USTUR Special Session
61st Annual Meeting of the Health Physics Society
Spokane, WA, July 19, 2016

The United States Transuranium and Uranium Registries (USTUR)

- Where We Have Been and Where We Are Going -

Ronald L. Kathren
Professor Emeritus and Director, USTUR (*Retired*)
Washington State University at Tri-Cities

"Learning from Plutonium and Uranium Workers"

By Way of a Preface

The research of the USTUR relies heavily upon postmortem autopsy findings and radiochemical analysis of tissues. The enormous debt owed to those now deceased registrants who unselfishly voluntarily participated in the USTUR program through postmortem donation of their tissues is hereby acknowledged with gratitude. The scientific findings derived from postmortem analysis of these tissues have been instrumental in advancing our understanding of the actinide elements in man, and led to refinement, validation and confidence in safety standards for those who work with these elements as well as the general public. To these generous and anonymous persons who made this ultimate contribution, this keynote talk is dedicated with great thanks and admiration.

Before the Beginning…

- Although there was some interaction, the actinides, a group of 15 heavy metallic elements with similar chemistry and atomic numbers 89 to 103 were unknown to man for centuries
- In 1789, German chemist Martin Klaproth identified uranium (element 92), the first actinide element to be discovered
- Plutonium, although its existence and properties had been hypothesized for a few years was not officially discovered until February 5, 1941 by Glenn T. Seaborg and his team at UC Berkeley
- Since for all practical purposes Pu is not found in nature, the necessity for biological study of both Pu and U was quickly understood in large measure because of the recent tragic experience of the radium dial painters
- Thus, from the outset of the Manhattan Project, extensive biological and toxicological research with animals was undertaken

Realization of Plutonium Hazards

Even before significant quantities of Pu were made, Seaborg, then in charge of MED Pu chemistry research, wrote to Robert Stone, MED Medical Director:

It has occurred to me that the physiological hazards of working with plutonium and its compounds may be very great. Due to its alpha radiation and long life , it may be that the permanent location in the body of even small amounts, even one milligram or less, may be very harmful . . . I would like to suggest that a program to trace the course of plutonium in the body be initiated as soon as possible. In my opinion, such a program should have the very highest priority. (Memo, Seaborg to Stone dated January 4, 1944)

A few days later, Seaborg suggested that 5-10 mg from the initial half gram from Clinton Labs be sent to Joseph Hamilton at UC Berkeley immediately for such studies. When the Pu became available a month later, 11 mg (2.2% of total) were sent to Hamilton.

First Human Studies with Plutonium

- To resolve conflicting animal data, for extrapolation from animals, and development of appropriate models and human safety standards
- 18 terminally ill patients injected between April 1945 and July 1947
- Urinary and fecal excretion followed for 138 days
- Study very controversial because of ethical concerns but information gained led to improved safety standards and hence better worker protection
- Results:
  - ✓ No major differences in tissue distribution between animal and man except for liver
  - ✓ Liver uptake and retention half time greater in humans
  - ✓ Retention uptake in humans much longer (av. 118 y) in humans than in animals
  - ✓ Excretion pattern differed from animals; human excretion curve developed by Langham by extrapolation of 138 day excretion data
  - ✓ Ultimately led to ethical concerns

Pre-USTUR Tissue Studies

Los Alamos

- Autopsy with tissue sampling formal program began in 1959 – Fallout tissue studies
- IPPU Club 27 members

Hanford

- Modest tissue sampling program began in 1949
- Objective to compare Pu in various tissues (bone, liver, lung; pulmonary lymph nodes added in 1960 with amounts calculated from excretion data)

Rocky Flats: workers (1960s)

USPHS, HASL, and others: population studies of weapons test fallout plutonium

Birth of the Registries

- July 1966 – USAEC meeting on Pu contamination in man held at Rocky Flats
- May 1967 – Hanford Biology Symposium
  - ✓ Tissue sampling results reported (Hanford)
  - ✓ Registry publicly proposed (USAEC)
- August 1968 – National Plutonium Registry created

