceding section are interesting and have been made by various individuals for many years. The question remains as to their usefulness and meaning in assessing a biological problem.

The primary use of radiation dose, in practice, is as a physical parameter to be used in correlating and extrapolating experimental data on biological effects on an empirical basis. Thus, the present limits for radiation exposure are based upon observations of effects in humans for whom the dose has been estimated. There is no *a priori* basis for assigning an effect to a given dose, since our understanding of the basic mechanisms of radiation carcinogenesis and the influence of cellular interactions is completely inadequate. Thus, radiation doses are meaningful only when related to empirical data on the outcome. As a corollary, the further one extrapolates from the experimental conditions under which the dose-effect relationship is measured, the greater the uncertainty. Thus, predicting the behavior of the effects on individual cells or aggregates of cells in a functioning organ from *in vitro* studies in cell culture is a very wide extrapolation which ignores the very different environment of the cells in the organ and the potential interactions which occur among cells. (Such *in vitro* studies, however, are of great interest for other reasons, such as studies of the mechanisms of damage at the cellular level.) Similarly, extrapolating from the effects of a partial organ irradiation to a full organ (or vice versa) can lead to a misestimate. It is for these reasons that most scientists have refrained from using dose calculations, such as those given earlier, to arrive at conclusions as to the effect of radioactive particles but have preferred to depend upon experimental evidence which bears more directly on the actual conditions.

A further factor of importance in the use of physical dose as a correlating concept is the exact method of expression of dose. That is, if a correlation with effect is established using one method of calculating the dose, it is not valid to apply this correlation if another basis for dose calculation is chosen. As an illustration which, incidentally, seems pertinent to the problem at hand, Vaughan[13] indicates that 90% of the ionization along an alpha particle track formed in unit density tissue is contained in a cylinder of 0.01-μm radius with the axis of the cylinder along the track. For an alpha particle with 5.15-MeV initial energy, the range is about 40 μm. The average dose to this limited volume, therefore, is about 6×10^6 rads, with even higher average doses for smaller radii and at the peak of the Bragg curve. For a 1000-g

organ of unit density tissue, the current occupational limit of 1.5 rads (15 rems) per year, even assuming homogeneous distribution of the alpha tracks, means that about 0.25 mm^3 of tissue is irradiated to doses above 4×10^6 rads, or if a dose of 1000 rads were chosen, a volume of some 1500 mm^3. Since unit density tissue was chosen for this illustration, the results do not compare with those for a particle using the Geesaman model. However, it is clear that even a "homogeneous" distribution of alpha radiation through a body of tissue results in considerable non-uniformity in dose distribution. Further, for the example chosen, one could express the limits as 15 rems to the 1000 g of tissue or as a limitation on the volume of tissue exceeding a given dose. For example, no more than 0.3 mm^3 of tissue shall exceed 4×10^7 rems or no more than 1500 mm^3 shall exceed 10 000 rems. Although the latter methods of expression involve numbers that are frighteningly high in more normal context, all three methods define the same total energy deposition. However, note that it would be highly improper to apply the 15-rems value to the dose along the track just as it would be improper to apply the dose along the track to the dose arising from an assumption of uniform tissue distribution.

A specific point in the Tamplin-Cochran dissertation[2] is the use of the "distribution factor" (DF) in calculating the dose in rems for internal emitters and is supported by the fact that a DF of 5 is used in calculating the dose for bone. They then indicate that a DF should be applied to lung. However, it must be realized that a dose calculation was not used to arrive at the present maximum permissible body burden for plutonium.[14] Instead, a comparison of biological effects (primarily on bone) was made between plutonium and radium. On the basis of these data, it was deduced that plutonium in the body is 2.5 times as harmful as radium on a microcurie basis. Since the maximum permissible body burden for radium had been established from studies of humans as 0.1 μCi, the maximum permissible body burden for plutonium was set at 0.04 μCi.

The dose considerations quoted by Tamplin and Cochran arose in an attempt to use these experiments, and others with strontium, to provide a physical formulation of the results which could be used for extrapolation to other bone-seekers. For the purpose of such calculations, it was *assumed* that radium was uniformly distributed in bone. Further, it was assumed that 90%, or essentially all, of the plutonium in the body was in bone. Since the individual plutonium disintegration liberated about half of the alpha energy of one disintegration of radium with its accompanying daughter products, the foregoing damage ratio of 2.5 on a microcurie basis becomes 5 on an average energy-delivered (dose) basis.

The key to this comparison lies in the assumptions. We know, for example, that radium is *not* uniformly distributed in bone. In fact, if anything, it is more non-uniformly distributed than plutonium. However, the deposition sites are different from those of radium so that the plutonium affects a different, and more sensitive, portion of the bone. One could presumably eliminate the confusion caused by the distribution factor by redefining the critical organ to include only the sensitive portion of the bone and comparing the dose to this region from plutonium and radium. We also note in passing that the more recent examination of the distribution of plutonium in animals indicates that only about 40 to 50% of the plutonium is in the bone. If this were true in the comparison animals (as seems likely), then the actual distribution factor for bone calculations should be 10 rather than 5.

We have introduced this rather lengthy discussion on bone dose calculations to indicate, once again, the difficulty in applying dose calculations and concepts derived for one use to a different problem without full understanding of what was done. In the above case, the salient feature is that radium is non-uniformly deposited so that some sections of the bone receive doses orders of magnitude greater than others.[15] The distribution factor is not intended to indicate greater localized dose from plutonium but, rather, that the distribution in bone is different from that of radium on a gross basis.

