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WHAT WE HAVE LEARNED ABOUT PLUTONIUM FROM HUMAN DATA*

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Abstract—Human data on plutonium deposition, internal distribution, and excretion have been obtained by observations after accidental occupational exposures, long-term follow-up studies on plutonium workers, and autopsy tissue analyses. No significant harmful effects have been noted in humans, although a small foreign-body type nodule around dermal implantations of plutonium has been described in eight persons. Methods used to estimate body burdens by urinary excretion values appear to be conservative generally compared to autopsy tissue burdens. Variations in autopsy tissue distribution appear to be related to the conditions of the plutonium exposure including mode of exposure, particle size, chemical composition, solubility in serum or tissue fluids, and time after exposure for internal redistribution. An important conclusion of this human data survey is the recognition of the inestimable value to be gained by continued careful studies on the life history of workers with higher plutonium exposures.

OUR KNOWLEDGE of plutonium toxicity is derived from both human data and animal radiobiological experiments. The available human data can be summarized as being scanty and fragmentary, consisting mostly of uncontrolled observations following exposures with accidental and unplanned experimental design. These characteristics of human data are applicable rather universally to most studies on human toxicology. Yet it is worthy of our attention to note the important role that human data have played historically as a means of identifying unknown toxic materials or unsuspected biological reactions. It has been rather common to have an offending agent identified, or brought more forcefully to our attention, as a result of witnessing only a very few "cluster" cases of human disease that have an unusual incidence in a small exposed population.

The history of beryllium toxicity exemplifies the ability of a few human cases to change the pace of toxicological investigations. Employees working on extraction of beryllium from beryl ore in Europe had been observed to develop lung disease as early as 1933 by Weber and Engelhardt. A number of human cases were reported subsequently in the European literature and some experimental animal studies showed lung lesions after beryllium exposure, but until the early 1940s it was still generally regarded as an innocuous substance in the United States. In 1943, the unusual incidence of four cases of lung disease, diagnosed as Boeck's sarcoid in workers of one plant was noted by Bowditch (SHIPMAN, 1966), which opened up intensive investigations of this toxic metal. In the next few years numerous cases were noted and chronic berylliosis was also reported in the immediate neighborhood of processing plants. The probability of identifying the potential of chronic berylliosis by animal experimentation alone is of interest. Extensive studies over many years were made to reproduce the identified human pathology—production of chronic beryllium-induced granulomas in animals proved to be an experimental challenge not to be taken lightly and has never completely duplicated the human reaction. As one would expect, after the disease state was recognized, protective standards were set on the basis of available data in humans, plant exposure conditions, available animal data, or toxicity estimates based on experience with other substances with similar toxic properties. A beryllium limit for workroom air (0.002 mg/m^3 as the time-weighted average concentration)

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was adopted by the USAEC in 1949 after several years of study by an advisory committee. This value continues to be used as the standard up to the present time.

The most recent occupational disease in which human disease has initiated an intensive investigation is the carcinogenesis produced by vinyl chloride and related products. The occurrence of three cases of a rare tumor of the liver, angiosarcoma, during the period of September 1971–December 1973, in a group of several hundred exposed workers at one plant was the trigger to the investigation. Although the cases were diagnosed by different physicians, this rare diagnosis in three individuals was surmised to be related with work exposures in a polyvinyl chloride plant (CREECH and JOHNSON, 1974). This finding was reported in January 1974 to the National Institute of Occupational Safety and Health (NIOSH). Seven additional cases were identified among vinyl chloride workers in the U.S. in the next couple of months. Less than 3 months later, a proposed permanent standard of near zero (below detectable limits) exposure was proposed by NIOSH compared to the former federal standard of 500 ppm and a temporary standard of 50 ppm that was imposed in April 1974. This example points out again that the discovery of a few human cases determined the need for more intensive research studies and better control technology.

The biological damage in humans caused by ionizing radiations has a similar history to those that could be cited for toxic metals and chemicals. In retrospect, it is interesting to note that Harting and Hesse published their first paper on the unusual incidence of fatal lung disease (subsequently proven to be bronchogenic carcinoma) in Schneeburg miners in 1879, long before the discovery of radioactive materials (IAEA, 1964). It is also noteworthy that their observations went unheeded until over 40 yr later when the study of lung cancer in miners was undertaken in a more intensive fashion.

The report of MARTLAND *et al.* (1925) first described the clinical effects of radium poisoning in luminous instrument dial painters and led to Martland's classic paper (1929) on the development of osteogenic sarcoma in these workers. His analysis on these cases is apropos to our subject today: "The incidence of two sarcomas of bone in fifteen cases of radium mesothorium poisoning is too large to be passed over as due to coincidence. Since this is the first time to our knowledge that sarcoma of the bone has been attributed to radiation, the case is of sufficient interest to be reported." This observation was the start of additional studies by H. S. Martland, R. D. Evans, and J. C. Aub in the problem of radiation oncogenesis due to radium. In 1941, a task group assembled by the U.S. National Bureau of Standards selected a tolerance dose of 0.1 μg radium residual body burden for workers based primarily on the study of about 20 individuals with substantial body burdens of radium. By the early 1950s, this radium standard and other radium studies were used in conjunction with relative radium/plutonium toxicity to set the plutonium standard (0.04 μCi) still in use. Today the Center for Human Radiobiology at the Argonne National Laboratory, a U.S. Atomic Energy Commission supported project, continues to follow about 1160 persons with radium burdens in order to refine and add to our understanding of minimal burdens that can produce pathological effects.

