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Title: Biokinetics and Dosimetry of Depleted Uranium (DU) in Rats Implanted with DU Fragments

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Biokinetics and Dosimetry of Depleted Uranium (DU) in Rats Implanted with DU Metal Fragments

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A number of U. S. veterans of the Persian Gulf War were wounded with depleted uranium (DU) metal fragments as a result of "friendly fire" incidents, in which Abrams tanks and Bradley fighting vehicles were struck by DU anti-armor munitions. Some of the crew members who survived were left with multiple small fragments of DU in their muscles and soft tissues. The number, size and location of the fragments made them inoperable in general, and therefore subject to long-term retention. Because there was inadequate data to predict the potential carcinogenicity of DU fragments in soft tissues, Hahn *et al.* (2003) conducted a lifespan cancer study in rats. As part of that study, a number of rats were maintained to study the biokinetics and dosimetry of DU implanted intramuscularly in male Wistar rats. Typically, four metal fragments, either as cylindrical pellets or square wafers were implanted into the biceps femoris muscles of the rats. Urine samples were collected periodically during their lifespans, and DU was analyzed in kidneys and eviscerated carcass (minus the implant sites) at death. The daily DU urinary excretion rate increased steeply during the first 30 d after implantation peaking at about 90 d at 3-10 x 10^{-3} %/d. During the first 150 d, the average excretion rate was 2.4 x 10^{-3} %/d, decreasing thereafter to about 1 x 10^{-3} %/d. Serial radiographs were made of the wound sites to monitor gross morphologic changes in the DU implant and the surrounding tissue. As early as 1 w after implantation, radiographs showed the presence of surface corrosion and small, dense bodies near the original implant, presumably DU. This corrosion from the surface of the implant continued with time, but did not result in an increasing amount of DU reaching the blood and urine after the first 3 mo. During this 3-mo period, connective tissue capsules formed around the implants, and are hypothesized to have reduced the access of DU to tissue fluids by limiting the diffusion rate of dissolved chemical forms of DU. Using a model of wound-site retention being developed by a committee of the U. S. National Council of Radiation Protection and Measurements (NCRP), it was found that the average retention of DU in the wound site could be described by a two-component exponential function in which 0.5% of the DU was retained with a half time of 80 d and the remainder with a half time of about 300 y.

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RATIONALE FOR EXPERIMENTAL STUDY

- U.S. soldiers wounded with DU metal fragments during Persian Gulf war; being followed up by U. S. Army
- Attending physicians need full knowledge of potential effects of embedded DU to prepare effective treatment plans
- DU-wounded veterans and soldiers need to know if DU-contaminated wounds are carcinogenic in humans, and at what level of exposure