"…to protect the interests of workers, employees and the public by serving as a national focal point for the acquisition and provision of the latest and most precise information about the effects of the transuranic elements on man"

Contract with Hanford Environmental Health Foundation

- ✓ WD Norwood named director
- ✓ Advisory committee of experts formed

- 1970 – renamed to US Transuranium Registry to reflect broader scope than just plutonium

National Plutonium Registry: *US AEC Vision*

National Plutonium Registry: *Blue Ribbon Committee*

Standing Left to Right: Carlos E. Newton, Jr., W. Daggett Norwood, H.D. Bruner, Philip A. Fuqua.
Seated Left to Right: Thomas F. Mancuso, J.H. Sterner, Robley D. Evans, Herbert M. Parker.
Not Photographed: Clarence C. Lushbaugh, Lloyd M. Joshel.

Startup Activities

- Identification of study population
- Establishing operational protocols
- Recruitment of registrants
- By June 1974:
  - ✓ 5,343 transuranium workers identified
  - ✓ 3,880 signed medical and health physics releases
  - ✓ 819 given autopsy authority
  - ✓ 45 autopsies carried out, 2/3 by/from Rocky Flats

Initial Scientific Findings

Results from analysis of first 14 cases reported at Hanford Biology Symposium in 1972 and revealed the following:

- Deposition estimates based on urinalysis were too high
- Plutonium distribution in tissues differed from ICRP
- Recommended biokinetic models (*e.g.* ICRP) were not representative and needed revision
- Operational radiation safety practices were more than achieving the sought after measure of control of plutonium intakes

Controversy

- Report of first 30 autopsy results (*Norwood and Newton, Health Phys 28:669-675; 1975*)
- Confirmed and extended previous findings and reemphasized need for analysis of all tissues in a single body
- Reported causes of death concluding that there was nothing unusual

Sidney Wolfe of Ralph Nader Health Research group took exception, creating a damaging national controversy

USTR + USUR = USTUR

- Parallel but administratively separate United States Uranium Registry (USUR) founded in 1978
- Operated on lines similar those of the USTR
- Recruitment slow – only 32 living registrants by 1991 and 12 autopsies plus 1 surgical sample
- Published 4 important reports on overview of health hazards from uranium
- In 1989 USUR director Robert Moore retired and USTR director Margery Swint assumed directorship of both Registries

Interlude: The Halfway Point

By 1992, the USTUR received and analyzed 5 whole body Pu/Am donations along with many more tissues from routine autopsy donors, plus a whole body from a Thorotrast (Th) case

Authored or coauthored to more than 50 papers in the peer reviewed scientific literature, including:

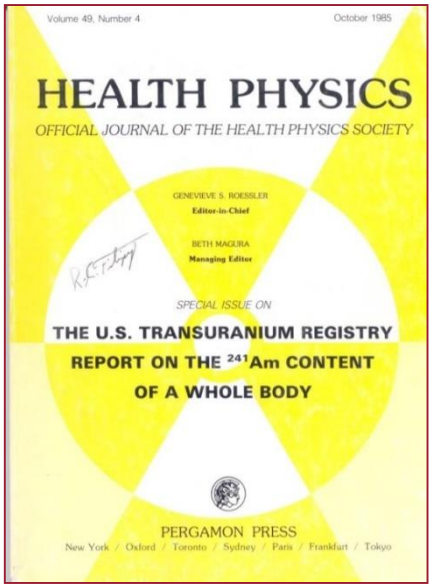
- 38-year follow up of a WWII UF_6 exposure
- Determined 40 year residual Pu deposition in some early Manhattan workers
- Determined relationship between bone ash fraction and Pu concentration in marrow and bone