C. Previous Guidance

An interesting point in the Tamplin-Cochran document is: "It is important to recognize that the ICRP has given no guidance with respect to non-uniform irradiation of the lung by insoluble alpha-emitters such as insoluble plutonium particles." They then quote one of many statements made by the ICRP[16] and other groups which indicate that there is no clear evidence as to whether the effect of the

non-homogeneous dose is greater or less than that of the homogeneous dose. They interpret this statement as: "In effect, the ICRP is saying that there is no guidance....." A quote from the NCRP follows concerning the significant volume of tissue which concludes: ".....For example, if a single particle of radioactive material fixed in either lung or lymph node might be carcinogenic, the averaging of dose either over the lung or even over one cubic centimeter may have little to do with this case."[12]

While we do not feel that it is useful to quote such bodies at length, there is evidence that the problem has been considered since the early days of the derivation of limits. One of the earlier statements arose from a Tri-Partite Conference in 1949[17] at which scientists from the United Kingdom, Canada, and the United States were arriving at the conclusions which were later applied by many of these same people in the ICRP and NCRP recommendations: "In relation to the possible pathological effects of radioactive particles in the lungs, Dr. Hamilton pointed out that the cells in the immediate neighborhood of a dust particle containing 1 or 2% of plutonium would be subjected to a dose of about 400 r/day. The general opinion which emerged from the discussion was that the carcinogenic effect per unit volume is probably considerably less for the irradiation of small masses of tissue than for large." This conclusion undoubtedly affected the practice of calculating dose as the average dose to an organ at that time and comprises definite guidance on the handling of such problems. However, the matter did not rest there, since several national and international groups continued investigation from that time to the present, with frequent statements as to the lack of definitive information.[16,18-21] However, in spite of the indications of periodic questioning and reviews, there has been no revision in the practices which they recommended of using the average organ dose as a basis for establishing standards.

From the above, it seems clear that the ICRP and the NCRP *did* furnish guidance on the pertinent dose to be used for standards-setting: the use of an average calculated dose to an organ, with full recognition of the non-uniform distribution of dose around the particle. In spite of numerous reviews of the question over the intervening years, they have reiterated this guidance by not changing it. It is difficult to support any claim of no guidance in view of this record on the part of bodies which have traditionally been in the forefront of recognizing potential problems (i.e., genetic effects) and providing generally conservative recommendations.

One recommendation of the NCRP[12] (while perhaps not completely applicable to the particle case as is shown by their example situation quoted earlier) is of interest when combined with Geesaman's estimate of a particle size above which cancer would not be expected due to cell death.[5] The NCRP statement is, "Simplifications in practice hinge largely on reporting a single representative protection dose for a limiting organ system even when the actual irradiation is grossly non-uniform. The representative dose is taken as the highest that can be obtained by averaging over a prescribed significant volume. The implication of this concept ..... is that any redistribution of a given dose within such a volume does not materially alter the radiation response. It is usually assumed that the 'significant volume' should be of the order of one cubic centimeter. This will be grossly conservative under most circumstances, and in special situations use of a larger volume is justified." It is not clear why the NCRP recommended a significant volume rather than a significant mass, since this results in averaging over a smaller mass in the lung than in other tissues due to the density difference.

However, if we calculate the dose over 1 cm^3 of lung tissue with an average density of 0.12 g/cm^3 for the "hot particle" of 0.07 pCi derived by Tamplin and Cochran,[2] we obtain a dose of only 0.055 rad or 0.55 rem per year. Thus, one would require an activity of 1.9 pCi to reach the limit of 15 rems per year for this single cubic centimeter of tissue (or an activity of 15 pCi for a single cubic centimeter of unit density tissue). Geesaman[5] quotes an activity for a 1-μm-diameter particle of ^{238}Pu as 60 pCi and arrives at a conclusion that ".....unless the source size, s, is smaller than or of the order of 0.25 μ the yearly flux will be lethal for all epithelial populations in the exposed volume. The source size condition will only be slightly less stringent for endothelial populations $s < 0.35$ μ." The implication of the above is that no cancer will

develop for particles larger than those described since the cells are killed. According to the constants used by Geesaman, a 0.25-μm particle would have an activity of about 2.5 pCi, which compares with the 2 pCi to give 15 rems to one cubic centimeter of tissue. Thus, if Tamplin and Cochran had chosen to use this available NCRP guidance along with the Geesaman study, their conclusions would have been considerably different.

IV. THE GEESAMAN HYPOTHESIS

The Geesaman hypothesis was published as a Lawrence Radiation Laboratory (now Lawrence Livermore Laboratory) report in February 1968,[5] with an addendum in October 1968[6] containing the quantitative estimates of cancer production. This work has never been published in the open scientific literature but remains an unreviewed and unrefereed study.

Since his conclusions seem to be based primarily upon the studies of follicular cancer produced in rat skin, we quote below those sections of the report in which he uses these data with his references and footnotes deleted.

"Albert's study of radiation-induced carcinoma in rat skin gives some quantitative description of a high-dose carcinogenic situation. Since such descriptions are rare, and since Albert's results have implications to risk analysis in general, his experiment is outlined here.

"A skin area of 24 cm^2 was exposed to electron radiation with various depths of maximum penetration. ..... In all cases the response scale at sufficiently high doses was large, ~1 to 5 tumors per rat at 80 weeks after exposure. It was noted by Albert that when the dose was normalized to a skin depth of 0.27 mm, the three response curves became continuous. Since this depth is near the base of the hair follicle which comprises the deepest reservoir of epithelial cells of the germinal layer, it was suggestive that this might be a critical region in the observed carcinogenesis. The suggestion gained significance from the observation that most of the tumors are similar to hair follicles, and that in the nonulcerogenic dose range the number of tumors per rat was in nearly constant ratio (1/2000 to 1/4000) with the number of atrophied hair follicles..... Thus the carcinogenesis in this experiment was remarkably correlated with the dose to and the specific damage of a particular skin structure. When exposures were made with stripe and sieve patterns of roughly 1-mm scale, geometrical effects were observed; most notably the cancer induction in the sieve geometry was suppressed at doses of 1700 R, but not at doses of 2300 R. The reduction, however, was again consistent with the reduction in damage as characterized by atrophied hair follicles.

"For perspective it is valuable to relate these observations to cellular descriptions. Carcinogenesis in Albert's experiment is maximum in the neighborhood of 2000 R. It is well documented *in vitro* and to a lesser extent *in vivo* that the fraction of mitotically competent cells as measured by clonal formation decreases in a nearly exponential fashion with the dose. From these results a surviving mitotic fraction of approximately 10^{-5} would be expected in a population of germinal epithelial cells exposed to 2000 R. Even in this pre-ulcerative dose regime the cell population suffers severe mitotic injury. It is significant that Albert's dose response curves show no simple relationship with the surviving fraction of mitotically competent epithelial cells. There is certainly no exponential decrease of the response in the neighborhood of D_{37}, and, in fact, the tumorigenesis is maximum in a dose region where the population of mitotically competent cells should be initially depleted by about 5 orders of magnitude.