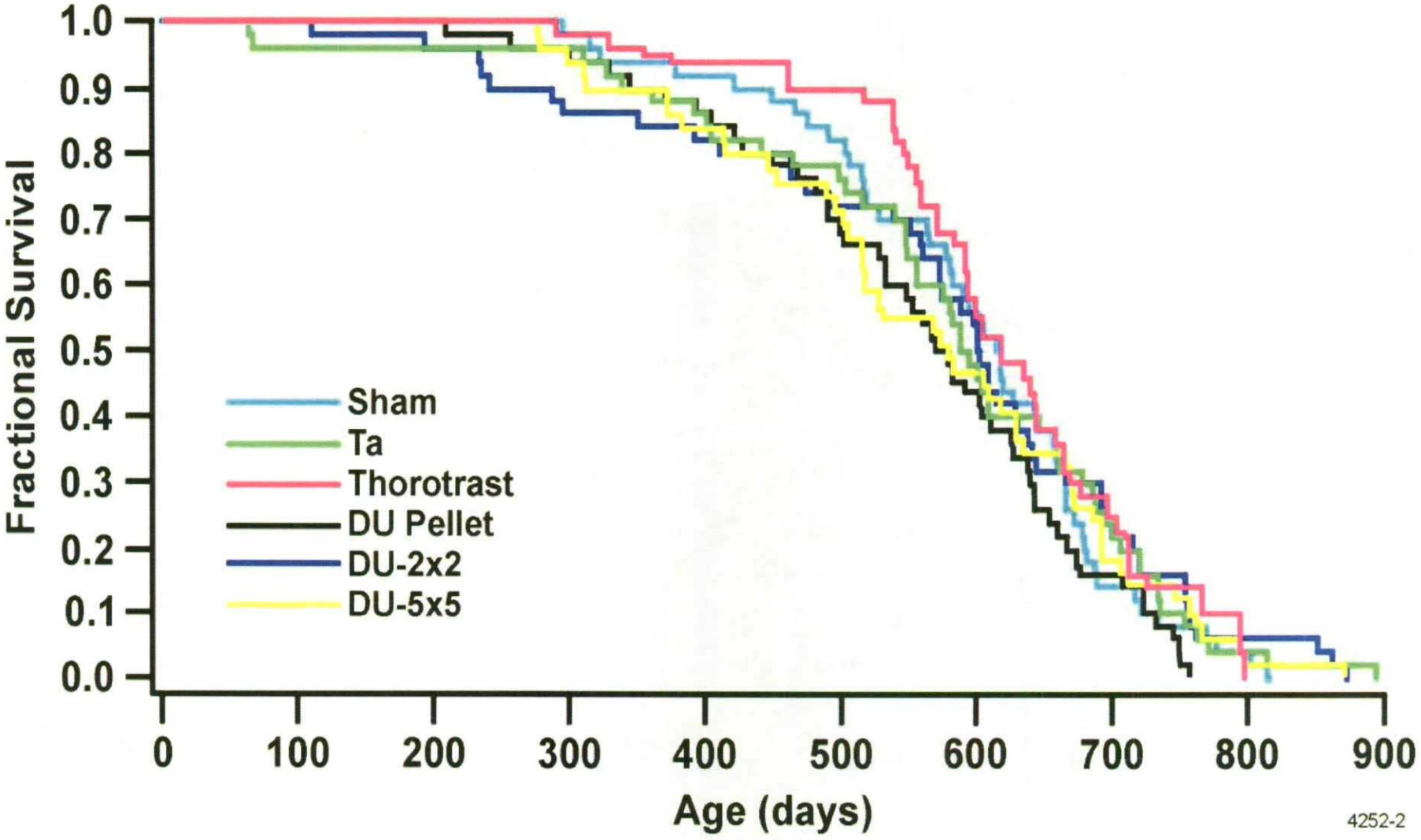
IMPLANT MATERIALS

- Depleted Uranium metal (alloyed with .75% Ti)
- Tantalum metal (Ta): solid-state carcinogenesis control
- Thorotrast® (colloidal thorium dioxide): radiation carcinogenesis control

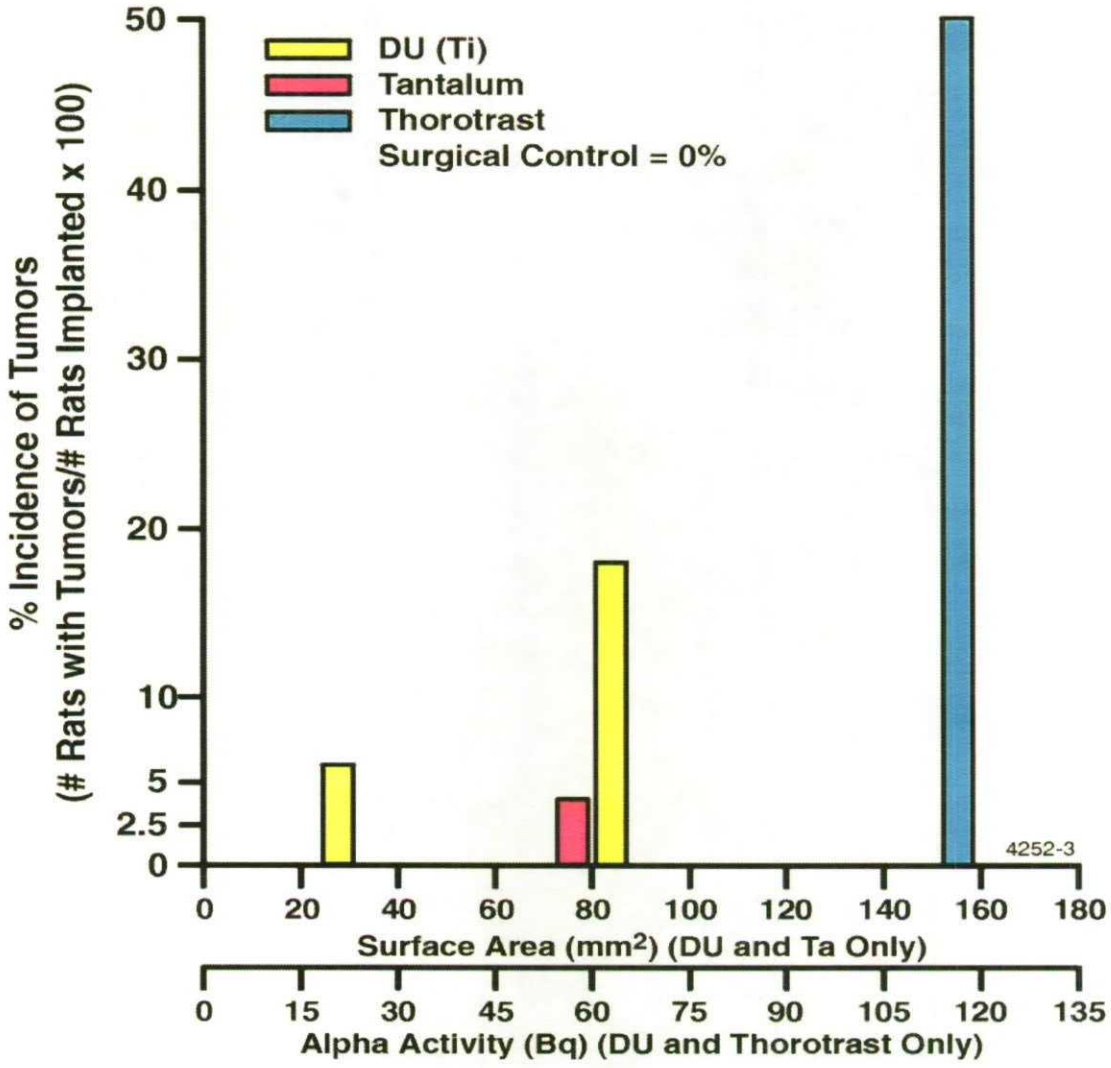
Carcinogenesis Study of Intramuscular Implants in Wistar Rats: Experimental Design

Type of Implant	Size of Implant (mm)	Number of Implants	Number of Rats
DU Pellets	2.0 × 1.0 diameter	4	50
DU Fragments	2.5 × 2.5 × 1.5	4	50
DU Fragments	5.0 × 5.0 × 1.5	4	50
Ta Fragments	5.0 × 5.0 × 1.1	4	50
Thorotrast Injection	0.050 mL	2	50
Sham Surgery	-	0	50
Total # Rats	-	-	300