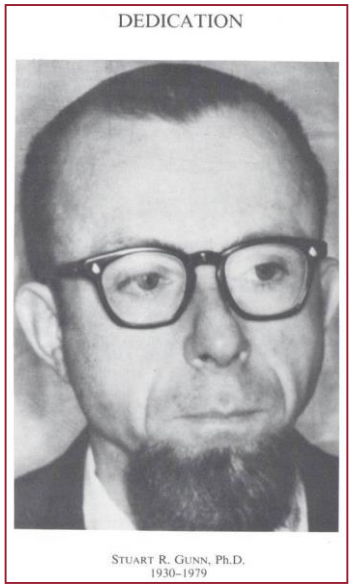
The Halfway Point (continued)

- Plutonium and americium lung clearance study
- Published results of first 5 whole body analyses for plutonium and compared *in-vivo* estimates via urinalysis with postmortem tissue measurements
- Compared skeletal distribution of plutonium and americium in man, monkeys and baboons
- Evaluated diurnal excretion pattern of uranium in men and validated simulated 24-h sampling protocol

First Whole-Body Donation: Case 0102

- ^{241}Am contaminated wound revealed at autopsy ~25 y post intake
- Systemic deposition: 82% skeleton, 6.3% liver; 11% other tissues
- Deposition described by sum of 2 exponentials with initial uptake fractions of 0.835 and 0.115 and elimination half times of 90 and 2 y, respectively for skeleton and soft tissues





USTUR Under Siege

- All was not sweetness and light. The 1980's and '90's were marked by allegations regarding the legality and ethics of the USTUR activities by many groups
  - ✓ The media (including 60 Minutes)
  - ✓ General Accounting Office
  - ✓ President's Commission on Human Radiation Experiments
  - ✓ Lawsuits
- Specific charges included body snatching, false reporting of results, failure to obtain releases for medical and exposure records, and failure to follow the Nuremburg Code

