2015 DOE Annual Occupational Medicine Workshop and Webinar (OMWW)
March 16-17, 2015, Washington, DC

US Transuranium and Uranium Registries and Research

Sergei Y. Tolmachev, Director

US Transuranium and Uranium Registries
College of Pharmacy, Washington State University

1845 Terminal Drive, Suite 201, Richland, WA 99354
www.ustur.wsu.edu

"Learning from Plutonium and Uranium Workers"

Acknowledgment

- Maia Avtandilashvili
- Florencio Martinez
- Stacey L. McComish
- Brian W. Miller
- George Tabatadze
- Elizabeth M. Thomas
- William J. Bair
- Alan Birchall
- Ronald E. Goans
- Ronald L. Kathren
- Richard E. Toohey
- Joey Y. Zhou

Annual BBQ with Friends and Families

Part I: What is the USTUR?

History and Mission

- 1966: US AEC meeting "Plutonium Contamination in Man"

Follow up occupationally exposed workers, from exposure through full lifespan, by studying the biokinetics (uptake, translocation and retention), and tissue dosimetry of the actinides

- 1968: National Plutonium Registry established at the Hanford Environmental Health Foundation (HEHF)
- 1978: US Uranium Registry established at the HEHF
- 1987: Two programs merged into the US Transuranium and Uranium Registries (USTUR)
- 1992: DOE grant to Washington State University for the management and operation of the USTUR

USTUR Registrants

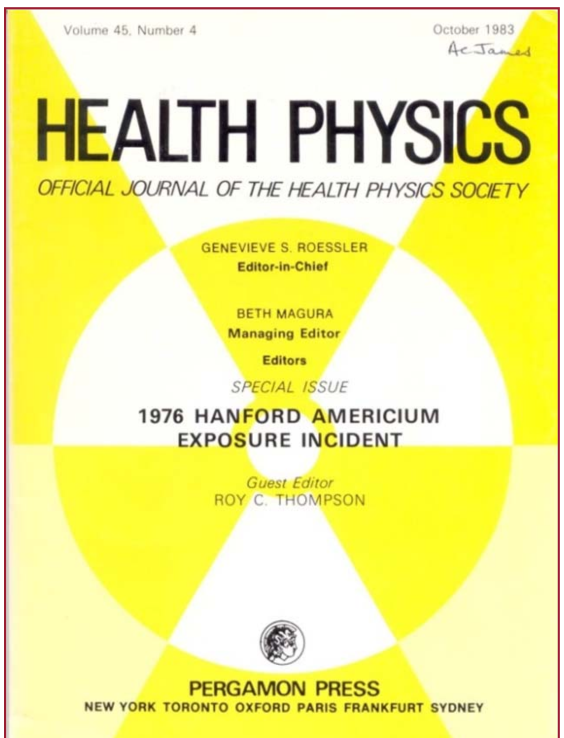
- Voluntary Tissue Donors (Posthumous)
- Former Nuclear Workers from DOE Sites
- Known (Documented) Radiation Exposure History
- Exposure Criteria:

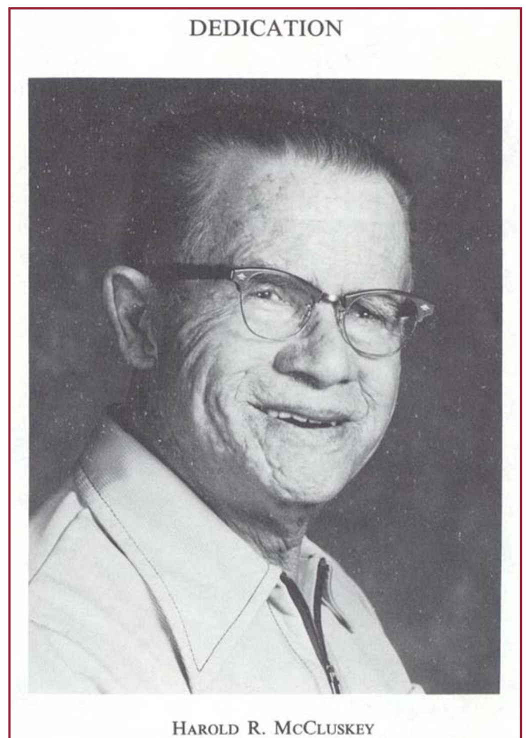
  Actinide internal deposition of ≥74 Bq (2 nCi)

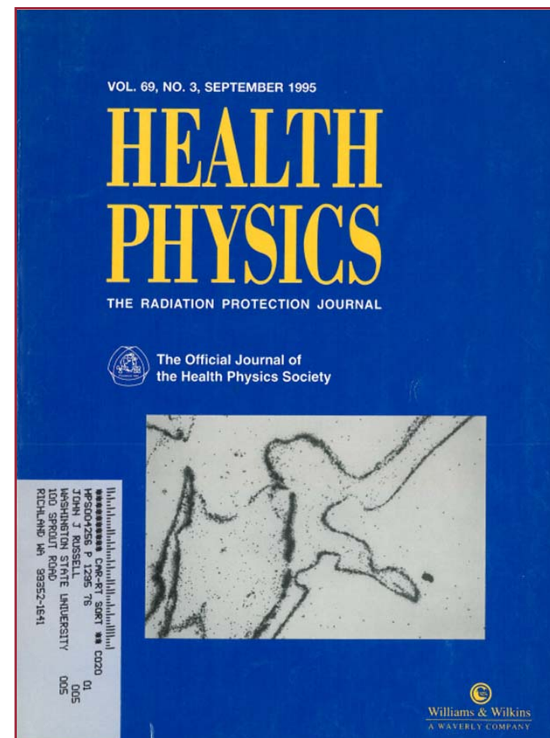
  External dose to the whole body ≥0.1 Sv (10 rem)

Landmark: (i) 1976 Hanford ^{241}Am Incident – ‘Atomic Man’ –

- Explosion of ion-exchange column with ~ 150 g ^{241}Am (19 TBq = 515 Ci)
- Chemical operator injured: acid burns, superficial cuts (face/upper body)
- Estimate of uptake > 40 MBq (1,080 µCi) – Ca/Zn-DTPA chelation therapy
- Systemic deposition – 0.5 MBq (13 µCi)

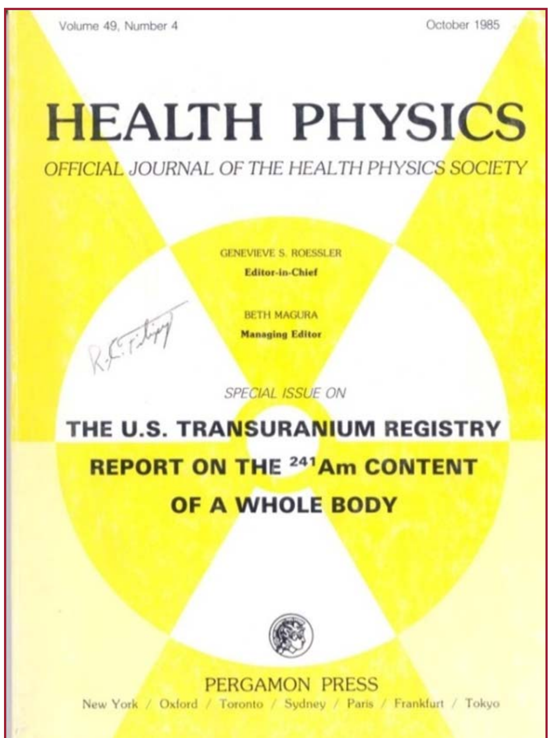


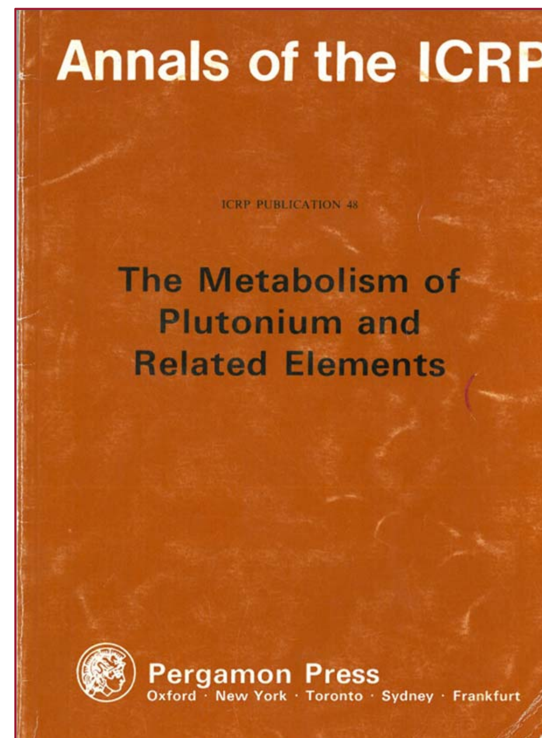




Landmark: (ii) 1979 First Whole-Body Donation

- Donor (radiochemist) worked with unsealed ^{241}Am source (1952 – 1954)
- First indication of intake was detection of ^{241}Am in urine sample (1958 routine surveillance program) – No chelation therapy
- Contemporary estimate of intake: 8 – 40 kBq (0.23 – 1.1 µCi)