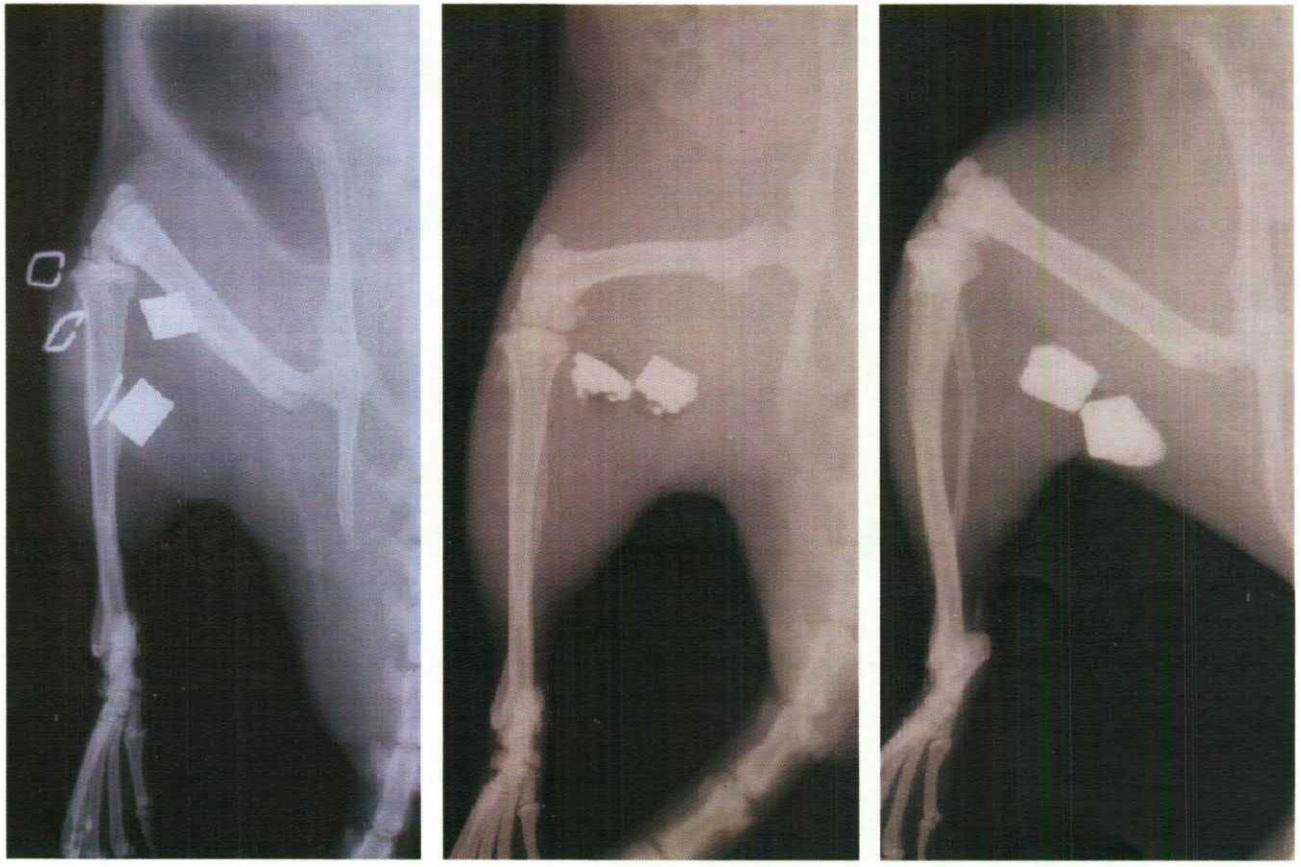
Survival of DU-Implanted Rats Compared with Controls



Incidence of Soft Tissue Tumors in Rats Implanted with DU, Ta, or Thorotrast®.