No investigation, official or unofficial,

has ever found any

evidence of USTUR noncompliance with legal requirements

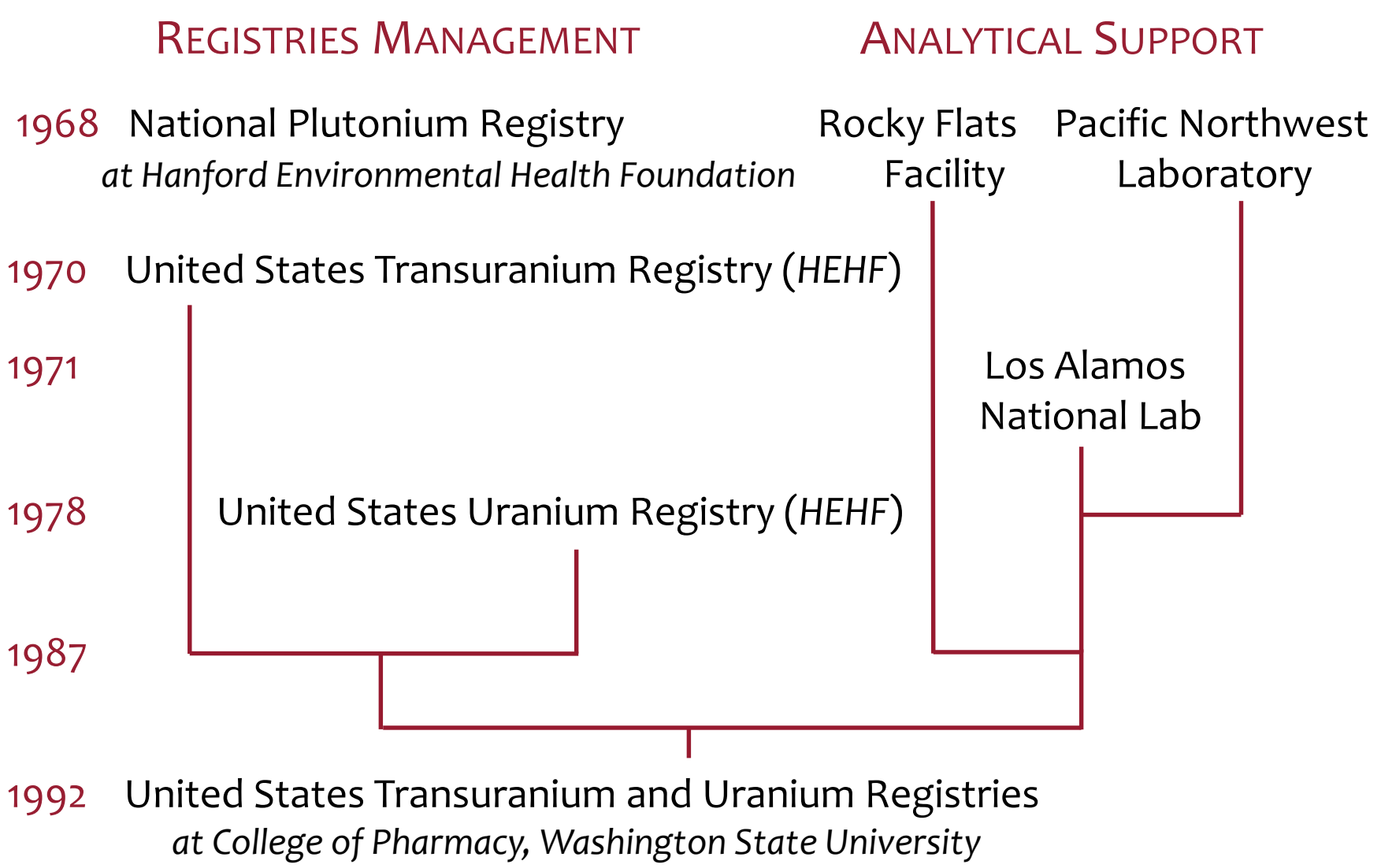
or

any ethical violation or wrongdoing, willful or accidental

Watershed: The Move to WSU

- A response to allegations of impropriety and "… *an undercurrent within the scientific community that the Registries were slow to publish and withholding data*"
- Accomplished 2/14/1992 under provisions of $3,760,000 3-y DOE grant instead of a contract
- Grant gave greater flexibility and independence from sponsor control and saved $$$
- Officially and formally combined the 2 registries and moved all activities under one roof

Genealogy of the USTUR



Registries' Directors

1968	National Plutonium Registry: W. D. Norwood
1972-73	U.S. Transuranium Registry: J. A. Norcross
1976	U.S. Transuranium Registry: B. D. Breitenstein, Jr
1978	U.S. Uranium Registry: R. H. Moore
1982	U.S. Transuranium Registry: M. J. Swint
1989	U.S. Transuranium Registry/U.S. Uranium Registry: M. J. Swint
1990	U.S. Transuranium & Uranium Registries: R. L. Kathren
2000	U.S. Transuranium & Uranium Registries: R. E. Filipy
2005	U.S. Transuranium & Uranium Registries: A. C. James
2010	U.S. Transuranium & Uranium Registries: S. Y. Tolmachev

Registries' Annual Budget

1992 – 2000: $1,250,000

2000 – 2005: $1,050,000

2005 – 2010: $1,025,000

2010 – 2017: $900,000

The WSU Era: Some Administrative Actions

- Complete review of every registrant file to ensure appropriate permissions and medical and health physics records on file
- Microfilmed data base
- Documented administrative policies and procedures
- Upgraded electronic data base capability
- Organized pathology slides and blocks
- Added labor representative to Advisory Committee
- Traced registrants and reestablished contact

Expanded Program Responsibilities

- Acquired USTUR tissues from LANL and radium dial painter tissues from ANL to create the National Human Radiobiology Tissue Repository (NHRTR). Tissues made available to others for legitimate research and collaboration
- Acquired from PNNL the National Radiobiology Archives -- a library of documents , pathology blocks, slides and similar materials from animal studies. A decade later was transferred to Northwestern University where it now resides