Although the exposures responsible for identification of a cluster of human cases are obviously excessive, the rapidity with which the incidence of disease rises above certain exposure levels is not always recognized. It should be noted that specific diseases of interest in toxicology may exist at only a very low natural incidence unless influenced by external factors. In the radium cases, the incidence of osteosarcoma was recognized as being unusually high. An increase of radium exposure of a factor of 5 or 10 above the point of recognizable toxicity produces an easily identified incidence of osteogenic sarcoma. The curve (Fig. 1) reproduced from EVANS *et al.* (1972) demonstrates the remarkable disease incidence witnessed after a significant exposure level was reached; the occurrence of tumors was zero in 503 persons receiving under 1000 CR, average skeletal cumulative rads, while the rapid increase in tumor incidence is apparent above 1000 CR. Compared to an incidence of over 20% seen above 1000 CR, the age adjusted death rate in the U.S. from all bone tumors, including osteosarcoma, is only about 1 per 100,000 persons per year (BURBANK,

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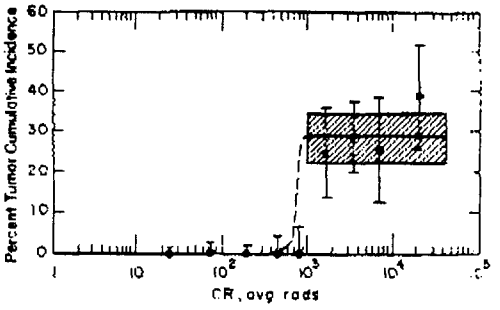

FIG. 1. The observed tumor cumulative incidence or occurrence in the "epidemiologically suitable" radium exposure cases. The shaded region corresponds to the mean occurrence $\bar{p} = 0.28 \pm 0.06$ between 1000 CR and 50,000 CR. (Figure reproduced from EVANS *et al.*, 1972.)

1971). One could use graphs of other toxic materials which plot exposure vs disease incidence to illustrate the marked effect of a factor of 5 or 10 in exposure above recognizable disease induction levels. This general conclusion is supported by the data of animal radiobiological experiments with plutonium shown at this symposium.

Based on these historical observations, it is suggested that human studies have generally been of value in the study of occupational disease in three major ways:

(1) Initial identification of toxic effects has not infrequently resulted from recognition of human disease and is then related to exposure to specific agents.

(2) These initial observations have often been made on only a few individuals without the use of a control population.

(3) As exposures reach significant levels, a relatively small change in exposure, a factor of 10 or less, will usually produce relatively large changes in the incidence of the specific disease of interest.

Thus we should recognize the potential importance of human data, both positive and negative, in our assessment of the toxicity of plutonium. The available data are limited, but include the initial observations after accidental occupational exposures, long-term follow-up studies on plutonium workers, and autopsy tissue data.

EVALUATION OF ACCIDENTAL EXPOSURE CASES

The initial human studies were related to the need to protect those persons working with plutonium on the Manhattan Project (1943–1946). Those studies were directed toward finding methods to measure the exposure to workers and to evaluate the consequences of accidental exposures.

The development of a plutonium urinary assay method at Los Alamos began in January 1944 and was applied routinely to plutonium workers there in the early part of 1945 (HEMPELMANN *et al.*, 1973a). This was followed by an intensive period of investigation to establish a relationship between concentrations of plutonium in urine to the plutonium deposition in the body. By 1950, Langham (LANGHAM *et al.*, 1950; LANGHAM, 1956) had derived a single power function equation to describe this relationship based on data obtained on human subjects with short life expectancy to whom plutonium citrate was given by intravenous injection. This subject has been critically reviewed and reanalyzed recently (DURBIN, 1972).

Since that time accidental exposures, whether through inhalation or wounds, were studied for absorption rates of plutonium, excretion values, and evaluation of possible treatment techniques. The urinary excretion curve following occupational exposure and the Langham equation were shown to be in reasonable agreement if numerous samples were collected over time periods of several years or more, and the plutonium deposition was available to the systemic circulation. Inhalation of less soluble plutonium forms into the lung may provide a lung deposition that is only slowly released to the systemic circulation. In these cases, the urinary excretion reflects the transfer rate from the lung deposition and it may take weeks or months before the excretion curve of the systemic body burden manifests itself. This slow release model, first formulated by HEALY (1957), is now well accepted but obviously the parameters that determine the transfer rate to the systemic circulation are dependent on chemical and physical factors of the aerosol inhaled and usually can be determined only by numerous

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measurements after a particular exposure. Figure 2 illustrates a delayed urinary excretion pattern from an inhalation exposure of "insoluble" ^{238}Pu compared to the Langham excretion curve. In this case the excretion rate was undetectable for several months followed by a rising excretion for over 2 yr, which reflects the slow solubilization after this particular plutonium inhalation. The major product of human studies after accidental exposure has been a better understanding of the uptake, metabolism, and excretion of plutonium.