Radiographs of DU Fragments



A B C

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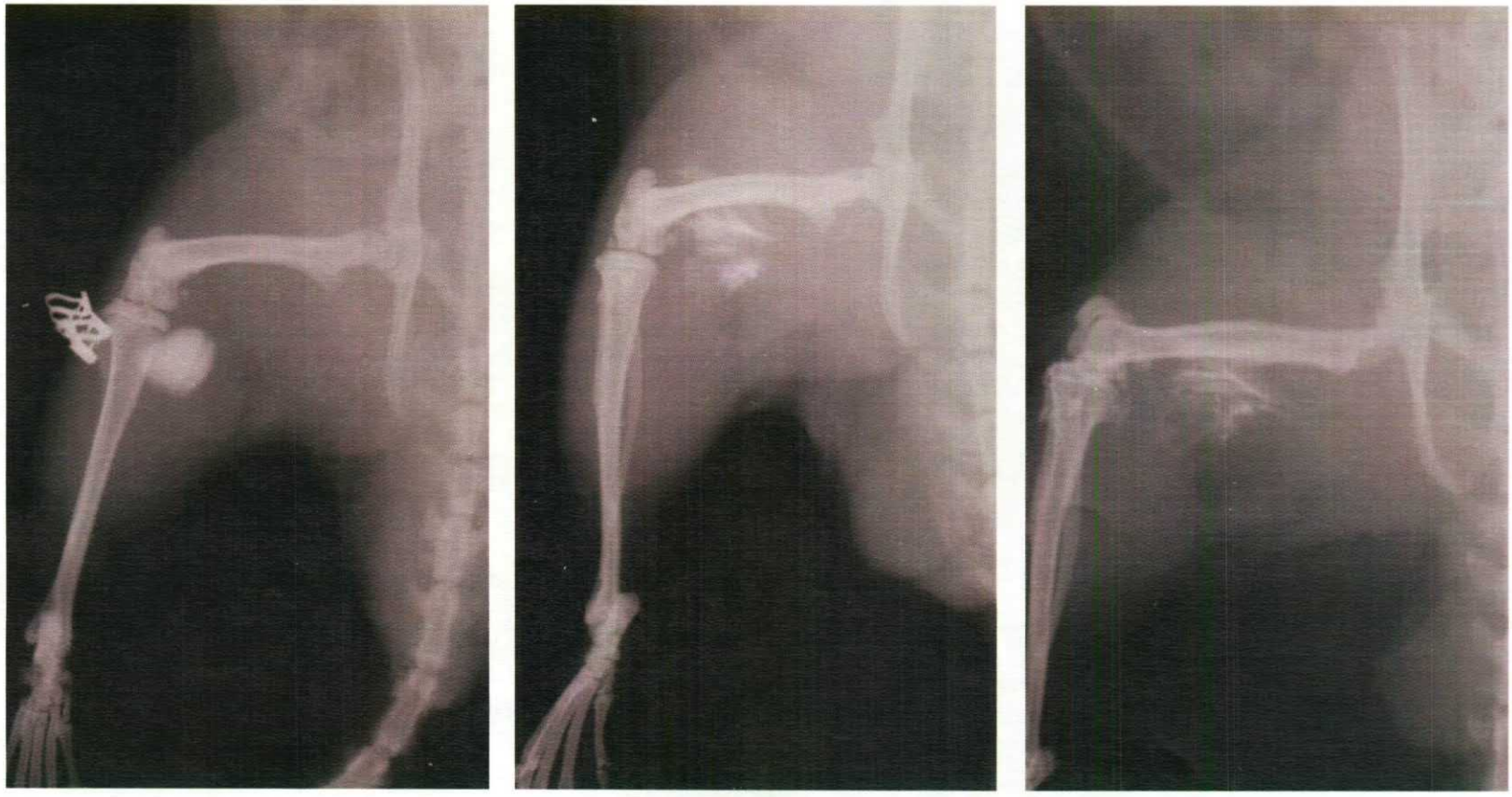
(A) on day of implantation
(B) 3 weeks after implantation
(C) 1 year after implantation.

Radiographs of Thorotrast® Injection

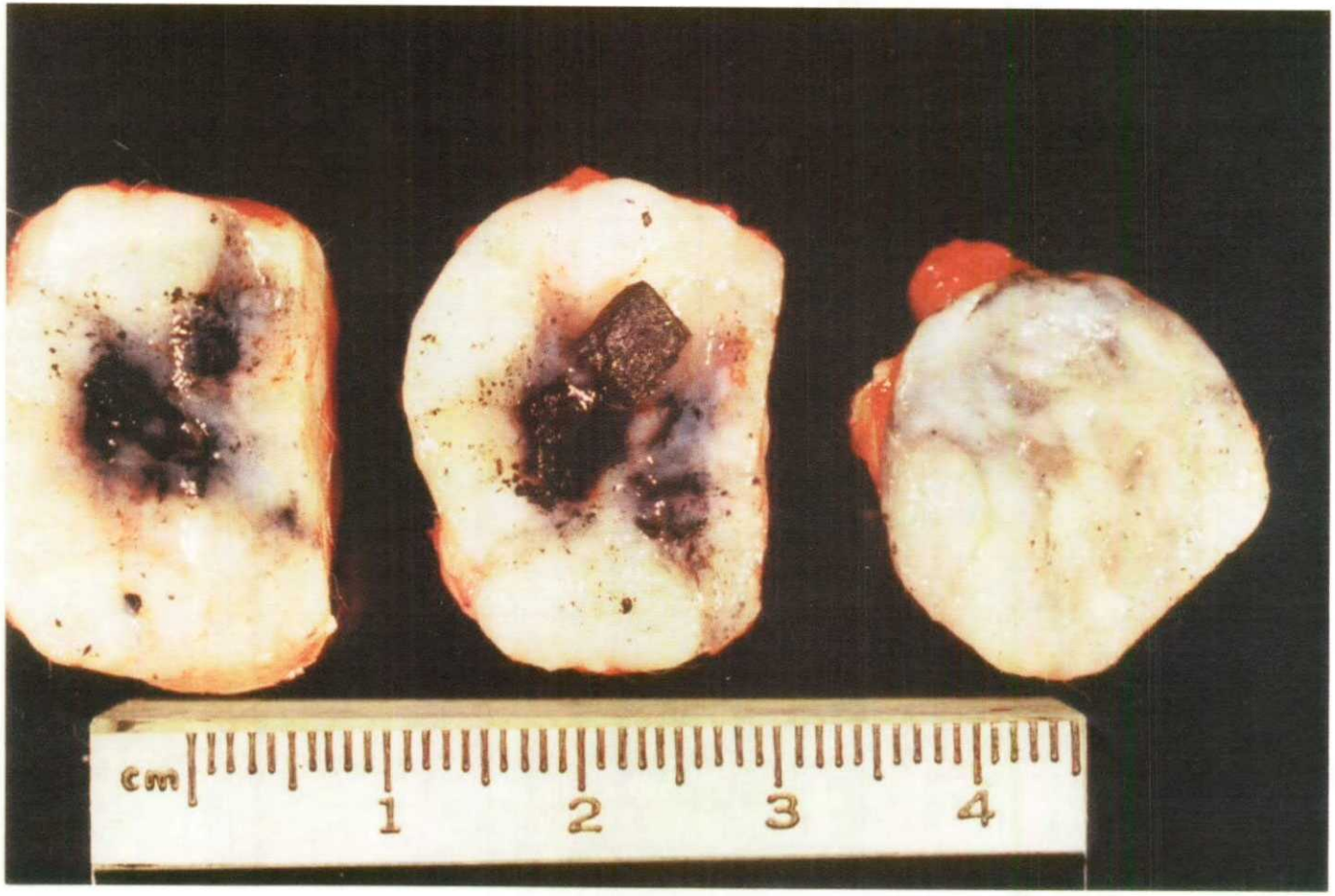


A B C

4530-3

(A) on day of injection
(B) 4 weeks after injection
(C) 1.5 years after injection