USTUR Today

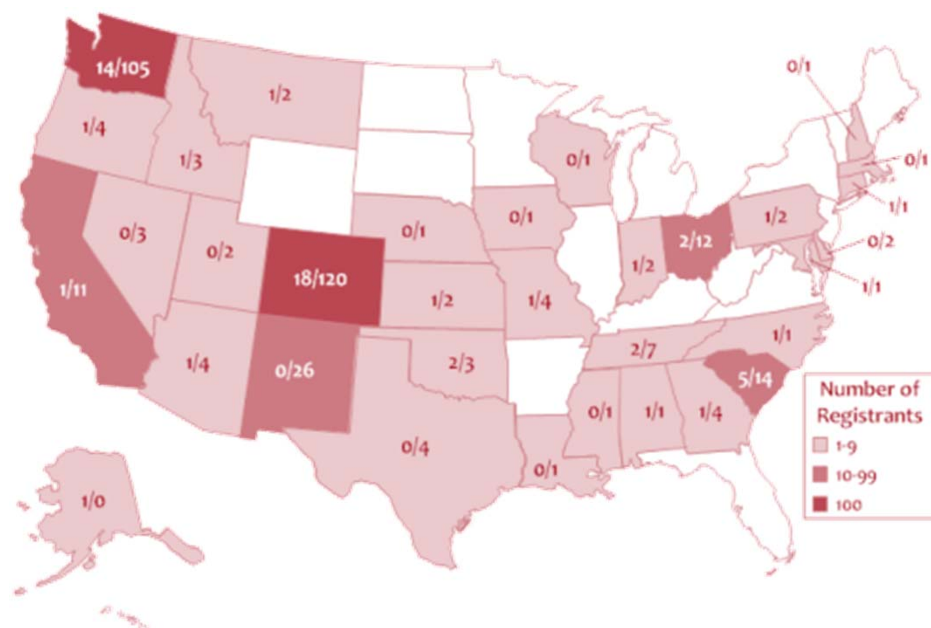
- The United State Transuranium and Uranium Registries (USTUR) is a federal-grant program funded by the U.S. Department of Energy (DOE) Office of Domestic and International Health Studies (AU-13)
- Operated by College of Pharmacy at Washington State University under Internal Review Board #11573-011

- Current 5-y Grant Period: April 1, 2012 – March 31, 2017
- Awarded Annual Budget: $900,000
- Supported Personnel: 6.0
- DOE Program Manager: Dr. Joey Zhou
- Location: Richland, WA
- Website: **www.ustur.wsu.edu**

Registrant Statistics

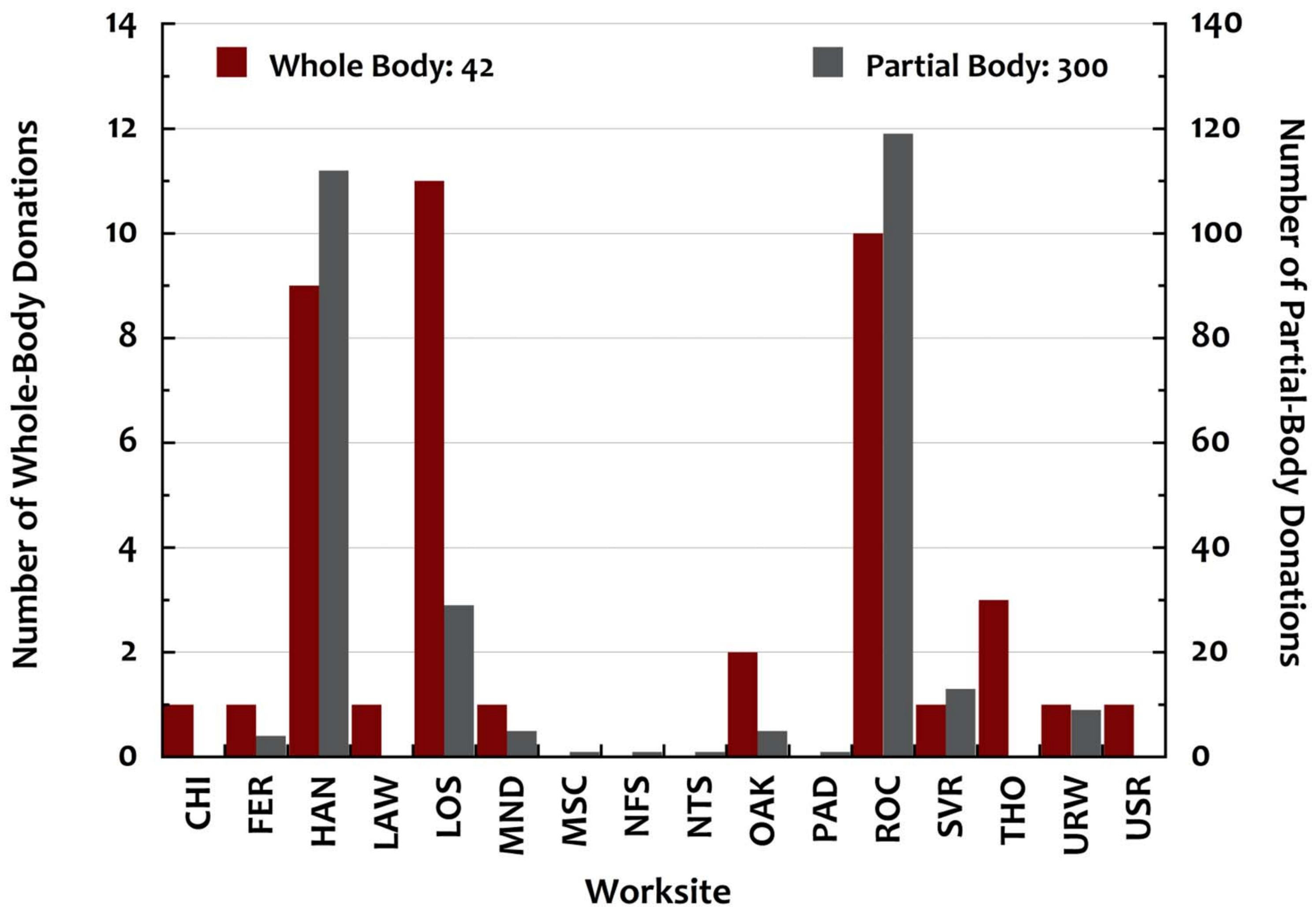
- Living Registrants: 58
  - *Whole-body donors: 8*
  - *Partial-body donors: 44*
  - *Special studies†: 6*
- Deceased Registrants: 347
  - *Whole-body donors: 42*
  - *Partial-body donors: 300*
  - *Special studies: 5*