The number of such investigations of occupational exposures is unknown, but is many hundreds if all minor wounds and air-borne concentrations that could result in potential body depositions of plutonium in man were collected. For example, more than 300 wounds were reported to indicate some degree of plutonium contamination by direct wound counting techniques at the Rocky Flats Plant

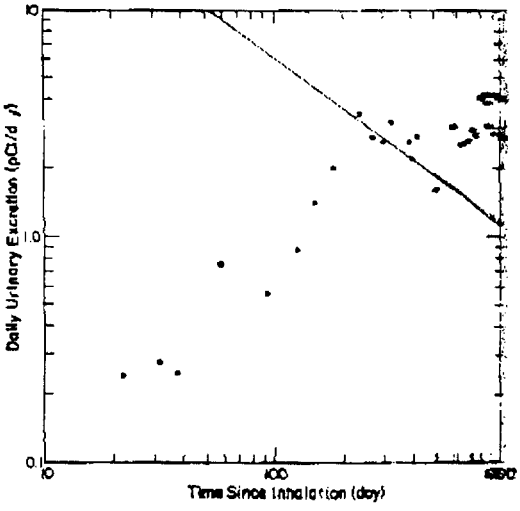

FIG. 2. Urinary excretion rate from a single inhalation of high-fired $^{238}PuO_2$ particles in a zirconium–molybdenum ceramic matrix. Symbols are the actual excretion rate while the solid line is the Langham power function estimate from the intravenous injection of citrate complexed plutonium for the same currently estimated systemic burden.

Table 1 AEC contractor personnel with internal plutonium depositions (1957–1970)

PER CENT OF OCCUPATIONAL PERMISSIBLE BODY BURDENS	NUMBER OF INDIVIDUALS
25 to 50	118
50 to 75	35
75 to 100	13
100 to 200	25
200 to 500	15
500 to 1000	7
Total	203

Ref: Data from Division of Operational Safety, U.S. AEC

for the period from 1957 to 1963 (HAMMOND and FUTCHER, 1964). The more significant exposures reported on AEC contractor personnel during the period from 1957 through 1970, are shown in Table 1. The importance of inhalation as the major route of entry for occupational exposures is apparent in Table 2.

Formal studies for delayed effects from these exposures have not been reported, so it is only possible to state that no cases of acute human pathology following plutonium exposures have been reported to date. Most of these workers have been followed with regular periodic medical examinations during their employment with AEC contractors. After termination of employment most workers have not been followed by medical examinations for the specific purpose of determining possible clinical effects from plutonium (or any other hazardous materials they may have encountered in their work).

As for chronic effects, it is noteworthy that the only clinical or pathological finding reported to date is the formation of fibrous nodules around the site of plutonium depositions in wounds within a few months to several years in a few instances. Eight such cases have been reported (LUSHBAUGH *et al.*, 1967) which describe a

Table 2 AEC contractor personnel with internal plutonium depositions (1957–1970)

ROUTE OF ENTRY	NUMBER OF CASES
INHALATION	131
WOUND	48
BOTH	8
UNKNOWN	16
Total	203

Ref: Data from Division of Operational Safety, U.S. AEC

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Table 3. LASL plutonium workers study

Fraction of MPBB*	Original Study	Total
5 - 10	3	3
3 - 5	5	6
1 - 3	10	19
0.1 - 1	7	228
	25	257
Deceased	1	12

* Maximum Permissible Body Burden (MPBB) is 40 nanocuries ^{239}Pu.

melanoma has been removed from the chest wall of one of the subjects. Another had a partial gastrectomy for a bleeding ulcer. There are the expected assortment of mild hypertension, ulcers and obesity.

No significant abnormalities were noted in the lungs or bones (chest, pelvis, teeth) except for one suspicious "coin lesion" in the lung that enlarged slowly on several chest X-rays. Surgical exploration revealed a benign lung lesion, a hamartoma. The surgical specimens were examined for plutonium, including autoradiography of a lymph node containing about 200 pCi ^{239}Pu/g (Fig. 4). These studies revealed the very non-uniform radiation dose distribution from plutonium particulate exposure and correlated well with body burden estimates.

Estimates of plutonium deposition in the lungs were made by *in vivo* chest measurements and positive counts were obtained for 14 of 21 persons measured. They all were low values (below 10 nCi) and none exceeded the detection limit of the counter at the 95% confidence level. One individual was known to have had a contaminated hand wound in 1945; this was precisely located by external counting and was estimated to contain 5.3 ± 0.4 nCi in 1971. There was no gross skin abnormality or nodule formation at the deposition site. This observation compared to the skin lesion described earlier (LUSHBAUGH and LANGHAM, 1962) may indicate that the depth of deposition in relationship to the basal epithelial layer of the skin may be important to nodule formation.

Sputum cytology showed no neoplastic changes; however, one 3-packs-a-day cigarette smoker was noted to have marked dysplastic cytological changes. Chromosome analysis of peripheral lymphocytes showed no abnormalities in this group.

As these studies are continued, it is obvious that the natural incidence of disease will provide interpretation difficulties as to the etiology of disease. The number of workers is so small in this study that to date it has not been considered necessary to establish a control group but rather to simply record our observations. It seems likely that if these exposures were grossly excessive, pathology as experienced with radium or other toxic materials could already have been apparent. The most likely pathology, based on knowledge from experimental animal studies, is lung carcinomas (after inhalation exposures), liver cancers, and osteogenic sarcomas of the bone. The probability of naturally occurring tumors in these organs based on disease incidence in the U.S. suggests one might expect about 0.8, 0.15 and 0.04 deaths respectively from such disease in a group of 25 persons (HEMPELMANN *et al.*, 1973b).

At the present time an expansion of the Los Alamos study is underway. The figures on Table 3 indicate the number of individuals with exposures above 10% of the maximum permissible body burden (MPBB) who will be included in the study. The table shows that the additional cases are generally below the MPBB and that the original study group has already included many of the highest exposed individuals.