Localized Sarcoma around DU Fragment



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BIOKINETIC STUDY

- Limited design
- Six rats (four 5x5x1.5mm wafers)
  - 24-h urine collections; graded times from -2 to 664 d
  - Samples analyzed by kinetic phosphorimetry
  - Data blank-corrected; cage wash results folded in
  - At death (300-664 d), kidneys and carcass analyzed
- Total U urinary excretion obtained by linear interpolation between successive collections and cumulative summing

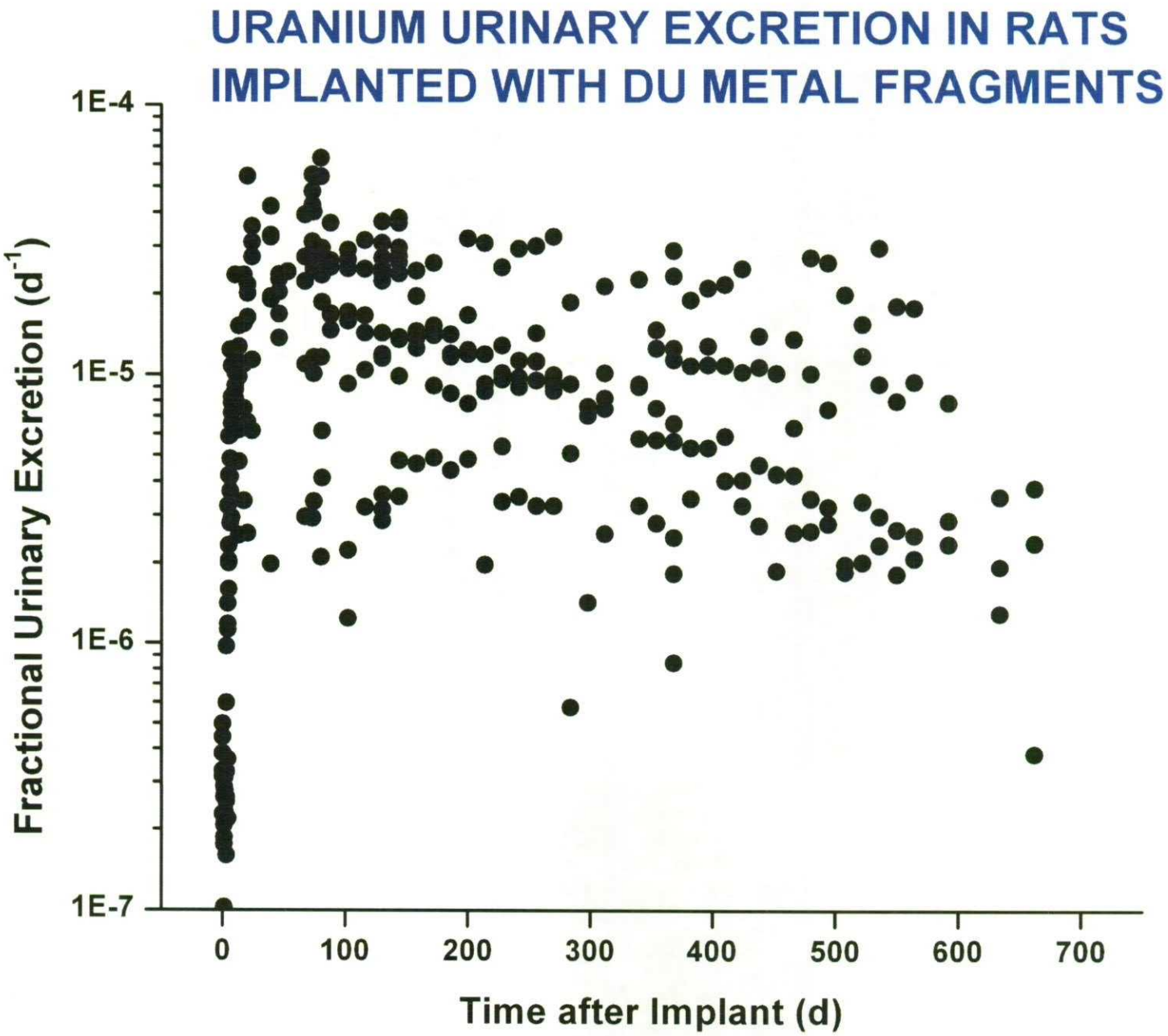
BIOKINETIC STUDY (continued)

