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U.S. TRANSURANIUM REGISTRY STUDY OF THIRTY AUTOPSIES

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Abstract—To aid in the evaluation of biological effects of transuranium radioisotopes in people, some 850 transuranium workers have now agreed to allow autopsies. Many more are expected to cooperate. This paper discusses results of the first 30 autopsies reported to the Registry. Where the estimated systemic body burden of plutonium based on urinalysis was greater than 5% of the permissible (0.04 μCi), this estimate was higher than that obtained by laboratory analysis of whole organs or parts of organs in a large majority of cases. For depositions less than 5% maximum permissible body burden, there was considerable variation depending upon individual AEC contractor reporting practices. Nonuniformity within organs was sometimes great, so whole organs (such as lungs, liver, kidneys, spleen, etc.) were usually obtained in the last 30 cases. In relatively high deposition cases (>0.02 μCi), as many as 40 organs were sampled in an effort to determine validity of applying animal data to man. The number of times that various organs had the highest concentration is tabulated.

INTRODUCTION: PURPOSE AND DESIGN OF STUDY

THE U.S. Transuranium Registry seeks to determine whether work with transuranium elements in the facilities of the AEC and its contractors and licensees is detrimental to the health of these employees.

There are really two primary parts of the study. The first is a study of the individual employees occupationally exposed to the transuranium elements to determine if any harmful effects may be related to the deposition of these elements and to compare the deposition in the body in the organs and in tissues found at autopsy with depositions estimated before death based upon urinary and/or fecal assay and/or *in vivo* measurements of radioactivity, particularly from the chest and wound sites. The second part of the study is to determine whether there is any statistically significant difference in the cause of death and in years lived between the worker with small depositions of transuranium elements and others who are as similar as possible in all respects except that they have not been occupationally exposed. At Hanford, substantial environmental and medical data are available to the Registry study from the AEC Health and Mortality Study. All Hanford employees, minus the transuranium workers, serve as one control group for comparison of longevity with the Registry's transuranium worker group at Hanford. Data on longevity of siblings (brothers of male and sisters of female workers), also available at Hanford, serve for comparison with the Registry transuranium worker group. At other facilities, such complete studies of siblings are not available at present; therefore, other controls will be sought.

Presently the best comparison appears to be between the causes of death and years lived by transuranium workers who have relatively high depositions with these same parameters in transuranium workers with low or no measurable deposition who are of the same age and sex and who live under the same general economic conditions. Since the relatively large number of deaths required to establish small differences in these groups has not yet occurred, the data in

this paper is concerned primarily with a discussion of the autopsy findings in the first 30 cases.

RELATIVE CONCENTRATION OF Pu IN TISSUES

In most of the first few autopsies, a quite limited number of organs were sampled. In these, the organs routinely sampled were lung, tracheobronchial lymph nodes (TBLN), liver and bone. As more experience was gained and larger samples because available whole lungs and livers were taken for analysis and the following additional organs are frequently sampled: thyroid, kidneys, spleen, gonads, muscle and fat. The area immediately surrounding earlier flesh wounds where transurainium elements had been deposited are sampled when possible, particularly where measurable depositions, considered to be significant, are found. Tissues not frequently sampled are included, as in the three autopsy cases presented in Tables 1 and 2. Included here are such organs as prostate, bladder, trachea and larynx, adrenal, aorta, gastrointestinal tract, brainstem, etc.

PLEURA AND LUNG

In a previously reported autopsy (Norwood *et al.*, 1973) (01AT 0100), the concentration of Pu in a large specimen of lung including pleura and subpleural parenchyma was 58 times that in a single large section of the parenchyma of the same lung. To determine whether this might be due to a relatively high concentration in pleura, separate samples of lung and of pleura from another case were analyzed. In this other case, the concentration in pleura was little different from that of the lung parenchyma being 1.74×10^{-3} dis/min/g in pleura and 2.22×10^{-3} dis/min Pu/g in lung parenchyma. Further study of this is needed.