† - not a tissue donor



Living/Deceased Registrants

Donations by Worksite

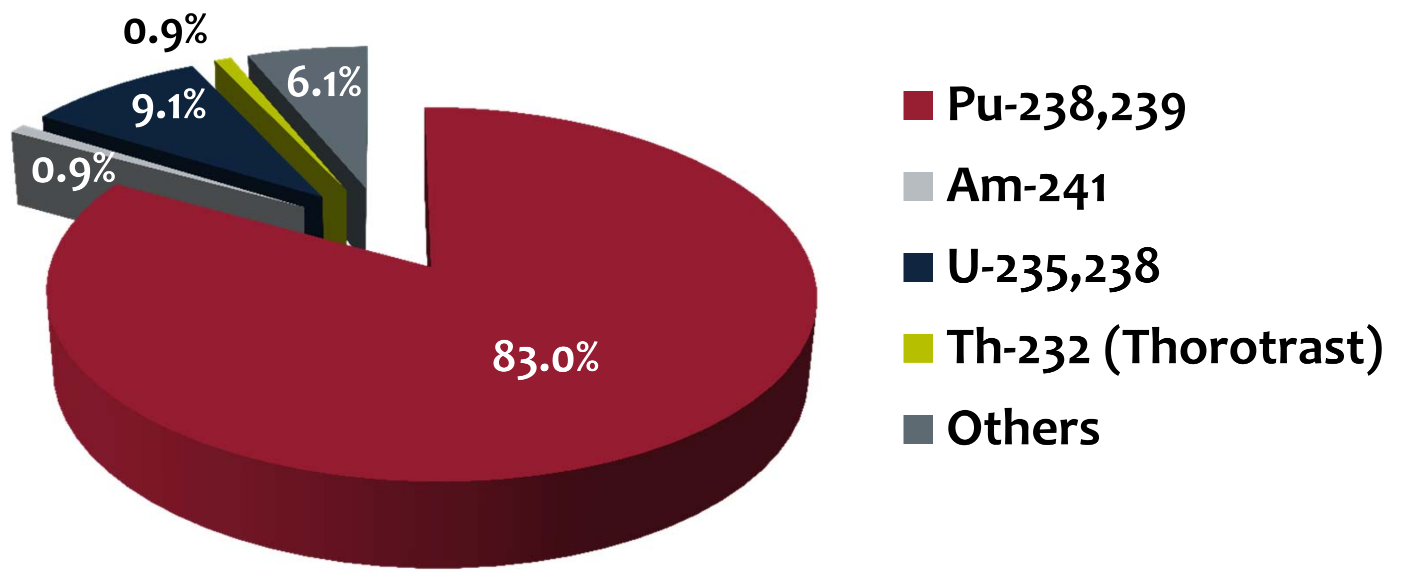


USTUR Demographics

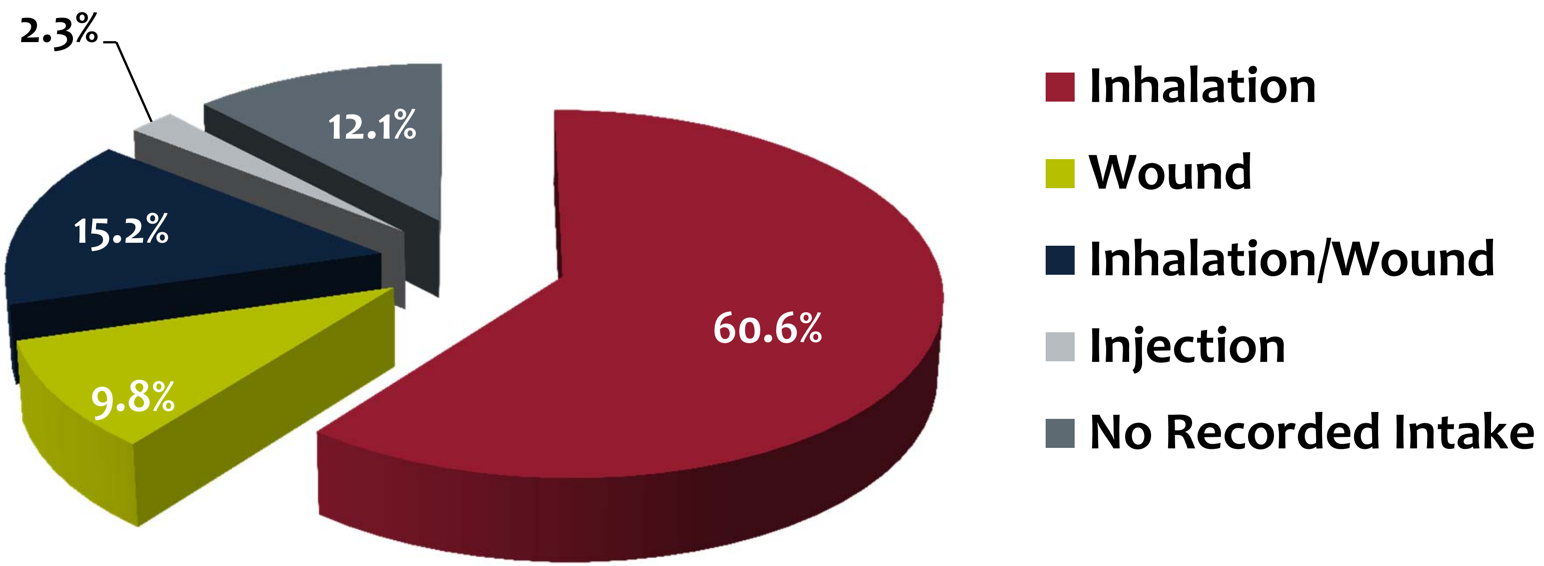
Age, y	Whole-Body	Partial-Body
Living		
Mean ± SD	80±9	82±10
Median	79	83.5
Range	63 – 90	44 – 94
Deceased		
Mean ± SD	79±11	68±13
Median	81	68
Range	49 – 96	25 – 97

(i): Occupational Exposure to Actinides

Primary Radionuclide of Exposure



Primary Route of Intake



(ii): Industrial Hygiene and Pathology

Self-reported Exposure to Asbestos

- Living Registrants:
  - *Reported – 28*
  - *Not reported – 21*
  - *Unknown – 3*
- Deceased Registrants:
  - *Reported – 67*
  - *Not reported – 115*
  - *Unknown – 160*

CHEMICAL EXPOSURE

		From	To
Beryllium	Y		
Chlorinate Solvents			
Other Toxic chemicals			
Asbestos	Y	1/1/1982	12/31/1984
Benzene, Tolluene			

Self-reported work with, work around, or exposure to chemicals taken from USTUR questionaires. A questionaire was completed at intake and in 5-y intervals after intake.

USTUR Database – "Chemical Exposure" Form

Self-reported Exposure to Beryllium

- Living Registrants:
  - *Reported – 29*
  - *Not reported – 19*
  - *Unknown – 10*
- Deceased Registrants:
  - *Reported – 79*
  - *Not reported – 110*
  - *Unknown – 153*

CHEMICAL EXPOSURE

		From	To
Beryllium	Y	1/1/1956	12/31/1988
Chlorinate Solvents	Y	1/1/1956	12/31/1988
Other Toxic chemicals	Y	1/1/1956	12/31/1988
Asbestos	Y	1/1/1956	12/31/1988
Benzene, Tolluene	Y	1/1/1956	12/31/1988

Self-reported work with, work around, or exposure to chemicals taken from USTUR questionaires. A questionaire was completed at intake and in 5-y intervals after intake.