The WSU Era: Scientific Activities

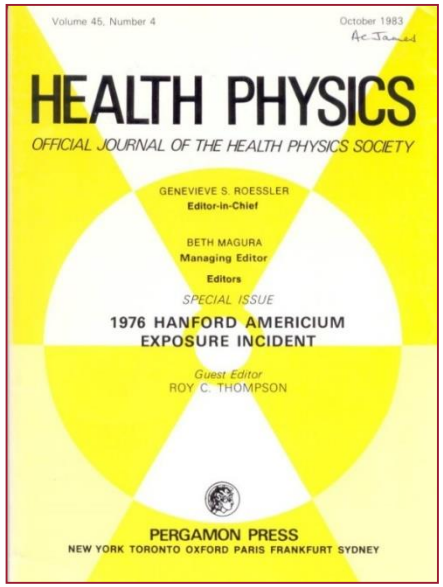
- Continued and expanded basic scientific efforts on biokinetics and modeling
- Productivity and breadth of study areas increased by the addition of adjunct faculty and graduate students – more bang for no buck!
- Collaborations expanded – close working relationships established with Russian counterparts and others, both international and domestic

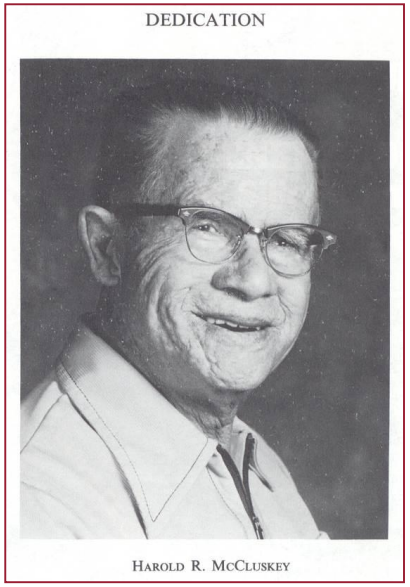
The Atomic Man: USTUR Case 0246

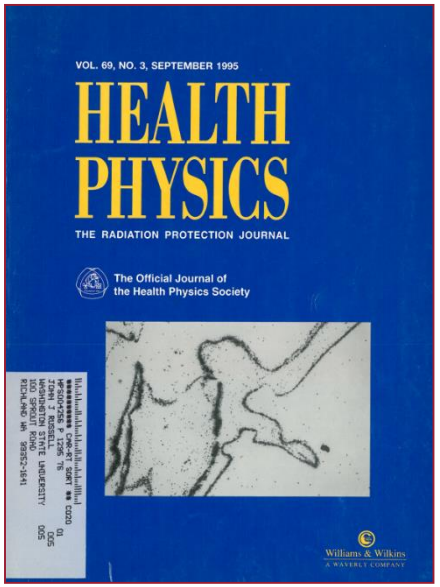
- A Hanford worker exposed to a massive amount of ^{241}Am from chemical explosion
- Survived 11 years
- Heavily chelated for 5 y with Ca/Zn DTPA
- Post-mortem findings supported USTUR Case 0102 and other routine autopsy cases modeling
- Body burden of 540,000 Bq , 90% in skeleton

The Atomic Man: Case 0246

- Body burden of 540,000 Bq (~ 15 µCi) , 90% in skeleton
- Dose to Bone: 360 Sv (3600 rem);
- Dose to Bone surfaces: 10,400 Sv (1,040,000 rem)







TAM-A.2: Carbaugh E.H. *KEYNOTE: The Atomic Man: Case Study of the Largest Recorded ^{241}Am Deposition in a Human*

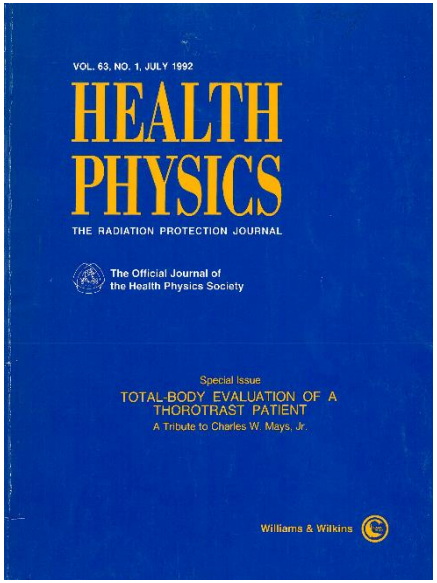
Thorotrast Study: USTUR Case 1001

- Female whole-body donor
- First study of thorium distribution in a human body
- Findings
  - ✓ Alpha risk coefficients for liver, skeleton, and leukemia
  - ✓ Showed destruction of spleen, deposition in RES
  - ✓ Clarified epidemiologic studies
  - ✓ Examined DNA and found deleted region of *c-fms* gene, interpreted as possibly radiation induced