"To summarize this important experiment, a high incidence of cancer was observed after intense local doses of radiation, and the carcinogenesis was proportional to the damage or disordering of a particular skin structure."

The reasoning leading from this information, plus a discussion of other experiments with high doses and particle sources leading to the conclusion (quoted earlier) of a cancer risk of 10^{-3} to 10^{-4} per particle, is not given but is presumed to result from the correlation with atrophied hair follicles from Albert's experiments.

There is a similarity between this work and the theory propounded by Virchow in 1863 that the cause of cancer is chronic tissue damage.* This

*We are indebted to Dr. Roy E. Albert, New York University, for this line of reasoning.

theory was disproved by experiments which showed that cancer can be produced by very potent substances that vary widely in their capacity to cause cancer, whereas many agents which cause damage do not cause cancer. Thus, while there is a frequent association between tissue damage and cancer, there are types of cancer and types of damage for which no association exists.

There are several aspects of the data from the skin experiments used by Geesaman, as well as information published later from the same series of experiments, which should force some modification of the proposal but are not included in the Tamplin-Cochran document. These and their implications for the Geesaman hypothesis are reviewed below.

A. Type of Tumor

In a 1961 paper, Albert *et al.* first explored the tumors resulting from irradiation of rat skin with ^{91}Y beta rays.[22] Two strains of rats were used with the tumor types and frequencies as given in Table I. They indicate the Holtzman strain to be similar to the Sprague-Dawley strain, but the animals were considerably older (~ 40 weeks compared to ~ 20 weeks for the Sprague-Dawley).

A variety of tumor types were obtained. In Fig. 2, we have plotted the dose-incidence curve

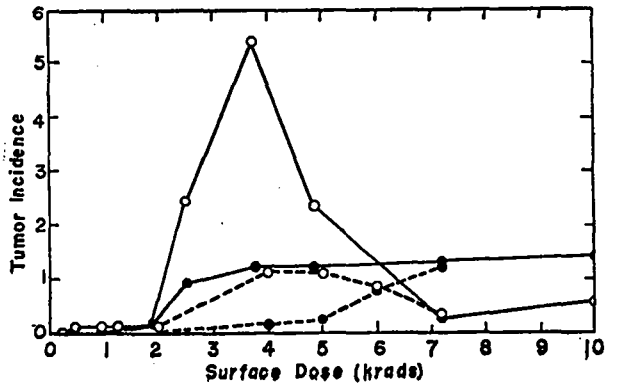

Fig. 2. Tumor incidence per animal vs surface dose of electrons: (——) Sprague-Dawley strain; (---) Holtzman strain; (-O-) adnexal tumors; and (-●-) other tumors.

for both strains for the predominant tumor type (follicle and sebaceous or "adnexal") and the sum of all other types. The incidences were corrected for the unidentified tumors by assuming these to arise in the same proportion as the identified ones. It is of interest to note the wide disparity between the response curves of the adnexal tumors and those of other types, as well as the disparity between the curves for the two strains (whether due to strain or age is not determined). Since the remainder of the experiments focused upon the adnexal tumors, with

TABLE I

TUMOR TYPES AND FREQUENCIES FROM IRRADIATION OF RAT SKIN

	Dose (rads)									
Sprague-Dawley Strain	10 000	7200	4870	3750	2500	1900	1225	950	470	230
Initial number of rats	12	12	13	14	15	10	15	23	25	24
Epidermoid carcinoma	9	11	6	5	5	1	0	0	0	0
Adnexal tumor	5	2	26	62	23	3	1	3	3	1
Connective tissue tumor	2	1	0	1	1	1	1	0	1	0
Squamous papilloma	0	0	6	6	3	0	0	0	0	0
Cysts	0	0	1	2	0	0	0	2	1	1
No pathologic examination	8	5	8	17	19	0	2	0	0	0
Total	24	19	47	93	51	5	4	5	5	2

Holtzman Strain	7200	6000	5000	4000	2000	1000	500
Initial number of rats	9	10	8	11	16	20	50
Epidermoid carcinoma	7	6	1	2	0	0	0
Adnexal tumor	2	7	6	11	2	0	1
Connective tissue tumor	0	0	0	0	0	0	1
Squamous papilloma	2	0	0	0	0	0	0
Cysts	0	0	0	0	0	0	0
No pathologic examination	3	4	3	3	0	0	1
Total	14	17	10	16	2	0	3

data on other types discarded, the information is aimed at a very specific tumor type even for the organ considered: rat skin.

B. Volume of Irradiated Tissue

As was discussed earlier, the extrapolation from one condition of irradiation or method of expressing dose to another must be done with great caution and a full understanding of the parameters involved. How, then, do the conditions of the rat skin experiments compare with those of the particle irradiation?

The particle doses typically involve tissue quantities of tens of micrograms (see Fig. 1). In the rat skin experiments, areas ranging from about 5 to 30 cm^2 were used with depths from about 0.4 to about 1.5 mm. Thus, the tissue volumes ranged from about 0.2 to about 5 cm^3 or, for unit density tissue, 0.2 to 5 g.[8,23-25] This is an extrapolation in tissue volume on the order of 10^3 to 10^5.