USTUR Database – "Chemical Exposure" Form

Pathology Database

- Personal Data: *De-identified*
- Information: *Death Certificate/Autopsy Report*
- Code: *ICD-9-CM and ICD-10*
- Report:

  Underlying Cause of Death (Rank 0)

  Contributing Cause of Death (Rank 1 – 7)
- Search:

  Case Number

  ICD-9/ICD-10 Code

  ICD Keyword

  Examiner's Notes

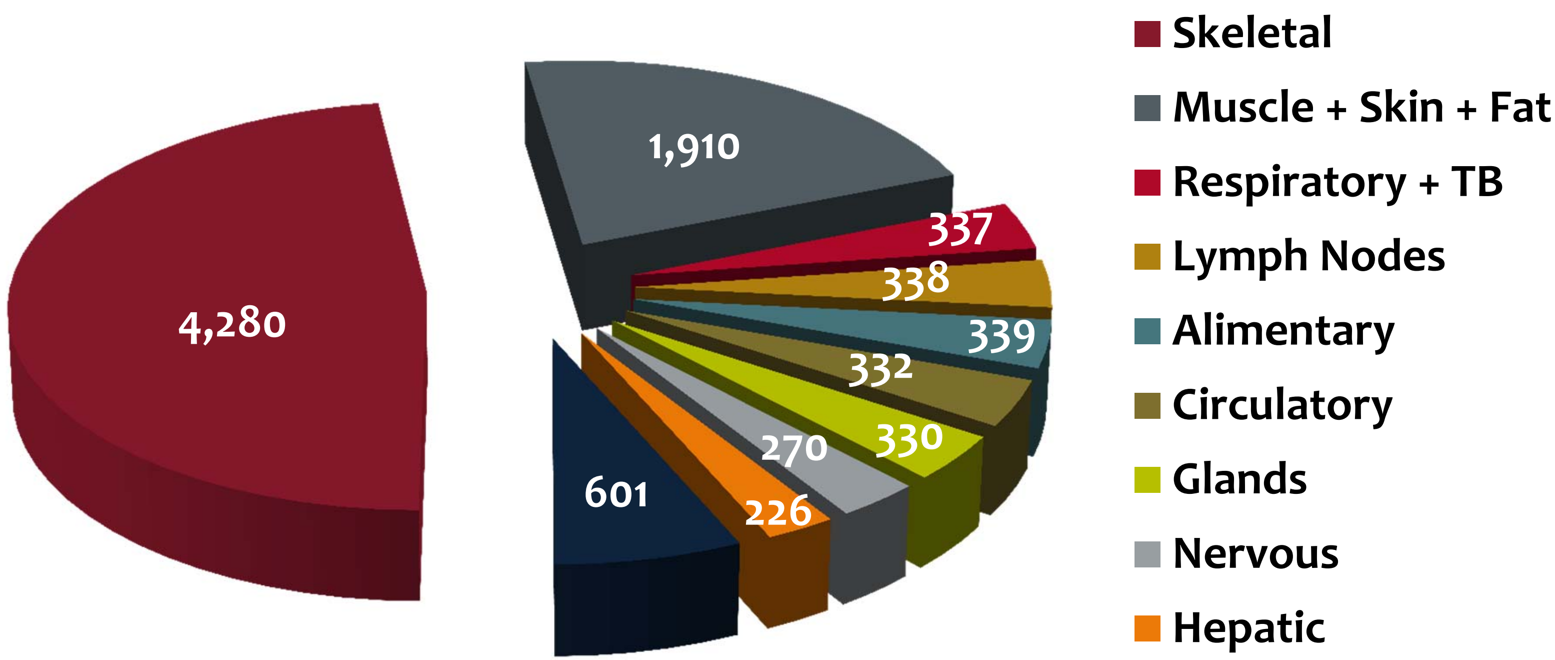
USTUR Laboratory Facility

- Radiochemistry Laboratory
- Autopsy Room
- National Human Radiobiology Tissue Repository (NHRTR)

6,500 sq. ft. building at Richland Airport Industrial Area

USTUR/NHRTR Tissue Samples

- NHRTR holds 8,963 frozen tissue samples from 142 donations



THEMIS Electronic Inventory Database Statistics

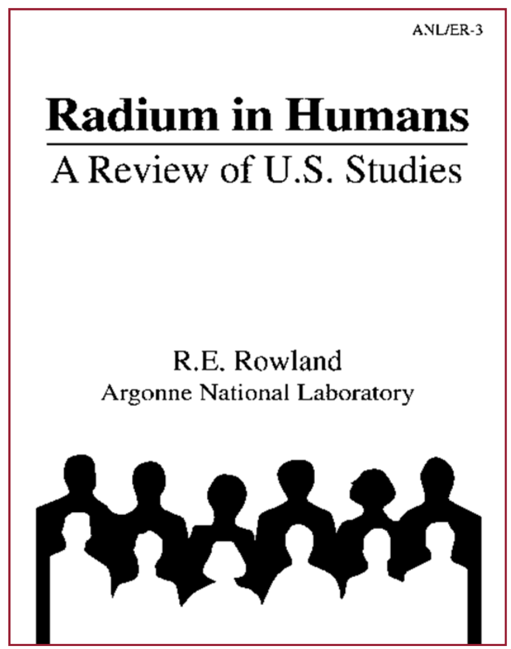
Inside NHRTR

NHRTR: *US Radium Studies*

- Frozen tissues, dry/plastic-embedded bones, pathology slides

  Radium Dial Painters: NJRRP → MIT → ANL

  Medical exposure: therapeutic injections



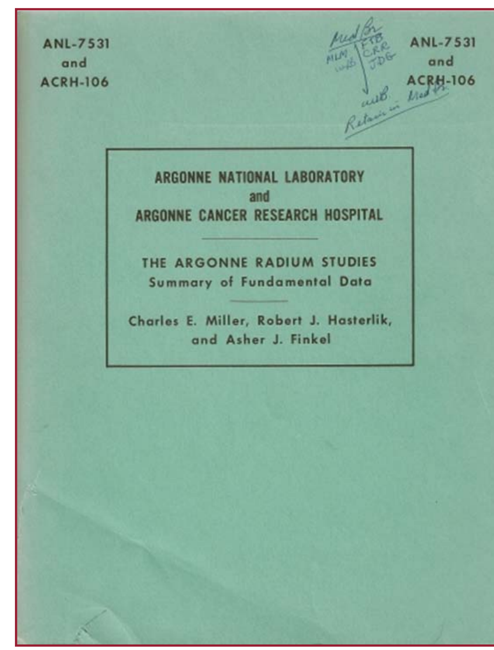
ANL/ER-3

Radium in Humans

A Review of U.S. Studies

R.E. Rowland

Argonne National Laboratory



ANL-7531 and ACRH-106

ANL-7531 and ACRH-106

ARGONNE NATIONAL LABORATORY and ARGONNE CANCER RESEARCH HOSPITAL

THE ARGONNE RADIUM STUDIES

Summary of Fundamental Data

Charles E. Miller, Robert J. Hasterlik, and Asher J. Finkel

NHRTR: *Plutonium Injection Studies*

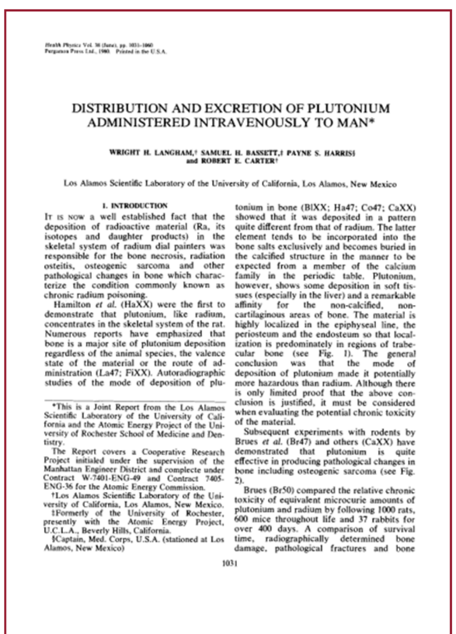
- Dry and plastic-embedded bones

  CHI-1: 6.5 µg (14.9 kBq) i.v. injection $^{239}Pu^{4+}$- citrate; M 68

  HP-2: 5.1 µg (11.7 kBq) i.v. injection $^{239}Pu^{4+}$- citrate; M 49

  HP-4: 4.9 µg (11.2 kBq) i.v. injection $^{239}Pu^{4+}$- citrate; F 18

  HP-9: 6.3 µg (14.5 kBq) i.v. injection $^{239}Pu^{4+}$- citrate; M 66



Health Physics Vol. 38 (June), pp. 1031-1060
Pergamon Press Ltd., 1980. Printed in the U.S.A.

DISTRIBUTION AND EXCRETION OF PLUTONIUM ADMINISTERED INTRAVENOUSLY TO MAN*

WRIGHT H. LANGHAM,† SAMUEL H. BASSETT,‡ PAYNE S. HARRIS§ and ROBERT E. CARTER†

Los Alamos Scientific Laboratory of the University of California, Los Alamos, New Mexico

I. INTRODUCTION

It is now a well established fact that the deposition of radioactive material (Ra, its isotopes and daughter products) in the skeletal system of radium dial painters was responsible for the bone necrosis, radiation osteitis, osteogenic sarcoma and other pathological changes in bone which characterize the condition commonly known as chronic radium poisoning.