$$\text{Wound}(t) = \text{Implant} - \text{U Absorbed}(t)$$

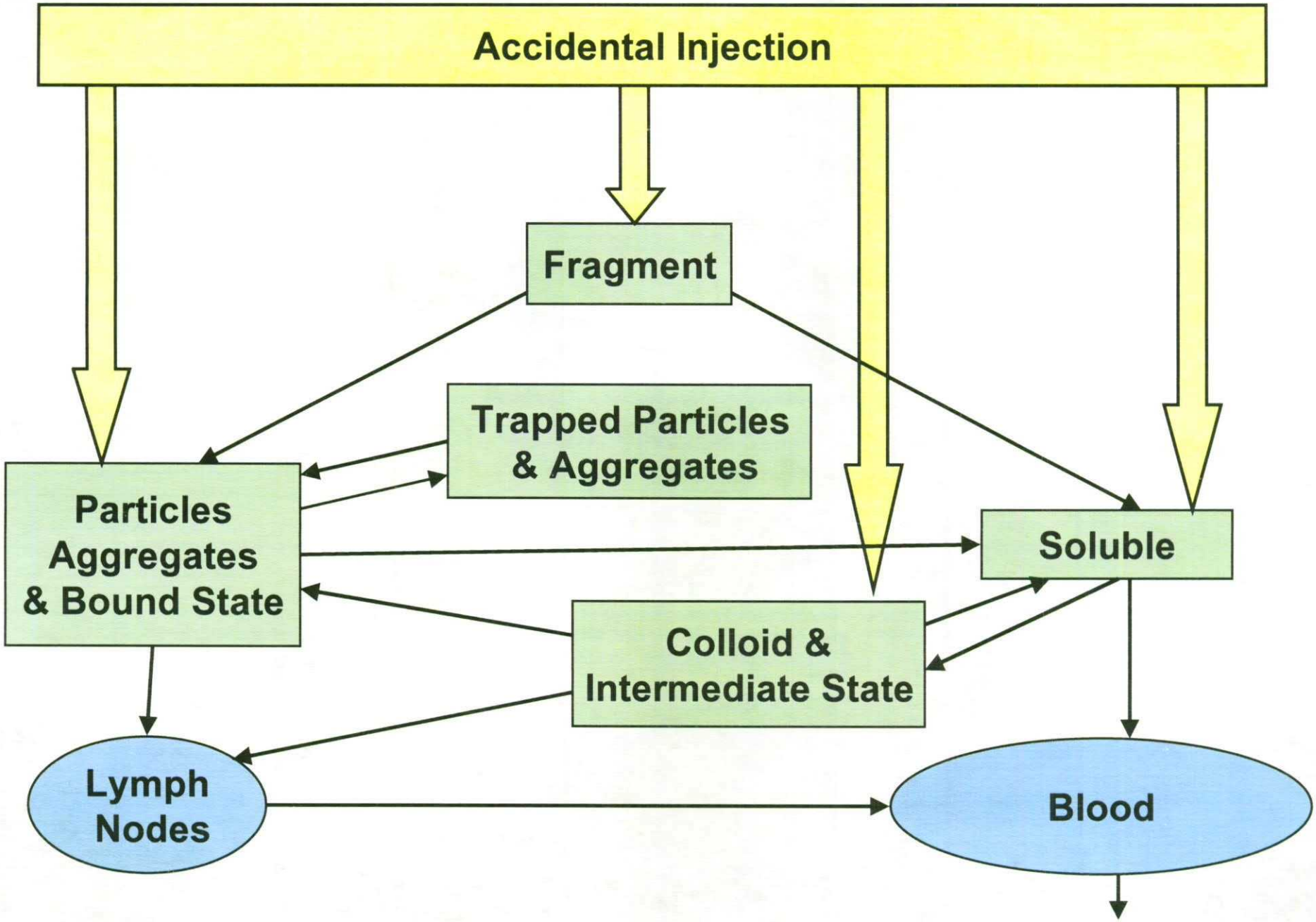
$$\text{U Absorbed}(t) = \Sigma\,[\text{Urine}(t)]/0.9$$