Thorotrast Study: USTUR Case 1001

First study of thorium distribution in a human body

- Female whole-body donor
- Medical exposure to Thorotrast® ($^{232}ThO_2$ colloidal)



- Results
  - ✓ Alpha risk coefficients for liver, skeleton, and leukemia
  - ✓ Spleen destruction
  - ✓ Clarified epidemiologic studies
  - ✓ DNA analysis: deleted region of *c-fms* gene, possibly radiation induced

Uranium in Man

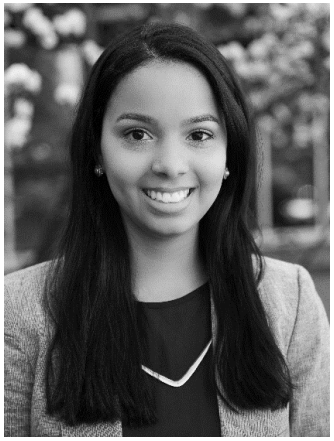
Environmental uranium in three whole-body donors

Findings:

- ~46% deposited in skeleton, largely in bone volume
- Uranium concentration
  - ✓ Bones: 3.8 μg U kg^{-1} wet weight
  - ✓ Soft tissues: 0.5 μg U kg^{-1} wet weight
- 0.38 μg U in kidney: *vs* 7.0 μg for ICRP Reference Man
- Skeleton deposition fraction: 0.14
- Skeletal residence half-time of 13.6 y: *vs* 4.1 y from ICRP