Hamilton *et al.* (HaXX) were the first to demonstrate that plutonium, like radium, concentrates in the skeletal system of the rat. Numerous reports have emphasized that bone is a major site of plutonium deposition regardless of the animal species, the valence state of the material or the route of administration (La47; FiXX). Autoradiographic studies of the mode of deposition of plutonium in bone (BlXX; Ha47; Co47; CaXX) showed that it was deposited in a pattern quite different from that of radium. The latter element tends to be incorporated into the bone salts exclusively and becomes buried in the calcified structure in the manner to be expected from a member of the calcium family in the periodic table. Plutonium, however, shows some deposition in soft tissues (especially in the liver) and a remarkable affinity for the non-calcified, non-cartilaginous areas of bone. The material is highly localized in the epiphyseal line, the periosteum and the endosteum so that localization is predominately in regions of trabecular bone (see Fig. 1). The general conclusion was that the mode of deposition of plutonium made it potentially more hazardous than radium. Although there is only limited proof that the above conclusion is justified, it must be considered when evaluating the potential chronic toxicity of the material.

Subsequent experiments with rodents by Brues *et al.* (Br47) and others (CaXX) have demonstrated that plutonium is quite effective in producing pathological changes in bone including osteogenic sarcoma (see Fig. 2).

Brues (Br50) compared the relative chronic toxicity of equivalent microcurie amounts of plutonium and radium by following 1000 rats, 600 mice throughout life and 37 rabbits for over 400 days. A comparison of survival time, radiographically determined bone damage, pathological fractures and bone

*This is a Joint Report from the Los Alamos Scientific Laboratory of the University of California and the Atomic Energy Project of the University of Rochester School of Medicine and Dentistry.

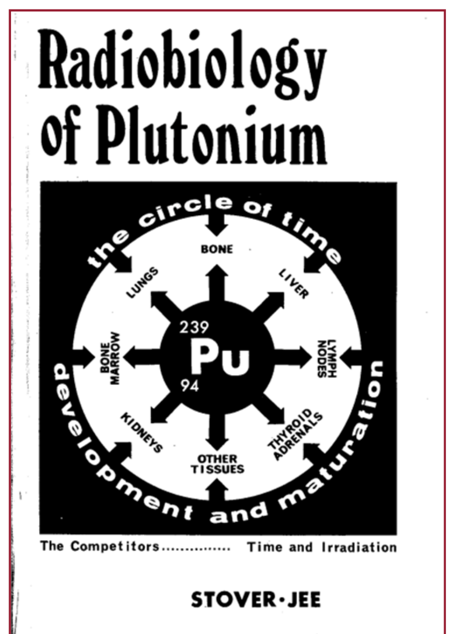
The Report covers a Cooperative Research Project initialed under the supervision of the Manhattan Engineer District and complecte under Contract W-7401-ENG-49 and Contract 7405-ENG-36 for the Atomic Energy Commission.

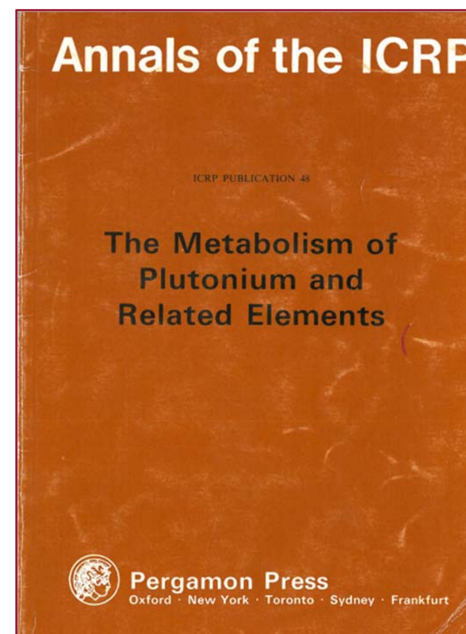
†Los Alamos Scientific Laboratory of the University of California, Los Alamos, New Mexico.

‡Formerly of the University of Rochester, presently with the Atomic Energy Project, U.C.L.A., Beverly Hills, California.

§Captain, Med. Corps, U.S.A. (stationed at Los Alamos, New Mexico)

1031





Part II: USTUR Research

Primary Research: Biokinetic Modeling and Dosimetry

Development, validation, and parameterization

Inhalation

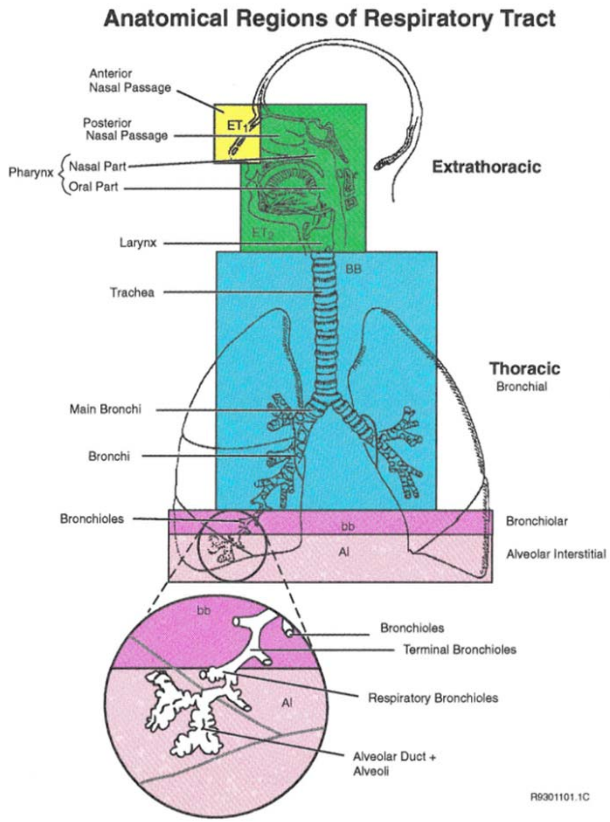
- *Americium Oxide (AmO_2)*
- *Refractory Plutonium Oxide (PuO_2)*
- *Plutonium Nitrate [$Pu(NO_3)_4$]*
- *Uranium Hexafluoride (UF_6)*

Wound

- *Americium Nitrate [$Am(NO_3)_3$]*
- *Plutonium Nitrate [$Pu(NO_3)_4$]*
- *Plutonium Oxide (PuO_2)*