where

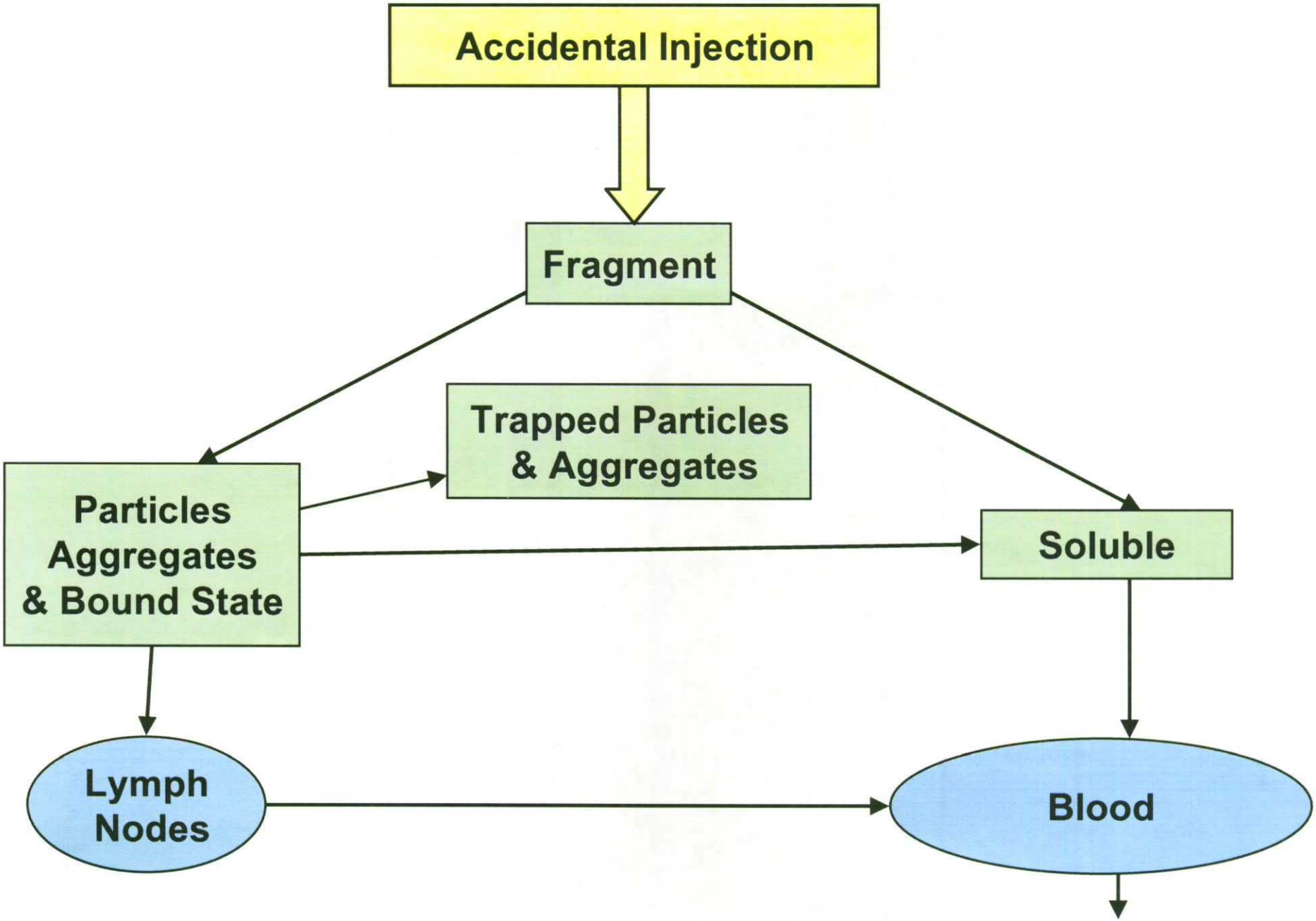
$$\text{Urine}(t) = 0.9\ \text{Systemic}(t)$$

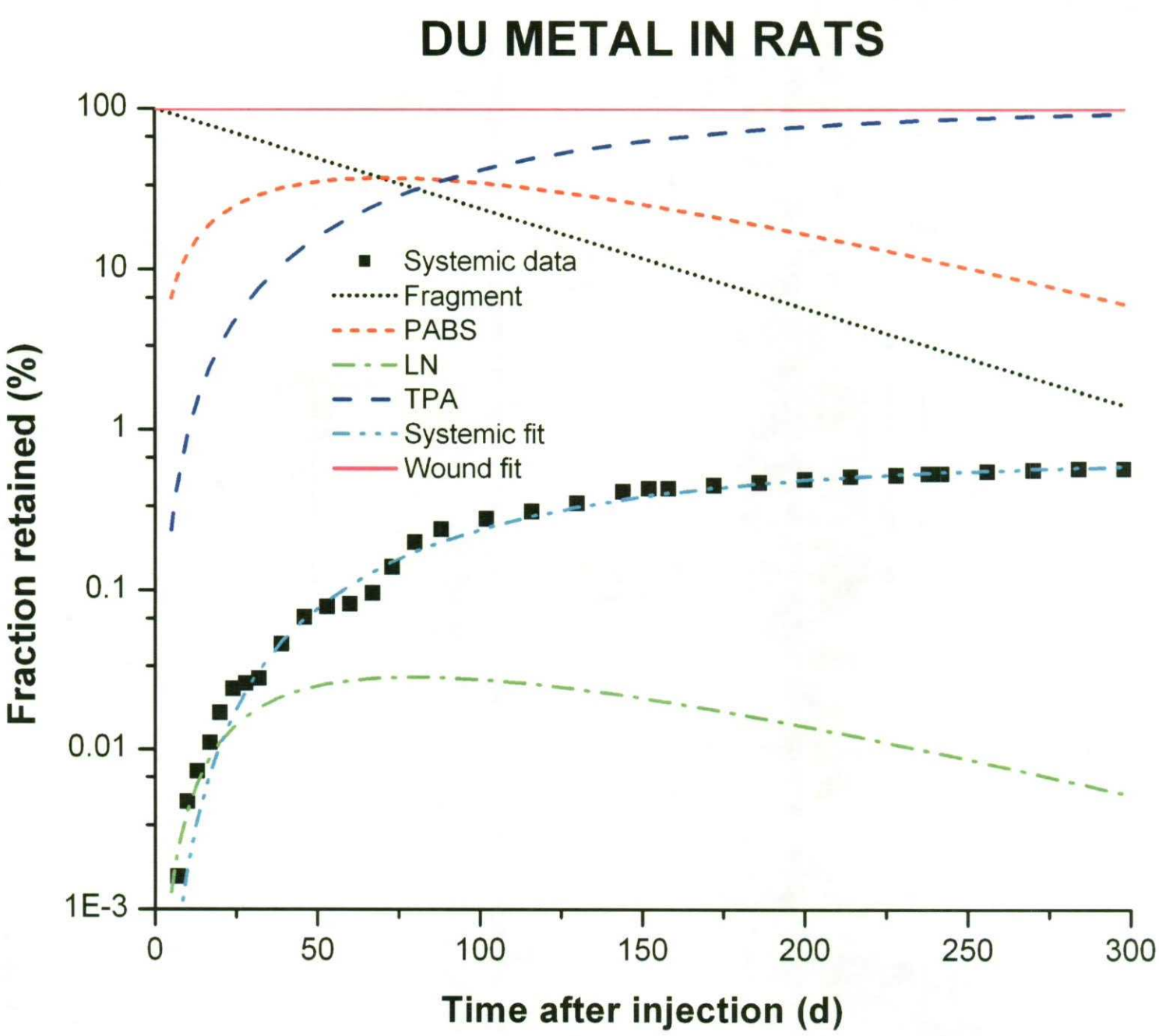

URANIUM URINARY EXCRETION IN RATS
IMPLANTED WITH DU METAL FRAGMENTS
Fractional Urinary Excretion (d-1)
1E-4
1E-5
1E-6
1E-7
0
100
200
300
400
500
600
700
Time after Implant (d)