Pu DEPOSITION IN MUSCLE

In cases in which muscle was assayed for Pu, the muscle contained the following per cent of

Table 1. *Three recent autopsy cases*

Registry case	Exposure	Chemical form	Estimated total body burden	Time deposition was in body
05TM 0005	Chronic inhalation	Metal and oxide	42.8 nCi	15 yr
01TM 0004	Chronic inhalation	Metal, oxide, nitrate	0.27 nCi	16 yr
01TM 0006	Acute inhalation	Metal, oxide, nitrate	42.2 nCi	17 yr

Table 2. *Relative concentrations of* Pu *in tissues*

Tissue concentration ÷ concentration in tissue having maximum concentration

Organs sampled	Relative concentrations 05TM 0005	01TM 0004	01TM 0006
Tracheobron. lym. nodes	1(34.2 × 10^{-2} nCi/g*)	1.8 × 10^{-1}	1.2 × 10^{-1}
Abdominal lymph nodes	3.6 × 10^{-4}		
Lungs	6.4 × 10^{-2}	7.9 × 10^{-3}	3.6 × 10^{-2}
Bones	2.1 × 10^{-3}	5.0 × 10^{-2}	2.2 × 10^{-1}
Liver	1.1 × 10^{-2}	1 — (1.71 × 10^{-4} nCi/g*)	1 — (6.3 × 10^{-3} nCi/g*
Thyroid	9.6 × 10^{-4}		
Kidneys	6.3 × 10^{-5}	1 × 10^{-2}	2.5 × 10^{-2}
Spleen		8 × 10^{-3}	3.8 × 10^{-2}
Testes	2.1 × 10^{-4}		2.8 × 10^{-2}
Muscle	1.2 × 10^{-4}		2.1 × 10^{-3}
Fat	8.5 × 10^{-5}		7.1 × 10^{-4}
Pancreas	2.0 × 10^{-4}		
Skin			6.6 × 10^{-3}
Prostate	1.5 × 10^{-4}		
Bladder	6.8 × 10^{-4}		
Trachea and larynx	1.0 × 10^{-4}		
Adrenal	2.9 × 10^{-4}	2.1 × 10^{-3}	1.6 × 10^{-1}
Aorta	1.2 × 10^{-3}		
Stomach	3.4 × 10^{-4}		
Large intestine	7.4 × 10^{-5}		
Small intestine	5.7 × 10^{-5}		
Heart	2.0 × 10^{-4}	1.3 × 10^{-2}	1.5 × 10^{-2}
Brain		5.3 × 10^{-4}	
Brain stem		1.8 × 10^{-3}	
Lowest concentration	Small intestine	Brain	Fat
Highest concentration	TBLN	Liver	Liver
Ratio $\frac{\text{Lowest concn}}{\text{Highest concn}}$	5.7 × 10^{-5}	5.3 × 10^{-4}	7.1 × 10^{-4}

* = Actual concentration

the total body burden—4.5, 2.8, 2.6 and 0.5%. The total body burden estimated from autopsy data in these four cases varied from 2.9 to 40 nCi. The deposits in muscle had no consistent relationship to where the major deposit was found at autopsy, i.e. lung and lymph nodes of the lung or liver, etc. Exposures for these individuals had occurred at facilities with exposures to high-fired and regular oxides of Pu and nitrate of Pu with no apparent difference occurring in the amount of deposition in muscle. More samples of muscle are needed to determine if this trend will continue. Average deposition was 2.6% of total deposition for these four cases.

Pu DEPOSITION IN FAT

Fat in two cases contained 0.6% and 0.1% of the total body content. More specimens of fat will be obtained in the future. A large single sample of omentum, composed of fat and other tissues, contained 7.5% of the total body content of Pu in another case indicating a need for further testing of omentum to determine which of its component tissues has the high concentration (lymph nodes may have been present in the sample).

Pu DEPOSITION IN SKIN

In only one case where skin was sampled, the deposition in skin was 0.2% of the total body burden. Total body weights of muscle, fat and skin are taken as those of standard man.