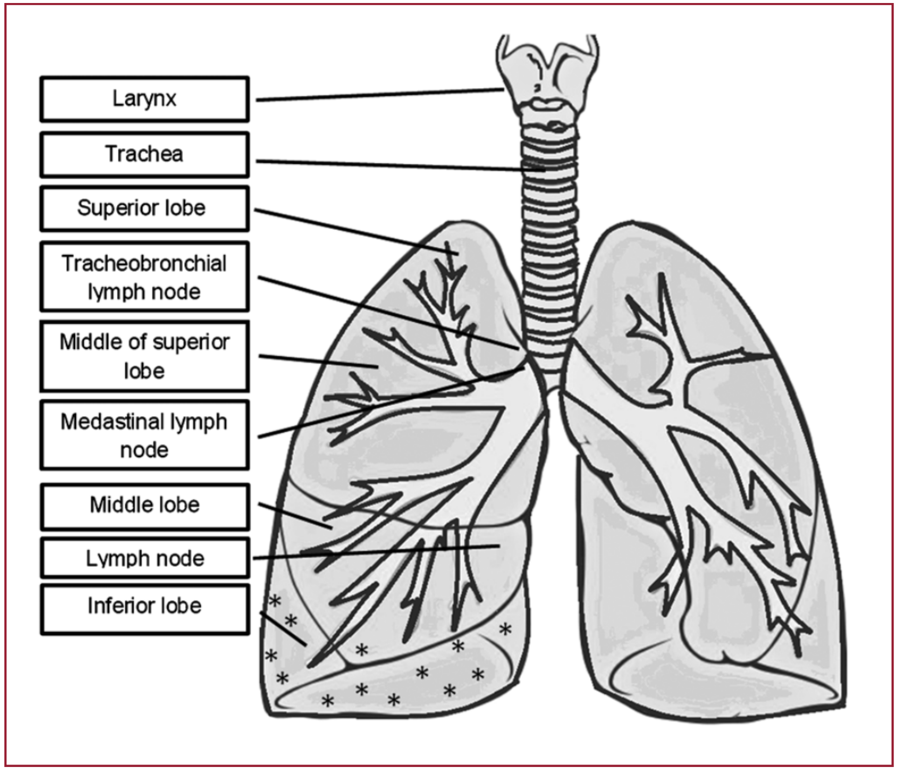
Chelation

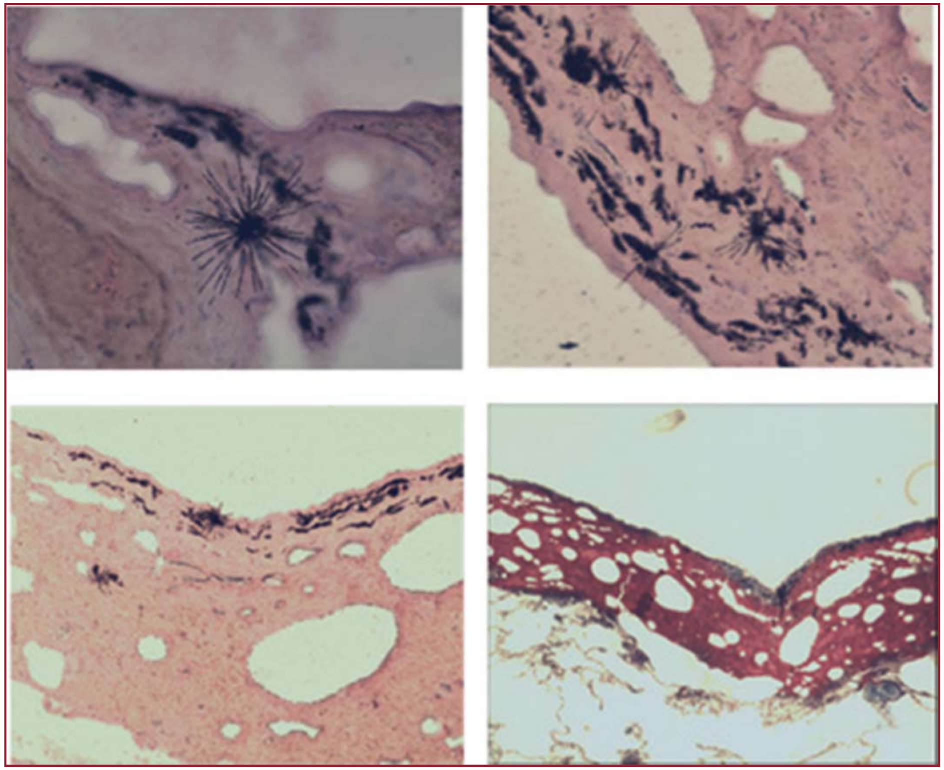
- *Americium Oxide (AmO_2)*
- *Americium Nitrate [$Am(NO_3)_3$]*
- *Plutonium Nitrate [$Pu(NO_3)_4$]*



Courtesy of W.J. Bair

Microdistribution and Long-term Retention of $^{239}Pu(NO_3)_4$





Nielsen, C. E., Wilson, D. A., Brooks, A. L., McCord, S. L., Dagle, G. E., James, A. C., Tolmachev, S. Y., Thrall, B. D. and Morgan, W. F. *Microdistribution and long-term retention of $^{239}Pu(NO_3)_4$ in the respiratory tracts of an acutely exposed plutonium worker and experimental beagle dogs.* Cancer Research. 72, 5529-36 (2012).

Carcinogenic and Inflammatory Effects of $^{239}Pu(NO_3)_4$

- Analysis: to determine genetic and inflammatory response pathways following plutonium exposure

  Possible pathways - tissue injury, apoptosis, and gene expression modifications

- Immunohistochemistry: to characterize lung lesions, visualize interstitial fibrosis, and other pathology
- RT-PCR: to quantify the expression of chemokine/cytokine regulatory genes thought to be involved in inflammation and carcinogenesis

  BCL-2, CASP-3, FASL, IL4, IL8 and TGFß-1

Nielsen, C. E., Wang, X., Robinson, R. J., Brooks, A. L., Lovaglio, J., Patton, K. M., McComish, S. L., Tolmachev, S. Y. and Morgan, W. F. *Carcinogenic and inflammatory effects of plutonium-nitrate retention in an exposed nuclear worker and beagle dogs.* Int J Radiat Biol. 90, 60-70 (2014).

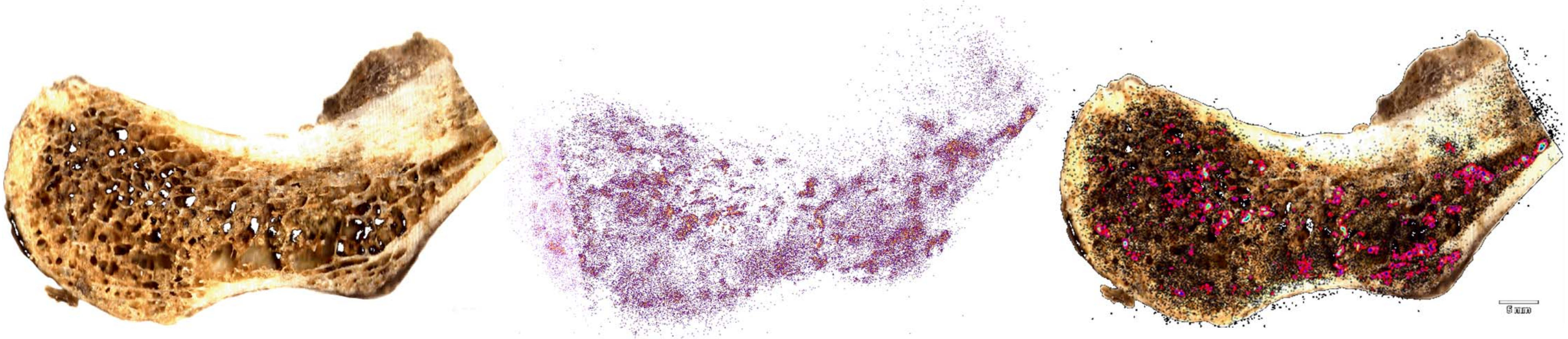
Radionuclide Bone Microdosimetry

- Digital Autoradiography: ionizing-radiation Quantum Imaging Detector (iQID)
- Radionuclides: ^{239}Pu, ^{226}Ra, ^{241}Am

  Plutonium injection study – ^{239}Pu: 14.9 kBq (0.4 μCi)

  Radium therapeutic injection – ^{226}Ra: 9.3 MBq (250.2 μCi)

  Occupational exposure – ^{241}Am: 40 MBq (1,080 μCi)



G. Tabatadze, B. W. Miller, S. Y. Tolmachev. *Radionuclide distribution measurement within anatomical bone structures using digital autoradiography.* (2015 in preparation)