The United States Transuranium Registry, operated for the U.S. Atomic Energy Commission by the Hanford Environmental Health Foundation, Richland, Washington, is responsible for maintaining records on all workers who volunteer for the Registry program. Most of the major AEC contractors cooperate in this program in which over 5000 workers have been identified who have worked in or around plutonium areas. This program has not included periodic medical examinations, but has concentrated on assembling available health physics and medical records and on promoting an autopsy examination program that can confirm clinical diagnoses and ascertain accurate plutonium content in the various organs. To date, over 800 workers have given permission for autopsy examination in the Registry program (NORWOOD, 1974).

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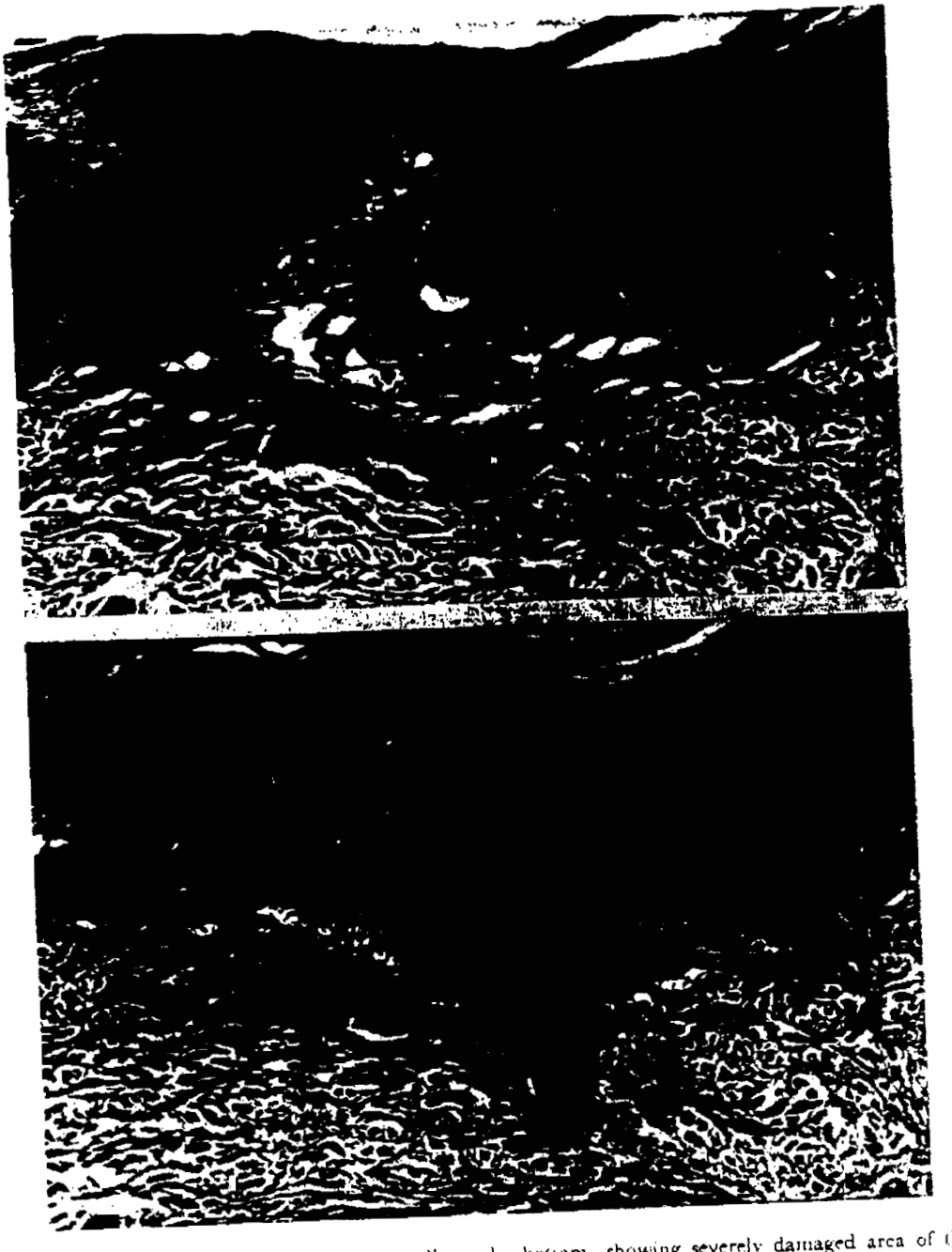

FIG. 3. Photomicrograph (top) and autoradiograph (bottom) showing severely damaged area of the corium due to α-emitting particles from 0.08 μg plutonium in a wound for 4.25 yr. Reduced about 30% from mag. ×120. (Reprinted from LISSMAYOR and LANGHAM, 1962.)