There are several observations in the rat skin experiments which are pertinent to the validity of extrapolation. In one series of irradiations, exposures were made through two grids which provided 1-mm-wide bars of irradiation area with one grid masking all except a third of the area and the other all except a sixth of the area.[23] In addition, a mask (sieve) with circular holes which permitted an exposed area of a third of the uniform area was used. From these data, it was noted that the response with the smaller areas was lower even though the total dose to the area (expressed in gram-rads) was in the vicinity of the uniform dose required to produce the maximum incidence of adnexal tumors. In other words, the delivery of a specific amount of energy to a given overall area of skin resulted in fewer tumors when the energy was delivered at higher doses but to smaller subareas. Geesaman correctly points out that this suppression occurred at 1700 rads but not at 2300 rads.[6] However, the 2300-rads value for the uniform irradiation is well past the dose of maximum tumor induction, and there has been a significant drop in the incidence for this condition. Therefore, it is difficult to attribute this effect to other than the oversaturation of the response. Albert *et al.* conclude from this work: "The experiments reported here indicate that, in a limited dose range, the non-uniform radiation pattern has the effect of reducing both chronic hair follicle damage and tumor formation."[23]

In the studies of the association between hair follicle damage and tumor formation, Albert *et al.* noted that the damage to the hair follicles across the irradiated area was not uniform, with the major damage occurring at the center of the area and considerably lower damage at the edges.[24] From other data, it appears that the dose across the area was reasonably uniform and that the effect was due to something other than non-uniform dose. From this and the preceding work, Albert *et al.*[24] conclude: "Two observations indicate the importance of the size of the irradiated area on the magnitude of hair damage: (1) the follicles along the margin of the irradiated area are relatively uninjured compared to the follicles in the center of the irradiated area..... (2) there is a suppression of follicle damage when the irradiation is delivered in a sieve pattern..... These observations strongly suggest that the pathogenic mechanisms for the development of both irreparable hair follicle damage and skin tumors depend upon both the dose and the *amount of skin irradiated*" (emphasis added).

Thus, the data and conclusions in the papers used by Geesaman to justify his work (and quoted by Tamplin and Cochran[2] as "biological evidence" supporting their contentions) strongly suggest that extrapolations to smaller tissue volumes may not be legitimate.

C. Species Dependence

We have alluded earlier to the difference in response curves for skin tumor formation occasioned by either the strain difference or the age of the rats used. In a paper subsequent to the Geesaman proposal, Albert *et al.*[25] repeated some of their studies using mice as the experimental animal, since it had been noted that the response of mouse skin is different, with relatively few tumors and most tumors being epidermoid carcinomas rather than adnexal tumors.

The results of this experiment confirmed the previous findings that adnexal tumors, noted as the most probable outcome in rats, were rare in mice and that the total number of tumors produced in mice was only 15 to 20% of those in rats for comparable conditions. The lack of adnexal tumors was attributed to the fact that the hair follicles in the mouse are more radiosensitive than those in the rat. As a result, little follicle atrophy is noted in the

mouse -- either the follicles remain intact or they are destroyed.

The results of this experiment indicate clearly the difficulties of applying results from one organ to another. Even though skin was the target in both cases, the differences in structure between rat skin and mouse skin caused a completely different outcome upon irradiation. The outcome upon comparison to a different organ such as the lung, where follicle structures or functions do not even exist, would seem to make the final conclusion by Geesaman one of sheer speculation.

D. Volume of Follicle Irradiated

In the original studies of rat skin response, Albert *et al.* used electron beams which had an approximate linear decrease in dose with depth.[8,22-24] The relation between dose at the tip of the hair follicle, lying at a depth of about 3 mm, was established by noting that the tumor incidence curves for electrons of various penetrations coincided when the dose was expressed as the dose at a depth of 0.3 mm.[8] However, it can be noted that the entire follicle was irradiated to this dose or greater.

To test the dependence of the effect of doses to various portions of the follicle, Heimbach *et al.* used the Bragg peak of alpha radiation produced by a cyclotron.[26] The energy of a 37-MeV alpha beam was adjusted by the use of aluminum absorbers in the experiments so that the Bragg peak fell at depths of 0.12, 0.35, and 0.55 mm. Since the Bragg peak can produce dose rates up to 5 times that along the early portion of the track, this enabled investigation of doses delivered to various parts of the follicle. The results indicated that the response curves coincided when the dose was expressed as minimum dose to any point along the hair follicle. The tumor types were identical with those found with electrons, and there was once again a correlation between tumors and atrophied hair follicles, with the ratio between tumors and atrophied hair follicles of about 1/9000.

From this experiment, the authors concluded that the entire hair follicle must be irradiated to produce tumors. The minimum penetration alpha radiation used did not irradiate the lowest part of the follicle and did not induce tumors. The authors then suggested: "The findings reported here can be explained on the basis that the hair follicle is reparable from cells originating at any point along its length, and that the capacity for such repair is inversely related to the degree of damage sustained by the part of the follicle minimally damaged. The existence of a 'critical depth' in skin of about 0.3 mm which was demonstrated with electron radiation ..... can be explained on the basis that the follicle tips, which received the minimum dose to the follicles, were the most protected part of the skin epithelium and, therefore, contained the critical reservoir of cells for replacing the more superficial and more heavily irradiated cells."[26]

Since the hair follicle is a few tenths millimeters long (several hundred μm) and the range of an alpha particle is about 50 μm, these results strongly suggest that a single alpha-emitting particle, even if it could be placed in rat skin, would not produce tumors. Thus, in the statement of the Geesaman hypothesis, "If the respiratory zone of the lung contains a structure analogous to the rat hair follicle, and if a radioactive particle deposited in the respiratory zone has the capacity to disrupt one or more of these structures....., then cancer risks of the order of 10^{-3} to 10^{-4} per particle can be expected."[6] The second conditional clause does not follow unless the first is modified to further redefine the hypothetical structure to a size where it will be fully irradiated by the particle (i.e., less than $\sim$100 μm). A further necessary condition is that such structures be located throughout the lung with such a frequency that the particle will irradiate one with a probability approaching unity. This appears to be stretching an already tenuous theory beyond the realm of credibility.

V. THE TAMPLIN-COCHRAN APPLICATION

In the Tamplin-Cochran interpretation of the Geesaman work,[2] they introduce the concept of a "critical architectural unit" in the following passage: "Now what are these experiments trying to tell us? Certainly a reasonable interpretation of these experimental results is: when a critical architectural unit of a tissue (e.g., a hair follicle) is irradiated at a sufficiently high dosage, the chance of it becoming cancerous is approximately 10^{-3} to 10^{-4}. This has become known as the 'Geesaman hypothesis'."

There are significant differences, however, in the statement by Geesaman and that quoted above. Geesaman states his theory as conditional: i.e., "If the respiratory zone ..... contains a structure analogous to the rat hair follicle....."[6] Thus, in the Tamplin-Cochran version there is a progression from "if" to "when," with no evidence or attempt to indicate what this critical architectural unit may be. Further, they imply that *any* hair follicle will be a "critical architectural unit," while Geesaman carefully refers to structures ".....analogous to the rat hair follicle."[6] We have seen earlier that mouse skin hair follicles do not fit the Geesaman description, since they are not analogous in their response.