SOFT TISSUES

Muscle, fat, and skin make up about two-thirds of the total weight of the body; and in the few cases described above, these tissues, it will be noted, contributed only an average of about 3% of the total deposition. Since the number of samples is small additional samples will be obtained for analyses to improve the validity of the data.

BLOOD

Blood has not been collected at autopsy for Pu assay as it often offers some technical difficulty of collection and it was felt that the concentration of Pu would be low. At Hanford, 23 employees with Pu depositions were recently sampled for Pu content in blood and urine and no correlations could be found. Estimated systemic depositions ranged from 6 to 400 nCi and years since deposition ranged from 9 to 22. Blood concentrations were low, ranging from 9.5×10^{-5} to 1.5×10^{-2} dis/min/g of blood.

BONE

Evaluation of the Pu content of the skeleton presents the most difficult autopsy problem because the deposition is not uniform, is relatively large and the specimens obtainable are relatively small. Fortunately, in the case of other possibly critical organs—lung and liver—whole organs are now usually obtained. The important trachcobronchial and mediastinal lymph nodes are also usually obtainable. An effort is made to secure parts of three or four ribs, the sternum and the anterior portion (about half) of three vertebrae and these are analyzed separately. These samples collectively weigh about 500 g. The Pu combined sample content is then extrapolated to the 10,000 g skeleton of an average man to estimate total bone content of Pu. Table 3 shows concentration in ribs, sternum, vertebrae, and two femurs obtained from 31 autopsies from four different installations. In Case 05TM 0005, there is some variation in concentration from one rib to another—the range being from 0.56 to 1.20. Ratios of concentrations in rib to that in sternum were from 0.64 to 4.6 except for one exceptional case which had a value of 30. The ratio of concentration in vertebrae to sternum ranged from 0.94 to 3 in six cases while the seventh was 17.

These cases indicate there is a considerable error in extrapolating from such samples to the total skeleton. Since the concentration of Pu in muscle, fat, and skin is so much lower than that in bone as discussed previously, the errors due to extrapolation in these cases are apparently not as serious. Willed bodies with easily measurable depositions of Pu are badly needed so that Pu content of all major bones may be assayed separately and concentrations compared with that of the total skeleton. The content of easily attainable bones (such as ribs, sternum, and vertebrae) could then be related to the average skeletal content of Pu to obtain a correction factor for use in all cases. This would greatly improve the reliability of extrapolations.

While there is a need to know total skeletal deposition, it is also essential to determine which bones have highest concentration and the

Table 3. Concentration of Pu *in bone specimens in* 31 *autopsy cases* (dis/min/g)

Case	(1) Sternum	(2) Ribs	(3) Vertebra	(4) Femur	Rib/St	Ratio Vert/St	Fem/St	Installation*
06UC 0001	0.17	—	0.16	0.97	—	0.94	5.7	06
05TM 0005	0.60	3 = 0.56 4 = 0.72 5 = 0.76 6 = 1.20 7 = 0.88 Av. = 0.82	1.60	Sec. of shaft 0.24 Head 0.91 Av. 0.58	1.4	2.8	1	05
01AT 0391	0.01	0.01	0.03	—	1.0	3		01
01TM 0002	—	1 + 4 + 5 + 6 = 0.0008	0.003	—	—	—	—	
01TM 0006	1.7	1.4	—	—	0.82	—	—	
01JA 0023	0.004	0.00	0.00	—	—	—	—	
01AT 0227	—	0.0002	0.003	—	—	—	—	
01TM 0049	0.01	0.02	0.02	—	2	2	—	
01TM 0004	—	0.02	0.02	—	—	—	—	
01AT 0100	—	0.22	0.77	—	—	—	—	
02TM 0009	0.28	0.18	0.31	—	0.64	1.1	—	02
02DO 0237	0.02	0.03	—	—	1.5	—	—	
02DO 0713	0.085	0.107	1.45	—	1.3	17	—	
02DO 0712	0.002	0.00	—	—	—	—	—	
02DO 0711	—	0.015	—	—	—	—	—	
02DO 0709	0.00	—	—	—	—	—	—	
02DO 0710	0.00	—	—	—	—	—	—	
02DO 0002	—	0.171	—	—	—	—	—	
02DO 0001	0.008	0.037	—	—	4.6	—	—	
02DO 0003	0.005	0.148	—	—	30.0	—	—	
02DO 0036	7.20	—	—	—	—	—	—	
02DO 0235	0.009	0.00	—	—	—	—	—	
02DO 0049	0.04	0.00	—	—	—	—	—	
02DO 0355	0.007	0.034	—	—	5	—	—	
02DO 0444	0.014	0.00	—	—	—	—	—	
02TM 0002	0.027	0.028	0.06	—	1	2.2	1	
02AE 0006	0.003	—	—	—	—	—	—	
02DO 0149	0.00	0.00	0.008	—	—	—	—	
02DO 0627	0.002	0.00	0.00	—	—	—	—	
02DO 0629	0.00	—	—	—	—	—	—	
02DO 0622	0.00	0.00	0.00	—	—	—	—	
No. samples	23	24	13	2	11	7	2	