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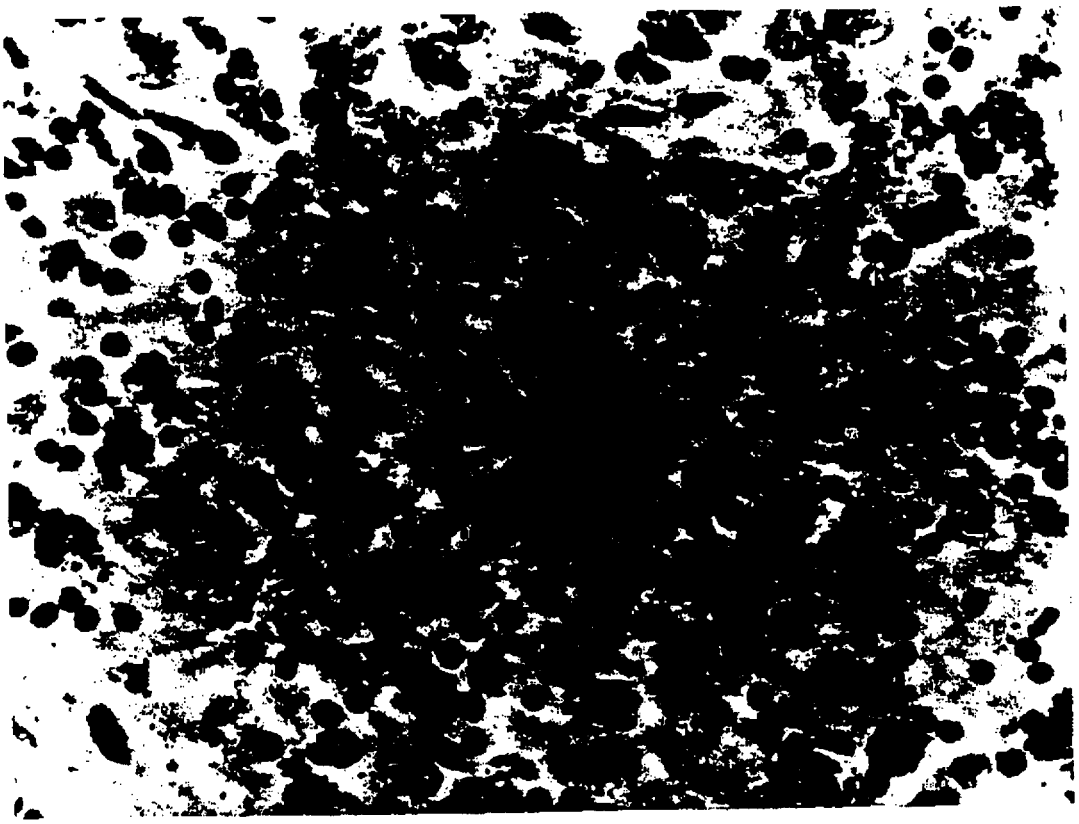

FIG. 4. Autoradiograph of lung section of subject No. 2 showing a radioactive particle.

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AUTOPSY DATA

Studies of plutonium content in tissues obtained through postmortem examinations started on an informal basis many years ago through the initiatives of several AEC contractor laboratories. These studies were started as early as 1949 at the Hanford plant, Richland, Washington (NEWTON, 1968) and by 1959 at Los Alamos (CAMPBELL *et al.*, 1973). There are now over 750 reported autopsy cases that have been studied for plutonium concentrations (CAMPBELL *et al.*, 1973, 1974; LAGERQUIST *et al.*, 1973; NELSON *et al.*, 1971, 1972; NEWTON *et al.*, 1968; and NORWOOD *et al.*, 1973). Of this total, about 63% of the cases are from the general population for fallout and background studies, about 23% are on persons who had worked around but not in plutonium areas (low exposure potential), and about 14% are on persons with a history of plutonium work.

Initially, these programs were designed to determine the tissue content of plutonium for correlation with estimated body burdens of plutonium workers from urinary excretion data. These studies were implemented primarily for evaluation of health protection practices rather than plutonium effects studies. Through the years, improved counting techniques have permitted the investigations to be extended to determining the very low levels of human assimilation of plutonium due to atmospheric weapons testing or other environmental sources.

The early results at Hanford (NEWTON *et al.*, 1966) on 41 autopsies showed no undue accumulation of plutonium in workers. It was noted that the tissue content was less than one might predict from measured air concentrations in the plant. The tissue values on these individuals were low and their exposures were apparently quite limited since only one individual had detectable plutonium excretion in urine.

The paper by Schulte at this Symposium presents some of the Los Alamos data pertaining to the comparison of the estimated body burdens from urine data to the tissue analysis from autopsy examinations. In six of eight cases, the comparison shows the urine excretion estimates of body burden to be high by a factor of about one to five, while in the two other cases the discrepancy is much greater.

It was noted earlier that the U.S. Transuranium Registry has had over 800 voluntary registrants who have consented to participate in the autopsy program. At the present time, the Registry has data on 41 cases (NORWOOD, 1974), and the preliminary results of some of these cases have been published (NORWOOD *et al.*, 1973; LAGERQUIST *et al.*, 1973). The studies on persons who had worked at the Rocky Flats plant (LAGERQUIST *et al.*, 1973) indicate that in 7 of 19 cases it was possible to make body burden estimates from urine assay results. In each case, the estimate exceeded the value derived from tissue analysis extrapolated to a systemic body burden. The ratios ranged from "less than" 1.7 to nearly 6. In the other cases the urine values were below detectable levels although small values of plutonium were present in the tissue samples.

In such comparisons, it is necessary to recognize the fact that tissue samples require large extrapolations to project the total "systemic body burden." Therefore, such comparisons indicate an order of consistency between two methods and not the precision of either method. It appears that the urine assay method may contain some conservatism in the derived values.