The second part of Geesaman's conditional statement indicates that ".....if a radioactive particulate deposited in the respiratory zone has the capacity to disrupt one or more of these structures and create a precancerous lesion....."[6] has been changed to indicate that when the structure is ".....irradiated at a sufficiently high dosage, the chance of it becoming cancerous is approximately 10^{-3} to 10^{-4}."[2] Thus, the hypothetical statement of the possibility of disruption and cancer formation has become, in translation, a statement of fact.

It is of interest that Tamplin and Cochran use the same probability of cancer formation for particles deposited in the lung that Geesaman states for the condition that the particle actually irradiates the hypothetical structure. We can deduce from this something of the character of this supposed structure. From Table III of the Tamplin-Cochran report, the mass of tissue irradiated to 1000 rems per year around a 0.07-pCi particle is 65 μg with the lung at half-inflation. Geesaman, for this condition and his cubical lattice lung model, estimates the range of an alpha particle to be between 335 and 1000 μm, depending upon the path through the lattice.[5] The experiments with alpha particles and rat hair follicles indicate that the full "analogous structure" must be irradiated,[26] which can only occur if the 65 μg of tissue surrounds the particle. Thus, we can conclude that the structure has a mass of 65 μg or less, since the probability of the particle lodging at the center would seem to be low. From the Tamplin-Cochran assumption that the probability of cancer for a particle lodged in the deep respiratory zone is the same as Geesaman's probability assuming the structure to be irradiated and damaged, it is apparent that the number and spacings of the structures must be assumed to be such that *each* particle will irradiate one. (Otherwise, the probability of the particle lodging close enough to irradiate the structure must be included in their estimates.) In a 1000-g lung, there must be greater than 10^7 such structures, each of which weighs less than 65 μg. It appears from this type of estimate that the "critical architectural unit" is any group of cells rather than an identified structure, as is implied by the comparison with the hair follicle.

The second change in interpretation introduced by Tamplin and Cochran is the minimum activity of a particle to produce cancer. This could logically follow from Geesaman's second conditional statement concerning the ability of the radiation to disrupt one or more of the structures.[6] However, the consequences of introducing such a threshold on the radiation response when the entire lung is irradiated are of interest. If one irradiates the full lung, obviously *all* of the hypothetical structures will be irradiated. If one assumes the disruption of these structures to be the sole cause of radiation-induced cancer and there were more than 1000 to 10 000 such sites in the lung, then the incidence would remain at zero until the threshold dose (1000 rems) was reached. The incidence would then increase rapidly above this to 100% or greater. If there are fewer than this number of sites (with a probability of 10^{-3} to 10^{-4} of producing cancer per site when irradiated), then obviously the probability of a particle irradiating the site must be included. There may be causes of radiation-induced cancer other than the mechanism of tissue disruption. These could result in a gradual increase in incidence below the threshold, but the response from the architectural unit mechanism postulated would still increase to 100% when the threshold is exceeded. This pattern does not conform to any known data on cancer incidence dose-effect relations for full lung irradiation.

It is of interest that the Tamplin-Cochran interpretations of the theory receive only minimal, if any, justifications. For example, there is no

attempt to identify the structure in the lung responsible for the effect, nor is it explained how one can extrapolate from the effects on a hair follicle to the effects in a lung which contains no unit even similar in function or structure to the hair follicle and sebaceous gland of the rat skin. Data on these tumors and their incidence, which have appeared since the original Geesaman postulation and which throw considerable light on the hypothesis, have been ignored. It can only be concluded that a more thorough and comprehensive study could have changed the conclusions of the document.

VI. THE HUMAN DATA

People have been exposed to plutonium during various uses of the material over the past 30 years. Tamplin and Cochran have chosen a few of these experiences, some to discount on the basis of their threshold theory and others to support their contention. Although we profess no special knowledge in the field of medicine, we will analyze their contentions on the basis of biological and health physics experience.

A. The Lushbaugh Report

In 1962, Lushbaugh and Langham reported on a lesion associated with plutonium in a wound.[7] The patient, while machining plutonium metal, received a wound which was later excised. Some 4 years after the accident, he noticed a nodule which, upon measurement, still contained some 0.08 μg of plutonium (~5000 pCi). Lushbaugh reported on the histological examination of the lesion, and the quotation appearing in the Tamplin-Cochran report arose from this paper: "The autoradiographs showed precise confinement of alpha tracks to the area of maximum damage and their penetration into the basal areas of the epidermis, where epithelial changes typical of ionizing radiation exposure were present. The cause and effect relationship of these findings, therefore, seemed obvious. Although the lesion was minute, the changes in it were severe. Their *similarity* to *known pre-cancerous epidermal cytologic changes*, of course, raised the question of the ultimate fate of such a lesion should it be allowed to exist without surgical intervention" (emphasis added). Following this quotation, Tamplin and Cochran indicated that ".....less than 0.1 μg of Pu-239 produced pre-cancerous changes in human tissue." They refer several sentences later to "this pre-cancerous lesion....." and state that this proves that a single ^{239}Pu particle ".....irradiates a significant (critical) volume of tissue and is capable of producing cancer." In other words, they manage, in the space of a few sentences, to move from ".....similarity to known pre-cancerous epidermal cytologic changes....." and expressed uncertainty on the part of the pathologist on the eventual outcome to a conclusion that cancer will result. We believe that the uncertainty expressed by the expert should be given proper weight in the conclusion.

In point of fact, examination of the autoradiograph in the Lushbaugh paper indicates very clearly that the lesion contained a number of small particles, since several points of origin of alpha particle "stars" can be discerned. Further, the author indicates the lesion containing the plutonium had a volume of 27×10^{-5} cm^3 or, for unit density tissue, a mass of some 27 μg. Reference to Fig. 1 would indicate that a single particle would deliver an alpha dose to only about 0.3 μg in unit density tissue.