* Registry installation code.

microscopic location of Pu in areas where concentration is highest.

Pu CONCENTRATION IN ORGANS

Table 4 lists the concentrations of Pu in commonly sampled tissues, together with averages for seven autopsies from one installation and one from another installation. It was hoped that comparisons of average concentrations could be made; however, the variations are so great as to make comparisons meaningless.

Based upon animal studies it would appear that route of entry, particle size and physical and chemical composition and elapsed time following deposition are very important parameters (Norwood, 1975). In industrial practice these factors are often difficult to determine, but their importance is such as to warrant a considerable investment of funds and talent to obtain the best possible estimates at the time of occurrence of accidents involving the transuranium elements.

PLUTONIUM IN TUMORS

Physicians, endeavouring to determine if radioactive depositions in the body caused a

Table 4. Average concentration of Pu *in organs* (dis/min/g)

Case	TBLN	Lungs	Liver	Bone	Spleen	Kidney	Remaining*
01AT 0100	585	5.48	1.52	7.8	0.078	0.091	0.062
01TM 0004	9.85	0.44	65.9	2.8	4.56	0.735	0.029
01JA 0023	4.5	13.5	0	9.0	5	0	2
01TM 0049	0.176	0.0096	0.33	0.034	0.035	0.0038	0.0038
01AT 0227	6	0.022	0.028	8	—	—	
01TM 0002	4.34	1.41	11.25	2.51	0.56	0.39	0.28
01TM 0006	1.58	0.48	13.3	2.72	0.40	0.23	0.0074
05TM 0005	1460	931	22.5	2.47	—	0.133	0.033
Av.	258.9	119	14.6	4.4	1.77	2.1	0.3

* Concentration in the remaining tissues is taken as being that of the lowest positive concentration in organs sampled.

primary cancer, sometimes ask if the radioisotope, that the deceased was potentially exposed to, was found in high concentration in the primary cancer. Most scientists feel that the likelihood of such findings is remote. The reasoning is that if the radioisotope was present in the original one or small number of cells, that became malignant, after millions of divisions to form the cells of the tumor, the concentration would become extremely low, unless malignant cells preferentially concentrate the isotope, being released from other body sites, or newly entering the body. This has not been found to occur in animal studies.

Studies in a terminal cancer case injected with radioactive sulfur-35 showed highest concentration at autopsy 13 days later in cancer of the breast and in the bone marrow (SIEGEL *et al.*, 1959). GOTTSCHALK *et al.* (1959) also found a relatively high concentration of ^{35}S in tumor tissue (chondrosarcoma) and in bone marrow and a rapid turnover in most tissues. In such cases, apparently the sulfur-35 did not cause the cancer but the cancer cells were a favoured site of deposition—at least for a relatively short time. It is not expected that ^{239}Pu would act in this manner since there is no reason to expect ^{239}Pu to enter into the metabolic processes of the cell.