The autopsy programs also provide data on the distribution of plutonium in various organs. CAMPBELL *et al.* (1973, 1974) have reported data on selected tissues from 370 autopsies. Of these, 15 individuals worked in plutonium areas with considerable potential for exposures, 45 worked at the Los Alamos Scientific Laboratory but not in plutonium areas so there was low potential for exposure, and 310 were on individuals with no potential for occupational exposure so they represent general population values. A summary of the data for selected organs is presented in Table 4. The occupational exposure potential was determined as being high or low by an independent evaluation of a health physicist who knew the individual's occupation and work locations, but not the analytical data from the tissue studies.

The organs measured in the Los Alamos study are primarily the lung, tracheobronchial lymph nodes, liver, kidney and bone. The data confirm the increased plutonium in those workers with higher exposure potential and show considerable individual variation in the activity found in the organs from case to case.

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Table 4. Summary of 370 autopsy cases

Plutonium-239

Median Concentrations in dis/min/kg

	General Population		LASL Worker Exposure Potential	
	1959-1971	1972-1973	Low	High
Lymph Nodes[1]	5.0 (164)*	25.0 (47)	15.0 (42)	900 (14)
Liver	1.4 (212)	2.5 (54)	3.0 (41)	100 (15)
Lung	0.8 (217)	0.6 (74)	4.0 (44)	300 (15)
Bone[2]	0.6 (166)	0.7 (56)	0.3 (25)	50 (13)
Kidney	0.6 (163)	1.5 (51)	0.1 (42)	10 (15)
Gonad	---	0.4 (38)	---	---

1 Tracheobronchial lymph nodes
2 Primarily vertebral bone samples
* (n) = number of samples

Ref: Campbell et al., 1975;1976.

The concentration of plutonium in activity per kg is nearly always highest in the tracheobronchial lymph nodes while the concentration in the lung and liver is generally somewhat higher than in bone.

Other autopsy data (LAGERQUIST *et al.*, 1973; NORWOOD *et al.*, 1973) also show highest concentrations in the tracheobronchial lymph nodes followed by lungs and liver after inhalation exposures. Wound deposition may cause higher concentrations in the nearest regional lymph nodes. Plutonium concentration in bone is frequently less than in the above organs, but due to the large organ size the total activity in bone frequently represents one half of the body burden or more. These distributions are highly variable. Furthermore, NORWOOD *et al.* (1973) point out that the concentrations found at autopsy are far different from those which might be expected from the assumptions upon which the present ICRP body burden calculations are based. It appears that the critical organ for any given individual case might be bone, lung, liver, lymph node or wound site. The most important determinant of the concentration is related to the conditions of the plutonium exposure including mode of exposure, particle size, chemical composition, solubility in serum or tissue fluids, and the length of time the body burden has had to redistribute itself. These factors vary with time after deposition so that dose calculations based on autopsy findings must consider the possible time-related transport and distribution effects. It is apparent that the physical and chemical factors at the time of exposure must be known better if good correlations on future cases are to be made more meaningful.

The Los Alamos data on the general population (Table 4) show that the concentration of plutonium in persons exposed only to world wide fallout, presumably inhalation exposures, shows relatively little variation between organs. All values are within a factor of 2 or 3, except for the tracheobronchial lymph nodes. Much of the increased concentration in lymph nodes in the 1972–1973 data is attributed to paying greater attention to dissecting the lymph nodes from other tissues. The 1972–1973 values are undoubtedly more representative of actual lymph node concentrations.

Even though such radiochemical analyses are done at extremely low counting rates, the interpretation of the data may reveal new physiologic processes in the redistribution of plutonium. For example, in Fig. 5 (CAMPBELL *et al.*, 1974) the concentrations of plutonium in liver and lung in the general population are plotted as a function of age at death. The slope of the liver data shows accumulation of plutonium with age, while the slope of the lung does not. The significance of this information is not yet fully understood, but illustrates potential distributional effects with time and age.

The autopsy programs have not contributed any information yet that is helpful with regard

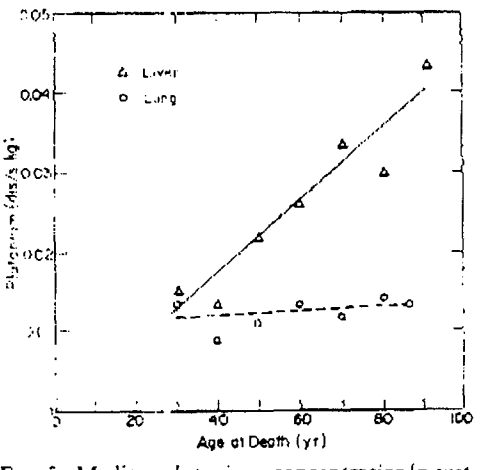

FIG. 5. Median plutonium concentration/g wet lung and liver tissue vs age at death.

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to possible effects in man. These data have the same type of statistical difficulties as discussed on the long-term follow-up studies on plutonium workers. The pathological descriptions do not help identify the etiology of any neoplastic diseases discovered and the number of cases that have come to autopsy so far does not permit any statistical conclusions. The desire to attempt preliminary statistical evaluation should be resisted since it can neither prove nor disprove any conclusion at the present time. In 131 published autopsies of workers who have been around or in plutonium work, there are 32 (23%) who have a neoplastic disease listed as the cause of death. The incidence and distribution of neoplasms do not appear unusual so far. It is mentioned only to point out the need to continue collecting information of this type.

CONCLUSIONS

Plutonium is a unique element in many ways, including our experience to date in humans. Unlike many materials that man has used, the potential toxicity of plutonium was recognized almost as soon as the element was discovered. After 30 yr, our human experience has not provided data that indicate harmful effects have occurred from the exposures to data. The credit for this accomplishment belongs to many physicians, health physicists and biologists interested in protection of workers in the nuclear industry. Their work resulted in setting an exposure limit to workers at an early data that was to provide reasonable assurance that work could be done safely. Human experience to date provides no examples of deleterious effects that suggest that the early guide has not served its purpose well.