In a subsequent paper, Lushbaugh *et al.* describe the result of the study of 8 such lesions resulting from plutonium in wounds in which the plutonium had resided for periods of time ranging from 0.5 to 8 years.[27] They indicate, "The lesions were found to vary morphologically in an orderly manner related roughly to the length of time the plutonium had been present. All were confined to the dermis. The size of the nodule depended on the dispersion of the particles present rather than the duration of the lesion. The largest nodule was about 2 mm in greatest dimension." They conclude in the discussion, "Although this study is based on too few small lesions to evoke much confidence in these retrospective interpretations, the conclusions may be warranted that metallic plutonium implanted in the skin in minute amounts elicits a foreign-body reaction of granulomatous type, which after subsiding in cellular activity becomes fibromatous." No reference is made in this paper to cancerous or similarity to pre-cancerous lesions.

These lesions are the most severe changes which have been reported in humans as a result of plutonium and, as such, require the question of wound

contamination to be taken seriously in radiation protection programs. However, to extrapolate these to cancers, in view of the uncertainty on outcome expressed by the pathologist, and especially to extrapolate to lung cancer seems to be an unjustifiable step.

B. The Gleason Case

The information available to the authors on the Gleason case is primarily that presented by Dr. Arthur R. Tamplin in the appendix of the Tamplin-Cochran document.[2] This involves the case of an individual who handled a crate containing a leaking carboy of ^{239}Pu solution and later developed a synovial sarcoma of the left hand.

In the initial analysis of this case, Tamplin indicates that the occurrence of this type of cancer is less than the total skin cancer death rate, since the prognosis for this type of cancer is poor. He concludes, "Thus it is highly unlikely that anyone who handled this crate would spontaneously develop this sarcoma on the contaminated hand....." This, of course, is not the question of interest, since the *a priori* condition that cancer did develop is given and the question is now whether there is evidence that indicates whether the plutonium was involved. Tamplin introduces evidence from animals that injection of 1 μg of ^{239}Pu into the skin of rats produced fibrosarcomas in 5% of the animals.[28] The relevance of this information appears remote, since these tumors were of a different type and arose from different tissues than the synovial sarcoma. (This is similar to the extrapolation from follicular tumors in the rat skin to lung tumors in the humans.) We know of no evidence, nor do Tamplin and Cochran produce any, that this type of tumor has been produced by radiation. However, in view of the ubiquitous nature of radiation as a carcinogenic agent, it would appear as a definite possibility providing that the proper critical tissue is irradiated (presumably the synovial membrane or the synoid capsule). It would appear that this would require something other than an injection into the dermis. Thus, the question to be examined is whether there is a reasonable probability that plutonium could have penetrated to the critical tissue under the conditions of the purported exposure.

Early in the discussion, Tamplin states: "There is little reason to doubt that this small amount of liquid (0.01 milliliter) or even more *found its way* below the surface of Mr. Gleason's palm" (emphasis added). It is our experience that plutonium does not "find" its way through skin, even though there is water exchange across the skin. The skin has been shown to be an excellent barrier to prevent the passage of many materials,[29] including plutonium.[30] Thus, some mechanism such as a break in the skin (wound) must be postulated and of such a depth and location that the critical tissue is involved.

The incident occurred on January 8, 1963. According to the Tamplin account, a survey was conducted on Mr. Gleason's home, clothing, and automobile on January 19, 1963. The results apparently were negative, or they would have been mentioned. It is indicated earlier when referring to Mr. Gleason's handling of the crate: "This could not have occurred without contaminating the palmar surface of his left hand, which was bare." It is difficult to see why the contamination should preferentially go to the *left* hand. Other portions of the body and the shoes presumably would also be susceptible. However, if a sufficient quantity to deposit 0.1 μCi (0.01 ml of a 160-μg/ml solution) were on the left hand, experience has indicated that such contamination transfers rapidly to other objects, including clothing and items handled such as tools or even the automobile steering wheel. The fact that these surveys, even 11 days later, did not detect significant contamination would indicate that not much was initially present.

Tamplin further indicates that urine samples collected subsequent to January 20 gave negative results and, "The only thing that this demonstrates is that no detectable level of Pu-239 was found." Later he indicates that negative findings in the feces and urine were obtained in April 1970 and, again, dismisses the results on the grounds that little is absorbed into the body. The latter conclusion is, of course, dependent upon the type of material used. As an illustration of a worst case, Johnson *et al.* injected plutonium oxide particles with a count mean diameter of 7 μm subcutaneously into dogs.[31] They found that the translocation to

the body occurred rapidly, with on the order of 0.25% of the plutonium recovered from other tissues. Assuming this very low translocation of PuO_2 to apply to the nitrate and using Langham's equations[32] for the excretion, we find that, for the 0.1 μCi postulated by Tamplin, urine samples should have indicated on the order of 0.2 disintegration per minute in the period around January 20. This level is easily detectable by adequate analysis. Of greater applicability to the soluble nitrate case is a wound described by Schofield *et al.*[33] Here the material was plutonium oxalate, and they estimated that, without treatment, about 0.1% of the material in the wound would have been excreted in the 10- to 20-day period and 0.08% in the 20- to 30-day period. For a postulated wound burden of 0.1 μCi of this soluble material, one would expect, therefore, on the order of 20 disintegrations per minute per day excretion in the urine or some 200 to 1000 times the detectable level for most analyses. The later analyses are also significant in that they indicate the lack of a source of relatively insoluble material continually leaching into the blood.

The physical examination by Dr. Roy Albert seems to be significant in several respects. While the details are not given, there is no mention of a wound or other break in the skin through which plutonium could enter. Further, the solution was undoubtedly very acidic to retain the plutonium in solution. Such shipments are usually made in nitric acid. There is no indication given that the medical examination showed any signs of acid reaction with the skin. (Nitric acid can produce a yellow discoloration even when no overt burn occurs.) In a later conclusion, Tamplin indicates that the deposition ".....may have occurred through a small cut or via a sliver." One can only speculate on the size of cut required to introduce the plutonium in a position to irradiate the critical tissue, but it is important to note that the medical examination, which presumably included questioning of Mr. Gleason, did not reveal any indication of such a wound or sliver. (Tamplin presumably is referring to a contaminated sliver of material other than that of the carboy, since there is no indication that it was broken.)

From the above evidence, we can only conclude that the association between cancer and plutonium is speculation. The subject did handle the carboy, but subsequent examinations showed no contamination, and urine and medical history provided no indication of plutonium deposition.