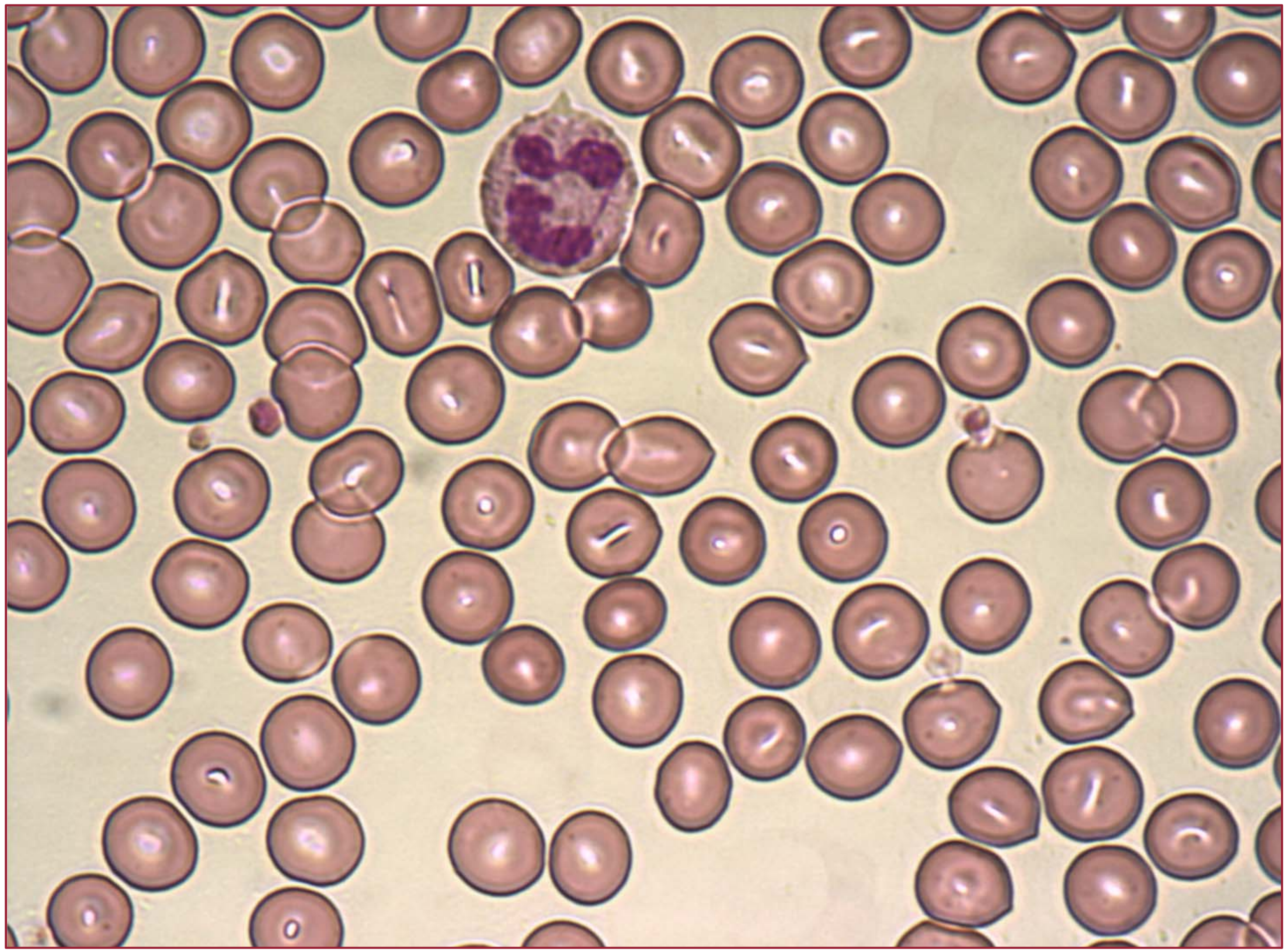
Biodosimetry of Incorporated Radionuclides

- Pelger-Huët Anomaly (PHA) in blood cells

Goans, R. E., Iddins, C. J., Christensen, D., Wiley, A. and Dainiak, N. Appearance of pseudo-Pelger Huet anomaly after accidental exposure to ionizing radiation in vivo. Health Phys. 108, 303-7 (2015)

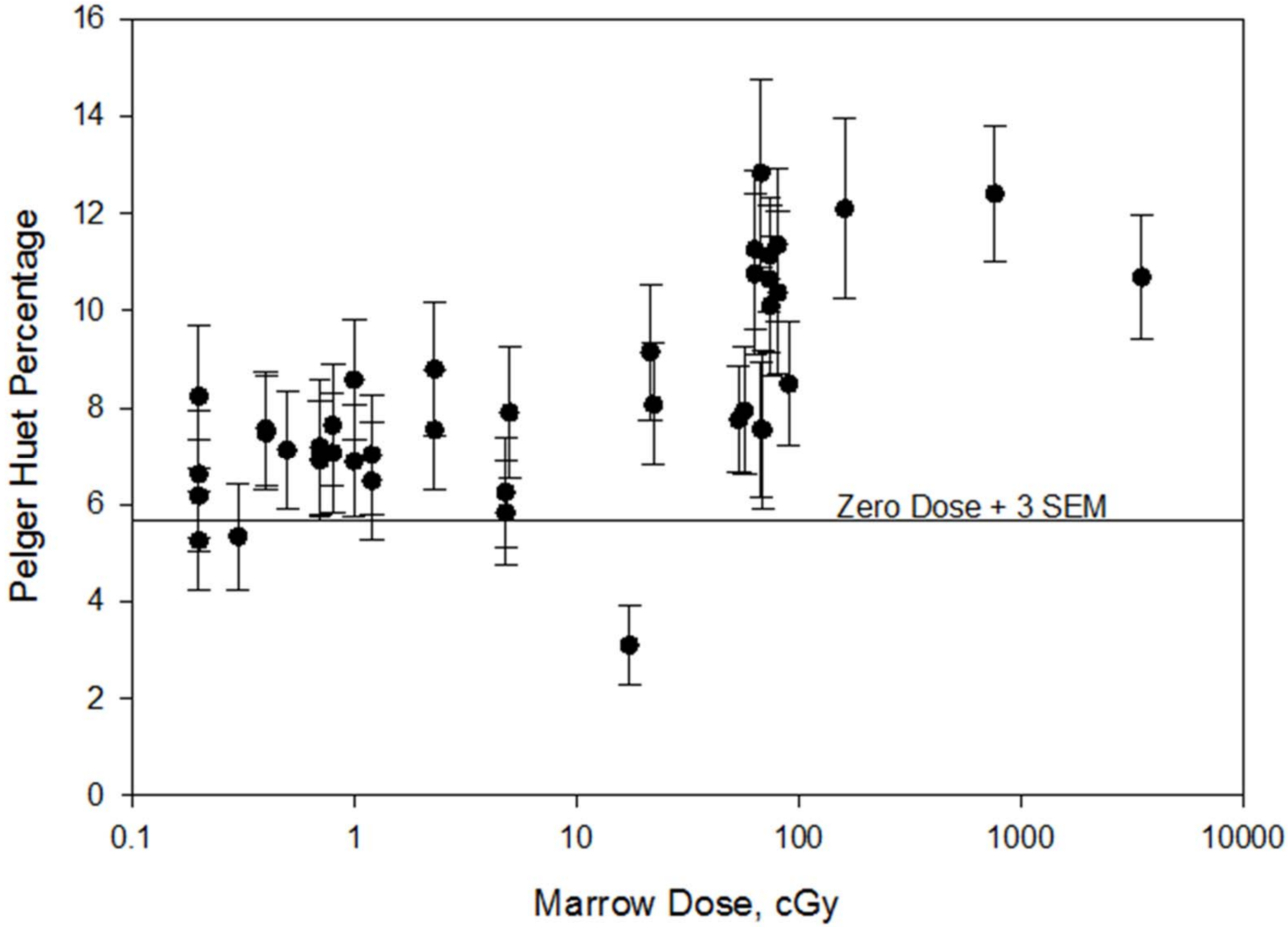
- Study of Radium Dial Painters
- Internal exposure to ^{226}Ra and ^{228}Ra
- Exposure in 1915 – 1925
- Exposure time 4 – 208 weeks
- Bone marrow dose 0.1 cGy – 3,400cGy
- Peripheral blood slides prepared in 1970 – 1975

New, Permanent Radiation-induced Biomarker



Pelger-Huët Anomaly: RDP 09-064; Started 1916; Exposed for 9 weeks

PHA – Marrow Dose Correlation



Part III: Significance of the USTUR Research

Half Century of Research

DOE International Health Studies and Activities

- *Atomic Bomb Casualty Commission / Radiation Effects Research Foundation (1946)*

DOE Domestic Health Studies and Activities

- *National Plutonium Registry/US Transuranium and Uranium Registries (1968)*

Academic Outreach

Since 1992

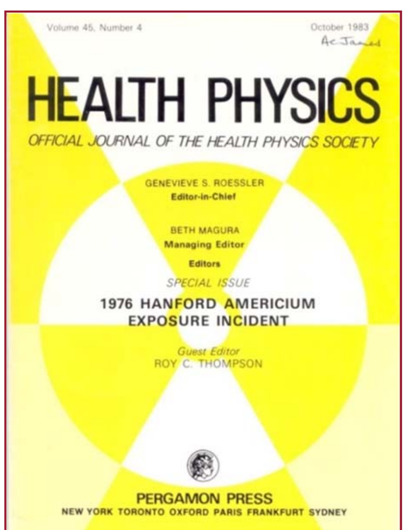
- Undergraduate Training – over 15
- Graduate Research Projects