Academic Outreach

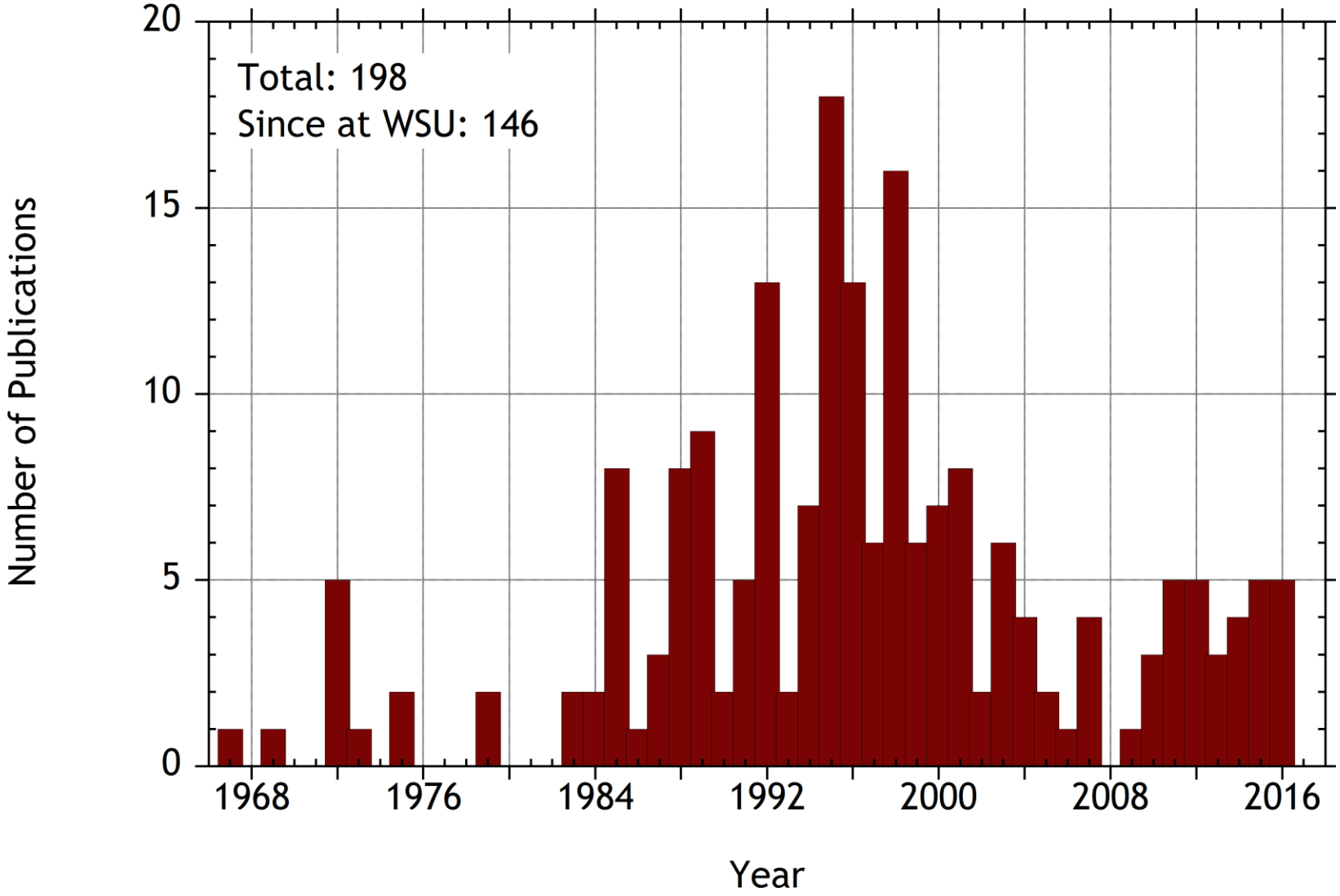
- Undergraduate Training – over 20
- Graduate Research Projects
  - ✓ Master – 8
  - ✓ PhD – 6



- Sara Dumit, COP PhD student

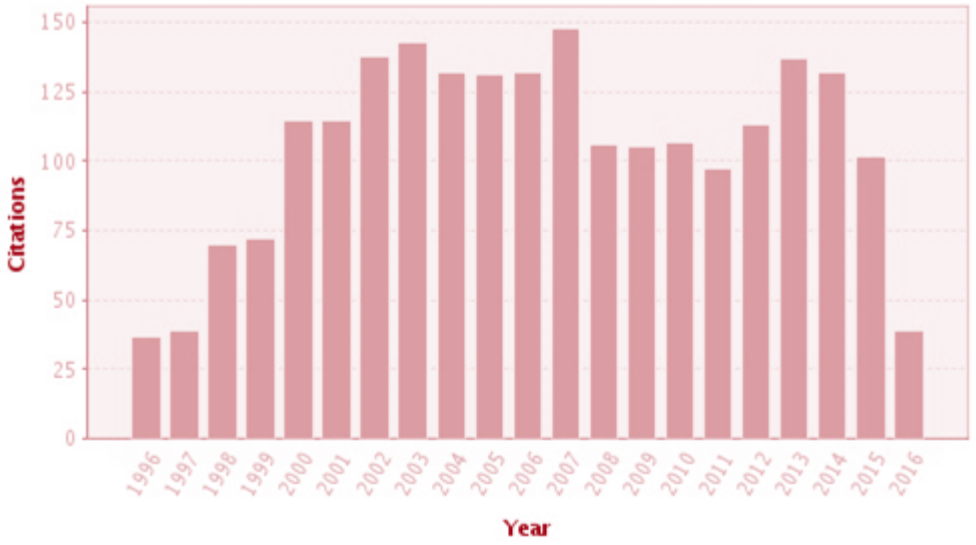
  TAM-A1.3 *USTUR Case 0785: Modeling Pu Decorporation Following Complex Exposure*