CONCENTRATION OF Pu IN MICROSCOPIC AREAS

In estimating potential for injury, it is very important to determine, as accurately as possible, the location of transuranium elements in tissue components such as in cells. This has been done in animal studies where the larger concentrations have made alpha track counting practical. Some effort in this direction has been made to determine Pu location in human bone. With the very small depositions, neutron activation and fission track dosimetry will be used. Methodology is being perfected and it is hoped that such techniques may be used with increasing frequency to determine more exactly the location of Pu in such tissues as lung and bone under varying exposure conditions.

SYSTEMIC Pu BURDENS—AUTOPSY FINDINGS vs ESTIMATES FROM URINE

Table 5 shows systemic Pu burdens determined from autopsy findings as compared to systemic burdens estimated from the output of Pu in urine in 30 cases. Plutonium in lung, tracheobronchial lymph nodes and wounds is not included in the systemic burden since these may not be estimated by urine sampling with much confidence. These are generally measured separately with a chest or a wound counter.

Installations vary some in the levels of Pu in the urine which they consider positive, depending upon the level of background measurements and the laboratory policies. From Table 5 it may be noted, however, that in all cases with a determination of a systemic burden of plutonium greater than 4% of maximum permissible by autopsy; the estimates before death from urinalysis were higher by factors ranging up to 6.7. Table 5 also lists the organs with highest concentration. It may be seen that, in the 30 cases, highest organ concentration occurred the following number of times: TBLN—12, lungs—6, liver—6, axillary lymph nodes—1 (wound deposition case), abdominal LN—1, muscle—1, pancreas—1, spleen—1 and thyroid—1.

CAUSES OF DEATH

It will be seen from Table 5 that the usual causes of death were encountered. Some of these were discussed in a previous paper (NORWOOD *et al.*, 1973). There were two cases of lymphatic leukemia, 02DO 0235 and 02DO 0444. Case 02DO 0235 was one of chronic lymphatic leukemia which has not been associated with radiation exposure in animals to date or in the Nagasaki, Hiroshima cases. The deposition of Pu found at autopsy in both of these cases was extremely low, being less than 1% of the permissible (40 nCi).

ORGAN DOSE DUE TO DEPOSITED Pu

In order that models may be developed to indicate the metabolism of Pu, it becomes important to relate the content of organs at given times following its introduction into the body to the initial deposit. Animals are sacrificed at varying times following introduction of Pu of measured particle size and chemical composition and such determinations are made. As humans bearing ^{239}Pu, come to autopsy it becomes important to obtain this same kind of information. For example, at one installation, several employees received measurable deposition of

Table 5. Comparison of systemic burden estimates—urinalysis vs autopsy

Case designation	Age at death	Cause of death	Installation	Autopsy %MPSB (40 nCi)	Urine %MPSB	Ratio Est-urine / Est-autopsy	Organ with maximum concentration of Pu
01AT 0100	54	Coronary infarction	01	6.4	40	6.3	TBLN
01TM 0004	81	General debility–Coronary insuf.		0.68	3.4	5.0	Liver
01AT 0391	67	Carcinoma (bronchogenic)		0.55	min	min / 0.55	Muscle
01TM 0002	70	Multiple–emphysema–atherosclerosis		0.16	1	6.3	Liver
01TM 0006	66	Ischemic heart disease		105	90	0.86	Liver
01JA 0023	62	Bronchogenic carcinoma		0.02	min	min / 0.02	Pancreas
01AT 0227	64	Coronary infarction		0.15	min	min / 0.15	TBLN
01TM 0049	66	Suicide		0.63	min	min / 0.63	Liver
05TM 0005	60	Undifferentiated CA—Primary site undetermined	05	110*	200*	1.8	TBLN
02DO 0713	58	Acute myocardial infarction	02	2.3	13.5	5.9	TBLN
02DO 0712	50	Acute myocardial infarction		0.3	0	0 / 0.3	Lungs
02DO 0711	50	Acute myocardial infarction		0.4	0	0 / 0.4	TBLN
02DO 0709	41	Methanol poisoning		3.8	0	0 / 3.8	Spleen (lung lost)
02DO 0710	56	Brain tumor (astrocytoma)		0.9	0	0 / 0.9	Lungs
02DO 0002	64	Carcinoma of bladder		3.8	8.0	2.1	Lungs
02DO 0001	29	Suicide		1.75	<3.0	<3.0 / 1.75	TBLN
02DO 0003	48	Cancer of stomach		1.2	0	0 / 1.2	TBLN
02DO 0036	59	Complications of heart surgery		156.0	541.0	3.5	Liver
02DO 0235	63	Chronic lymphatic leukemia	02	0.3	0	0 / 0.3	Lung
02DO 0040	49	Suicide		1.5	5.4	3.6	Axillary LN
02DO 0355	50	Cardiac embolism pulmonary		2.0	6.4	3.2	Lung
02DO 0444	65	Acute lymphoblastic leukemia		0.5	0	0 / 0.5	TBLN
02TM 0002	63	Ruptured aneurysm		1.3	<3.0	<3.0 / 1.3	Liver
02AE 0006	55	Adenocarcinoma–bronchus and lung		0.6	0	0 / 0.6	TBLN
02DO 0449	60	Myocardial infarction		0.3	0	0 / 0.3	TBLN
02DO 0627	49	Melanoma—primary site undetermined		0	0	Bkg. / Bkg.	TBLN
02DO 0629	46	Adenocarcinoma of kidney with metastases		0.6	0	0 / 0.6	TBLN
02DO 0622	51	Auto accident		0	0	0 / 0	Lung
02TM 0009	53	Cirrhosis of liver Liver		8.7	19	2.2†	Abdominal lymph nodes
02DO 0237	60	Myocardial infarction with ventricular wall rupture		0.23	0	0 / 0.23	Thyroid