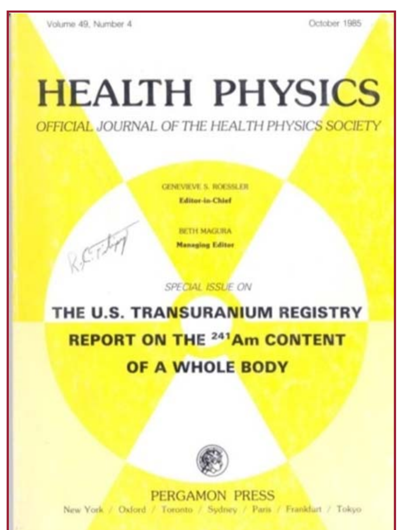
  Master – 8

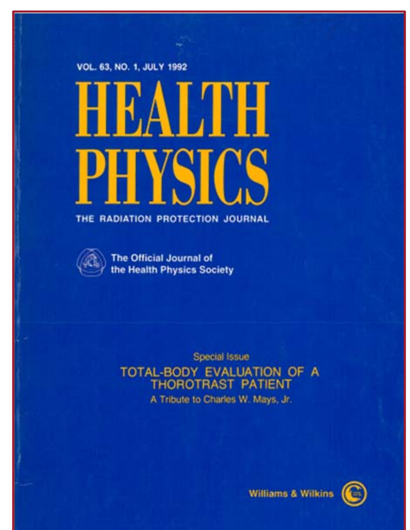
  PhD – 6

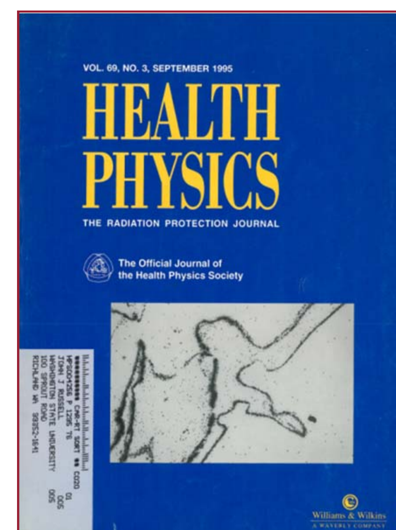
Health Physics Journal Special Issues

- 1983, 45 (4): *1976 Hanford Americium Exposure Incident*
- 1985, 49 (4): *The U.S. Transuranium Registry Report on the ^{241}Am Content of a Whole Body*
- 1992, 63 (1): *Total-body Evaluation of a Thorotrast Patient*
- 1995, 69 (3): *1976 Hanford Americium Exposure Incident: Update*









Impact on National Council on Radiation Protection & Measurements

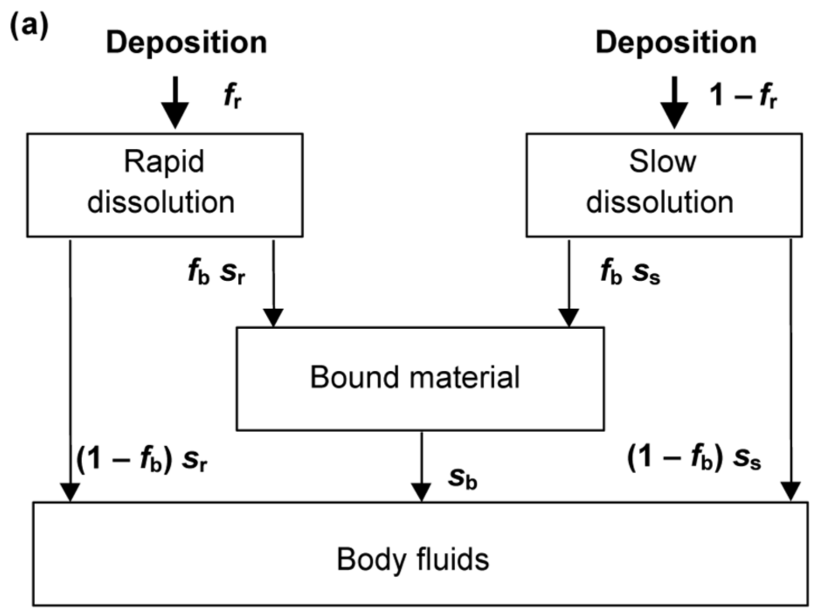
- Report 164: *Uncertainties in Internal Radiation Dose Assessment (2009)*
- Report 163: *Radiation Dose Reconstruction Principles and Practices (2009)*
- Report 156: *Development of a Biokinetic Model for Radionuclide-Contaminated Wounds for Their Assessment, Dosimetry and Treatment (2006)*
- Report 135: *Liver Cancer Risk from Internally-Deposited Radionuclides (2001)*
- Report 128: *Radionuclide Exposure of the Embryo/Fetus (1998)*

Impact on International Commission on Radiological Protection

- Publication 130: *Occupational Intakes of Radionuclides Part 1 (2015)*
- Publication 70: *Basic Anatomical & Physiological Data for Use in Radiological Protection - The Skeleton (1995)*
- Publication 69: *Age-dependent Doses to Members of the Public from Intake of Radionuclides - Part 3 Ingestion Dose Coefficients (1995)*
- Publication 66: *Human Respiratory Tract Model for Radiological Protection (1994)*
- Publication 67: *Age-dependent Doses to Members of the Public from Intake of Radionuclides - Part 2 Ingestion Dose Coefficients (1993)*
- Publication 56: *Age-dependent Doses to Members of the Public from Intake of Radionuclides - Part 1 (1989)*
- Publication 48: *The Metabolism of Plutonium and Related Elements (1986)*

Human Respiratory Tract Model: Absorption to Blood

- Human Respiratory Tract Model (HRTM): Publication 66 (1994)



Lung Clearance: Absorption to Blood

- Bound material fraction: f_b
- ICRP 66 HRTM: $f_b = 0$

Why f_b is important?

Bound Plutonium: Effect on Lung Dose

Chemical Compound	f_b(%)	Increase in Lung Dose (%)
Oxides	0.1%	0%
	1.0%	2%
	10%	21%
Nitrates	0.1%	20%
	1.0%	200%
	10%	2010%

Calculation by Puncher & Birchall (PHE)

Quantifying the Bound Fraction

- Collaboration with Public Health England (UK)
- USTUR Case 0269: exposure to plutonium nitrate – soluble material (Type M)
- Estimated intake: ~58 kBq (1.6 µCi)
- Puncher, M., Birchall, A., Nielsen, C. E. and Tolmachev, S. Y. *MWDS 2013: A re-analysis of USTUR Case 0269 to determine whether plutonium binds to the lungs (2015 in preparation)*

- Bound fraction for soluble material: f_b = 0.4 – 0.7%

- Proposed for implementation in ICRP Publication 130 (2015)

Future Research

- Actinide Biokinetic Modeling and Dosimetry
- Chelation Therapy Modeling
- Radiation Biomarkers
- Quantitative Microdosimetry
- Beryllium in Humans

USTUR: Take-Home Message

- Studying biokinetics of plutonium, uranium and other actinides
- Unique resource of data from former nuclear workers
- Obtain, analyze, and preserve tissue samples for future research
- Significant impact on national and international radiation protection advisory bodies
- 50-y research funded by US DOE

Disclaimer

- *This presentation was prepared as an account of work sponsored by an agency of the United State Government. Neither the United States Government nor any agency thereof, nor any of their employees, make warranty, expressed or implied, or assumes any legal liability or responsibility for the accuracy, completeness, o usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any specific commercial product, process, or service by trade name trademark, manufacturer, or otherwise does not necessarily constitute or imply its endorsement, recommendation favoring by the United States Government or any agency thereof. The views and opinions of authors expressed herein do not necessarily state or reflect those of the United States Government or any agency thereof.*