Peer-reviewed Publications



Citation 1980 – 2016

- Platform: Web of Science
- Peer-reviewed publications: 198
- Cited articles: 165
- Total citations: 2,447
- Average citations: 14.8
- *h*-index: 27



Contribution to NCRP

- 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)*

National Council on Radiation Protection and Measurements

Contribution to ICRP

- Publication 130: *Occupational Intakes of Radionuclides Part 4 (2016)*
- 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)*

ICRP INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION

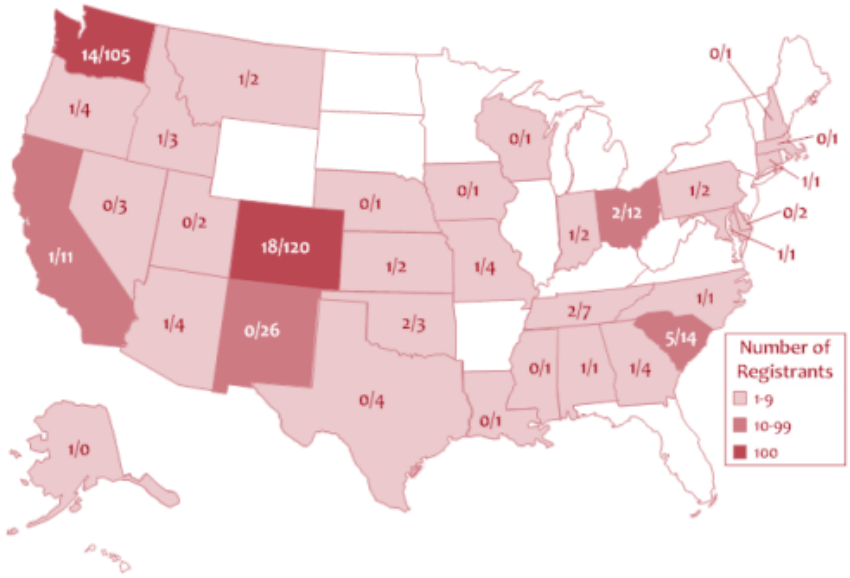
So Where Are We Going???

- Piecing together the biokinetic puzzle through continued refinement of ICRP models and Reference Man data for actinides leading to more accurate *in vivo* estimates
- Validation or provide refinements to biokinetic parameters and established models to assure their adequacy
- Greater support of operational health physicists and of students
- Additional collaborations and utilization of USTUR expertise, data bases and materials by other investigators, both national and international

Registrant Statistics

- Living Registrants: 50
  - *Whole-body donors: 8*
  - *Partial-body donors: 37*
  - *Special studies†: 5*
- Deceased Registrants: 352
  - *Whole-body donors: 43*
  - *Partial-body donors: 303*
  - *Special studies: 6*

† - not a tissue donor



Living/Deceased Registrants

Expanding Horizons

- Refractory PuO_2 inhalation: 22 cases
- Soluble plutonium (UPPU): 12 (26) cases
- Plutonium in wound : 14 cases
- Plutonium-238 biokinetics: 9 cases
- Actinide decorporation therapy: 13 cases
- Plutonium distribution in skeleton: 31 cases
- Uranium nano-particles in brain: 1 case
- Uranium in women: 3 cases
- Beryllium in human: 6 cases

Expanding Horizons

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

A Look in the Crystal Ball

- Linking radiation and chemical exposure records, bioassay data, and radiochemistry results to improve scientific understanding of actinide biokinetics and radiation-related health effects
- Utilizing the NHRTR materials for:
  - ✓ Cytogenetic studies to look for biomarkers to determine disease origins
  - ✓ Study of other, than actinides, elements, *e.g.* beryllium
- Further expansion of the tissue banks to provide additional support for collaborative research
- Increasing student support and peer collaborations including sabbaticals

Acknowledgements

The support and assistance of USTUR Director Sergei Tolmachev and other members of the USTUR staff is hereby acknowledged with great appreciation

I couldn't have done it without you