* Total body deposition. Lung deposition at autopsy—27.08 nCi, TBLN—1.33 nCi. min = minimum systemic deposition— < 0.2 dpm in daily urine sample.

† Pre-autopsy estimate of lung and TBLN deposit was zero while at autopsy 9.2 nCi were found.

high fired plutonium oxide due to a fire involving plutonium. Sizes of the particles in the vicinity were measured. As some of these employees come to autopsy organ depositions may be related to the inhalation of this chemical form and size of Pu particles. As the retention of depositions is related to time it becomes possible to estimate organ dose, assuming uniform distribution.

As detailed studies indicate concentration factors and distribution, these may be applied to determine dose in rems. Since no isotope of Pu is available for human experimentation, such methods of human study, while very slow and costly, appear to be the only way to secure good human data.

CONCLUSIONS

From an analysis of 30 autopsies of plutonium workers, some tentative conclusions may be drawn as follows:

(1) Deposition of plutonium in the human body is generalized. To understand the metabolism of this element in man it becomes necessary to determine concentration in many different organs at specific times following incorporation of the compound of specific physical and chemical composition. It is also important to study detailed histological depositions to determine effect of large doses caused by a particle or concentration of particles in a tissue.

(2) Highest concentrations have been found in tracheobronchial lymph nodes, lung and liver in 26 of the autopsies, while highest concentrations were found in a single autopsy in axillary lymph nodes (hand wound), abdominal lymph nodes, muscle, pancreas, spleen and thyroid.

(3) Deposition in muscle, fat and skin, which account for much of the body mass, is usually quite low amounting to about 3% of the total deposition.

(4) Assuming uniform distribution, concentration of Pu in bone was not greatest in any case. Total bone content was greater than any other organ in a few cases. Since a relatively small portion of the entire skeleton is obtainable at autopsy and considerable variation occurs in concentration in various bones the error in extrapolating to the total skeleton may be large. Willed bodies with estimated total depositions exceeding 5 nCi of Pu are needed to better assess the deposition in most of the individual bones and muscles not readily obtainable at the usual autopsy.

(5) Critical organs may be bone, lung, liver, lymph nodes, the area of a plutonium wound or possibly others.

(6) More careful analysis of conditions surrounding accidental depositions is needed. The parameters of most importance appear to be solubility of the particles under conditions in the lungs, particle size and other physical characteristics, chemical composition and time of deposition and method of entry into the body. In operating practice particles may be assumed to be polymeric, that is of diameter greater than 0.01 μm unless proven otherwise.

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