It is noted that history of other industrial toxins shows that gross exposures as well as relatively smaller excesses of exposure have produced recognizable disease in workers. Fortunately, this has not occurred with plutonium and suggests that the basis for the current occupational exposure limit has been reasonably accurate. One may argue over smaller differences in possible risks or relative safety compared to other standards or other hazards at work, but experience in humans to date does not suggest that there are differences of large magnitude, say a factor of 10 or more required in the plutonium standards to maintain safe working conditions.

Human studies and autopsy results have provided a body of information on excretion data, distribution in the body from various exposure conditions, and long-term follow-up effects data that are invaluable and can be ascertained definitively in no other way. This information is just beginning to emerge into a sufficiently large data base that potential long-term effects on man can be identified. The data in man already extend well beyond any animal experiments that could be contemplated and one of the more important conclusions at this time is to recognize the inestimable value of more careful studies on the life history of workers with higher plutonium exposures. The opportunity is here now; the subject requires more intensive study, particularly during the next two decades as the earliest plutonium-exposed workers reach retirement age and beyond.

The issues discussed at this Symposium on plutonium toxicity play a central role in the nuclear industry and its health management functions. The health issue will be the pivot of many decisions. Our worker populations may provide some of the needed answers. Ten to fifteen years from now, as the next series of long-term animal experiments at lower exposure levels are being studied for terminal effects data, the early plutonium workers will have a life history of forty to 45 yr of exposure data. Careful planning and accumulation of these data could answer many of our questions of today. In my opinion, our planning and execution on these studies is not yet appropriate to the value of these data even though the overall effort and interest is gradually being increased. Unfortunately, in most cases, these interests are still secondary to other responsibilities of the investigators. There is a continuing need to assure that study plans and review procedures of the proposed data collection, analytical procedures and assessment studies will provide the most useful and reliable answers.

REFERENCES

BURDANK F., 1971, National Cancer Institute Monograph 33, U.S. Dept. of Health, Education, and Welfare, National Cancer Institute, Bethesda, Md.

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0006258J

00130015.010

CAMPBELL E. E., MILLIGAN M. F., MOSS W. D., SCHULTE H. F. and MCINROY J. F., 1973, Los Alamos Scientific Laboratory Report LA-4875.

CAMPBELL E. E., MCINROY J. F., MOSS W. D., EUTSLER B. C. and SCHULTE H. F., 1974, Annual Report of the Biomedical and Environmental Research Program of the LASL Health Division, 1973, compiled by C. R. Richmond and E. M. Sullivan, Los Alamos Scientific Laboratory Report LA-5633-PR, 27.

CREECH J. L. and JOHNSON M. N., 1974, *J. occup. Med.* **16**, 150.

DURBIN P. W., 1972, *Radiobiology of Plutonium* (Edited by STOVER B. J. and JEE W. S. S.), p. 469 (Salt Lake City: J. W. Press).

EVANS R. D., KEANE A. T. and SHANAHAN M. M., 1972, *Radiobiology of Plutonium* (Edited by STOVER B. J. and JEE W. S. S.), p. 431 (Salt Lake City: J. W. Press).

HAMMOND S. E. and PUTZIER E. A., 1964, *Health Phys.* **10**, 399.

HEALY J. W., 1957, *Am. ind. Hyg. Ass. Quart.* **18**, 261.

HEMPELMANN L. H., LANGHAM W. H., RICHMOND C. R. and VOELZ G. L., 1973a, *Health Phys.* **25**, 461.

HEMPELMANN L. H., LANGHAM W. H., VOELZ G. L. and RICHMOND C. R., 1973, *Proceedings of the Third Congress of the International Radiation Protection Association*, Washington, D.C.

International Atomic Energy Agency (IAEA), 1964, *Radiological Health and Safety In Mining and Milling of Nuclear Materials*, Vol. I, p. 3 (STI/Pub/78, IAEA, Vienna).

LAGERQUIST C. R., HAMMOND S. E., BOKOWSKI D. L. and HYLTON D. B., 1973, *Health Phys.* **25**, 581.

LANGHAM W. H., BASSETT S. H., HARRIS P. S. and CARTER R. E., 1950, Los Alamos Scientific Laboratory Report LA-1151.

LANGHAM W. H., 1956, *Am. ind. Hyg. Ass. Quart.* **17**, 305.

LUSHBAUGH C. C. and LANGHAM J., 1962, *Archs Dermatol.* **86**, 461.

LUSHBAUGH C. C., CLOUTIER R. J. and HUMASON G., 1967, *Ann. N. Y. Acad. Sci.* **145**, 791.

MARTLAND H. S., CONLON P. and KNEP J. P., 1925, *J. Am. med. Ass.* **85**, 1769.

MARTLAND H. S. and HUMPHRIES R. E., 1929, *Archs Pathol.* **7**, 406.

NELSON I. C., HEID K. R., FUQUA P. A. and MAHONY T. D., 1971, Battelle Northwest Laboratory Document BNWL-SA-4077.

NELSON I. C., HEID K. R., FUQUA P. A. and MAHONY T. D., 1972, *Health Phys.* **22**, 925.