C. The Los Alamos Cases

In referring to the exposures of 25 individuals exposed to plutonium some 30 years ago during the Manhattan Project,[34] Tamplin and Cochran indicated that the exposures were to insoluble plutonium and, hence, of interest. However, they discount this experience on the grounds that 14 of the 25 subjects worked in plutonium recovery operations and were exposed to droplets of plutonyl nitrate: "A droplet 1 u in diameter ($0.5\ u^3$) would therefore contain only 6×10^{-4} pCi compared with a 0.07 pCi particle of PuO_2." However, no justification is given for the assumed drop size, which appears to be very small based on attempts to produce particles by evaporating droplets from a nebulizer. For comparison, fog has a particle size of 5 to 50 μm and mists of 50 to 100 μm. If we assume the particles to be the size of fog particles, then the plutonium content would range from 0.16 to 160 pCi* -- well within the range of the definition of the "hot particle."

A summary of particle size measurements for various operations using plutonium is given in Table II.[35,36]

The aerosol from the Rocky Flats fire was generated by high-temperature condensation of PuO_2 in a manner perhaps not unlike fume formation in the wartime reduction processes. In addition, it is similar to those aerosols measured at the Los Alamos Scientific Laboratory in connection with the operations of fluorination and reduction. The lathe operation is not typical of the wartime operations, and the resuspension aerosol from cleanup is quite different from the others, although this distribution undoubtedly occurred during the wartime exposure. As a best estimate of the aerosol involved in the Los Alamos exposures, we have considered the 0.32-μm mass median diameter (MMD) with a σ_g of 1.83 μm, along with the estimates of deposition in these individuals.

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*For a 1-μm-diameter droplet containing 40 g/liter of ^{239}Pu with a specific activity of 0.0614 Ci/g but still assuming unit density for the solution, we obtain 1.3×10^{-3} pCi.

TABLE II

PARTICLE SIZE MEASUREMENTS FOR PLUTONIUM OPERATIONS

Source	Mass Median Diameter (μm)	Geometrical Standard Deviation, σ_g (μm)	Mass Fraction as "Hot Particles"[a]
Rocky Flats Fire	0.32	1.83	0.15
Fluorination of Nitrate	0.45	1.55	0.23
Reduction to Metal	0.32	1.62	0.10
Lathe Operation	0.26	1.44	0.01
Cleanup	1.90	1.80	0.97

[a]Diameter greater than 0.6 μm.

TABLE III

ESTIMATED "HOT PARTICLE" BURDENS OF LOS ALAMOS WORKERS

Diameter (μm)	Incremental Mass Fraction	Activity (pCi/particle)	Activity (nCi/man)	Particles (per man)
0.6 - 0.7	0.05	0.09	20.0	2.22×10^5
0.7 - 0.8	0.033	0.14	13.2	9.4×10^4
0.8 - 0.9	0.022	0.20	8.8	4.3×10^4
0.9 - 1.0	0.015	0.28	5.9	2.2×10^4
1.0 - 1.2	0.015	0.44	5.9	1.4×10^4
1.2 - 1.4	0.007	0.72	2.8	3.9×10^3
1.4 - 1.8	0.0057	1.34	2.3	1.7×10^3
			Total	4.0×10^5

The number of "hot particles" from an aerosol of this distribution was calculated by numerical integration in given particle size ranges above 0.6 μm. It was further considered that the total of 2.5 μCi of plutonium in these 25 men was 10 μCi at the time of exposure to allow for subsequent elimination. On this basis, the total number of particles in various size ranges is given in Table III.

The process of pulmonary deposition would not significantly distort the deposition in this range since, for more than 90% of the mass range represented, the pulmonary deposition fraction varies only in the ranges of 0.2 to 0.32. Thus, if the lung cancer per particle estimate of 10^{-3} to 10^{-4} given by Geesaman[6] were valid, we would expect some 1000 to 10 000 lung cancers in this group. Exposure has been for 30 years, so that a significant portion of the lifetime has passed with no cancers developing.

In a recent study, McInroy *et al.*[37] measured the distribution of plutonium particle size in a lymph node of a deceased worker by the autoradiographic technique. Although this individual was exposed at a later time than those discussed above, it is of interest that these estimates also indicated that 15% of the plutonium was in particles larger than 0.07 pCi.

D. The Rocky Flats Workers

Tamplin and Cochran discuss the 25 individuals exposed to plutonium during a fire in 1965.[35] They compare the lung burdens in these individuals with the lung burdens in the beagles which developed lung cancer by noting, ".....it is significant to note that in the experiments reported by Park *et al.*, the beagle dog with the smallest lung burden, i.e., 0.2 μCi, developed lung cancer. The highest burden in Table V is comparable to the lowest beagle exposure; the lowest exposure ....., the 19 cases with lung burdens in the 0.24 uCi range, are only an

order of magnitude less than the lowest beagle exposure." The fact that they are, in this case, using microcuries rather than numbers of particles leads to the conclusion that they are referring to radiation dose to the lung, yet they neglect to point out the difference in size between the beagle lung and the human lung -- a factor which would make the human dose about an order of magnitude lower than that of the dog with a comparable burden.

It is of passing interest that the lack of cancer in these Rocky Flats workers is dismissed on the grounds that only 9 years have passed, which is not adequate to produce cancer. We concur in this statement but note that Tamplin argues strongly for the production of a synovial sarcoma, in spite of the lack of evidence of exposure, in a matter of a few years after the incident. (Times are not given in his report, but the accident occurred in 1963 and the report of Dr. Wald, referred to by Tamplin and Cochran, was submitted in 1973, indicating that the cancer was well developed by this time.)

VII. EVIDENCE ON PARTICLE DOSE EFFECTS

As was indicated in an earlier section, those groups charged with providing safe limits for radiation exposure have consistently utilized the average dose to an organ as a basis for the limiting quantity of radioactive material. That is, the dose is calculated as though the energy were uniformly distributed through the organ. In the earliest of these recommendations, the opinion was undoubtedly based upon meager direct evidence plus the knowledge of radiation biology of those involved, and cautions as to the uncertainty of the procedure were appropriate (and still are, since full and complete data will require some years to accumulate). However, as evidence has accumulated, such cautions refer to a much narrower range of uncertainty. It is the purpose of this section of the report to summarize briefly some of the more pertinent information which can be used in assessing the question of particle dose but is not included in the Tamplin-Cochran document.