NEWTON C. E., JR., LARSON H. V., HEID K. R., NELSON I. C., FUQUA P. A., NORWOOD W. D., MARKS S. and MAHONY T. D., 1968, *Diagnosis and Treatment of Deposited Radionuclides*, p. 460 (New York: Excerpta Medica Foundation).

NORWOOD W. D., NORCROSS J. A., NEWTON C. E., JR., HYLTON D. B. and LAGERQUIST C., 1973, *Radionuclide Carcinogenesis*, AEC Symposium Series 29, CONF-720505, p. 465.

NORWOOD W. D., 1974, personal communication.

SHIPMAN T. L., 1966, in: *Beryllium, Its Industrial Hygiene Aspects* (Edited by STOKINGER H. E.), p. 12 (New York: Academic Press).

TAMPLIN A. R. and COCHRAN T. B., 1974, Natural Resources Defense Council (NRDC) report, Washington, D.C.

DISCUSSION

SHREVE, J.: You mentioned tissue burdens being less by a factor of 2 or 5 from that expected from urinalysis; I was curious about whether there was any whole-body counting done and whether that would be anticipated as you locate some others for the UPPU Club?

VOELZ, G. L.: The comparison was made primarily with urine data, which is our primary indicator for plutonium burdens. I would say that whole-body counting for plutonium in low-order exposures, which these autopsies primarily represent, hasn't given us good information.

SHREVE, J.: Was it detected though?

VOELZ, G. L.: We have used whole-body counting operationally in studying people but, for the most part, our exposures in lung are below our limits of plutonium detection; we can see americium, but we don't see plutonium in our chronic, long-term workers.

PARKER, H. M.: Isn't the present sensitivity of the external method lacking by two orders of magnitude of that needed to measure what you find in the bulk of these autopsy cases?

VOELZ, G. L.: That is right, and even if we have the sensitivity in some cases of exposure, the statistical significance is very marginal.

MCCLELLAN, R. O.: As I recall, at an earlier time, some plans were being made for radioanalysis of the complete body on a few individuals. I am wondering if some of that has been done and completed and, if so, to what extent the analysis in terms of major tissues such as lung and liver provides an accounting of the body burden of the individual?

VOELZ, G. L.: The answer is, no, we have not had complete body autopsies to date.

NORWOOD, W. D.: This is a good chance to ask anybody if they may have had an opportunity to talk to people who have, say, an estimated quarter of a body burden to allow a whole-body autopsy. We would like very much to get all of the bones of the

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body and a large number of muscles and fat and other tissues which we now have to extrapolate by a factor of 20 or more from a small sample that we can get at autopsy.

WALD, N.: Since we are talking about what we have learned from humans about plutonium, I think it might be appropriate to add a comment about a case which was not included by Dr. Voelz, since nothing was learned from it. I am referring to an appendix of the Tamplin–Cochran petition which is a dissection of a consultation report which I prepared concerning an individual who was alleged to have developed cancer and died of it as a result of a plutonium exposure. The appendix omitted the consultation report and simply dissected their view of it. The reality is that there was no evidence for plutonium exposure in that individual at the time of the incident in which he was involved, at which time there were bioassays of urine and feces as well as a careful medical examination by Dr. Roy Albert. About 4 yr later, he did develop a neoplasm of the hand and, at the request of the defending U.S. Attorney, I examined the individual; whole-body counting showed nothing, and urine and fecal bioassays showed nothing. We obtained the initial tissue biopsy when the first lesion developed in this individual; radioautography as well as counting showed nothing. We obtained additional tissue at amputation, and again radioautography and counting of the clavicle showed nothing. Therefore, there was no basis for associating plutonium as a cause for the neoplastic disease which unfortunately killed this individual. The case was settled before coming to trial; however, in my view, this does not constitute any acceptance of plutonium as a causation in this case.

VOELZ, G. L.: Some information which I did not include in my presentation might be of interest to you. We are still looking for new techniques of measurement, one of which is a detector which might look at lymph nodes in the chest. If you could place a detector into the esophagus to the level of the we just very recently have tried such a device. A sodium iodide detector with a light pipe connected to an external photomultiplier was placed in an individual to the level of the carina, and measurements were made also above and below this level. We got positive signals of both americium and plutonium. I think the testimony of this particular volunteer was (and I might say, we could not see plutonium on the external count) that he would be willing to do it again.

SINKE, G. J.: Dr. Voelz, early in your speech, you talked about having 30 yr of experience showing very few or no cause–effects data on humans and gave credit to good control of exposures. Could part of this good experience have been attributable to DTPA treatments, debridements of wounds, and other methods?

VOELZ, G. L.: The individuals whom we have followed for 30 yr had no treatment, either DTPA or debridement of wounds. Wound debridement at Los Alamos has been very limited over the last decade; we have had about 12 to 15 wounds a year that we monitor, of which perhaps one has detectable activity in it, and these were low enough levels that we have not generally had to excise them.

MAYS, C. W.: You stated that you are not expecting to see many cancers. The question is whether, when they do appear, they can be related to irradiation or to other factors. You should make a detailed effort to obtain data on their histories while these patients are still alive so that, when the results do come in, you can perhaps correlate some of these other factors. I think it is important that you include in this study not only the highly exposed individuals but also those individuals exposed at lower dose levels who can act as pseudo controls for trying to separate out these effects.

VOELZ, G. L.: We have tried to do this in our history taking. There are some individuals in this long-term follow-up group who worked with materials, a list of which reads like your chemical text book, including beryllium and others. However,