Two reviews on the question of particle dose have appeared in the past year.[38,39] The first[38] focused on the general question of whether the non-uniform dose distribution in an organ is more or less hazardous than the uniform distribution (i.e., in Tamplin-Cochran's appraisal, is the distribution factor appropriate to the particulate situation greater or less than one?). The conclusion, from the evidence available at that time was ".....that the preponderance of the evidence indicates that the use of an average lung dose is appropriate in limiting exposures and may well be conservative." The second review was a more complete examination of all of the information available on plutonium and other isotopes in the lung, with emphasis on the particle question. The conclusion of this review was similar to that of the first. We will not, here, pursue again all of the evidence but will provide a brief description of some of the pertinent results. While these experiments are selected because of the way in which they illustrate the results, we would also note that neither of the reviews found evidence which indicated the particle dose to be more harmful than the uniform dose.

Little *et al.*[40,41] administered ^{210}Po (an alpha emitter) intratracheally to hamsters both with and without iron oxide. The administration with iron produced agglomerations (effectively particles) of the ^{210}Po on the iron oxide particles, while the administration without iron produced a more uniform distribution as was shown by autoradiographs. Sanders[42] performed experiments with inhalations of both $^{238}PuO_2$ and $^{239}PuO_2$ prepared in the same manner in rats. The $^{238}PuO_2$ behaved in such a manner that it appeared to be more soluble and provided a more homogeneous dose to the lung. Both of these experiments led to the conclusion that the homogeneous distribution is more effective in producing cancer than the particulate distribution (i.e., the DF for the particulate is less than 1). Dolphin[43] quotes Lafuma as reporting ".....greater toxic effects including cancer in rats following deposition of curium-242 in lungs compared with equal amounts of plutonium-239 activity. This he attributes to the diffuse nature of the curium deposit and the particulate nature of the plutonium, as shown by autoradiographs."

In studies with beta emitters in the lung, Cember[44] concluded, ".....the carcinogenicity of a given amount of absorbed radiation energy increases up to a point, as the absorption of the energy is spread out, both time- and space-wise. From a practical point of view, this means that, for a given

total amount of absorbed energy, low-level, continuous exposure of the total lung may be more carcinogenic than the same amount of energy delivered acutely to a restricted volume." Thus, there is evidence that the same effect may be true for beta radiations.

Current experiments at the Los Alamos Scientific Laboratory provide a direct test of the Geesaman theory in that the particles are carried to the lung by the bloodstream and are lodged in immobile positions in the capillaries. Here they are in position to irradiate the surrounding tissue in patterns little, if at all, different from those administered by inhalation or intratracheally. However, they do not agglomerate or move about so that the results can be ascribed to a fixed particle and the dosimetry examined. In the first experiment,[45] particles of $^{238}PuO_2$ of 180-μm diameter were used in rats. Although a lesion similar to the one described by Lushbaugh[7] developed, it did not affect the well-being of the animal, and no cancers developed in 32 animals sacrificed from 120 to 400 days after implantation or in a group of 6 animals allowed to live out their lifetime. It is estimated that the radiation energy from this particle, if averaged over the lung of the latter 6 animals, would have delivered a dose of 2 500 000 rads (or 25 000 000 rems). Such a dose to the full lung would have caused very early death and is many orders of magnitude above that at which increased incidence of cancer is noted.

In an experiment currently in progress,[46,47] uniform-sized microspheres (10-μm-diameter) of ZrO_2 are used with intermixed PuO_2 to provide particles of differing activities, and these are introduced into the lungs of hamsters by the above technique. In the first study in this experiment, 8 groups of 60 animals each were injected with 2000 such particles, with the plutonium content of each particle ranging from 0.07 to 59.4 pCi. Essentially all of animals have now died, with only two lung cancers observed. (Three other cancers in the exposed animals occurred in organs other than the lung.) The dose rates to the lungs of those animals, when calculated as the average dose to the lung, ranged from 13 rads per year (130 rems per year) to 12 000 rads per year (120 000 rems per year). This is a range over which one would expect high tumor incidence and, in fact, premature death from pulmonary inefficiency if the material had been distributed homogeneously. Since the survival curves of the individual groups did not differ from those of the controls and the total tumor incidence was low, one can only conclude that the DF for plutonium in particulate form must be less than one. In the continuation of this study, some 1900 hamsters have received 1.6×10^8 microspheres.[48] As of October 1974, the minimum time of exposure has been 50 weeks,* which is comparable to or longer than the tumor induction times observed by Little *et al.* in their experiments with more uniformly distributed ^{210}Po. In fact, only three lung tumors (including the two observed in the first study) have, as yet, developed from the microsphere exposures. While this study is as yet incomplete, the very low tumor incidence again indicates a low effectiveness of the particles in inducing lung cancers as compared to more homogeneously distributed alpha emitters, as well as the failure of the Geesaman hypothesis to correctly forecast the results of this experiment.

VIII. DISCUSSION

There appear to be few further conclusions which can be drawn. The preceding review has indicated that the Tamplin-Cochran conclusions are based upon a hypothesis which requires considerable extrapolation of the data upon which it is based. Later evidence, of the same nature as was used in the derivation (i.e., rat skin data), does not support the assumptions of the original model. The Tamplin-Cochran interpretation of the model not only fails to take into account the later evidence but appears to present the hypothesis as fact. The supporting evidence on human data which they present are based upon unsupported assumptions and distortions of the words of the authors they quote. Most importantly, they fail to use or acknowledge direct evidence on the effect of radioactive particles. Such evidence indicates that the basic damage model which they use overestimates badly the carcinogenic effects of radioactive particles. We conclude,

*Reference 48 indicates that ".....by the spring of 1974....." these exposures had been attained. The intent was to indicate progress to the time of preparation of the paper. The administrations were actually completed in September 1973.

therefore, that the application of the average organ dose to the establishment of limits is still appropriate, although experimentation to narrow existing uncertainties on the effects of non-uniform dose distribution should continue.

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