"THE DRAFT NCRP WOUND MODEL"

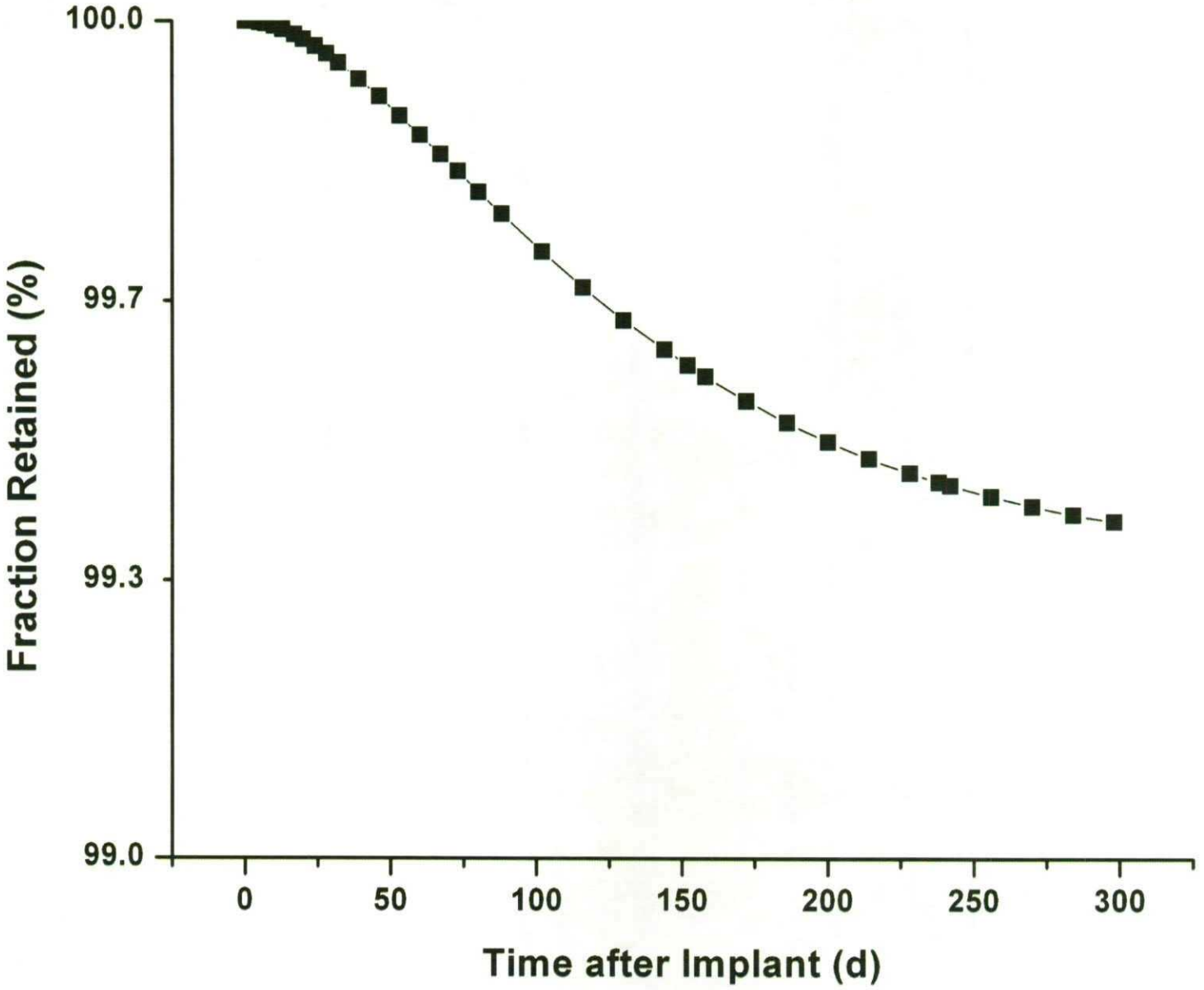


"FRAGMENT MODEL"




DU METAL IN RATS
100
10
1
0.1
0.01
1E-3
Fraction retained (%)
0
50
100
150
200
250
300
Time after injection (d)
Systemic data
Fragment
PABS
LN
TPA
Systemic fit
Wound fit

U RETENTION IN WOUND SITE



BIOKINETIC MODELING RESULTS

- Wound retention very prolonged
  - $R(t) = 0.005\ e^{-0.0086t} + 0.995\ e^{-0.0000065t}$ (t in days)
  - Half times of about 80 d and 300 y
- Urinary excretion reflects slow but persistent release of U to blood
  - $3 \times 10^{-5}\ d^{-1}$ (90 d)
  - $2.5 \times 10^{-5}\ d^{-1}$ (150 d)
  - $1.0 \times 10^{-5}\ d^{-1}$ (600 d)
- Kidney content reflects urine excretion rate
- Bone content increases slowly with time

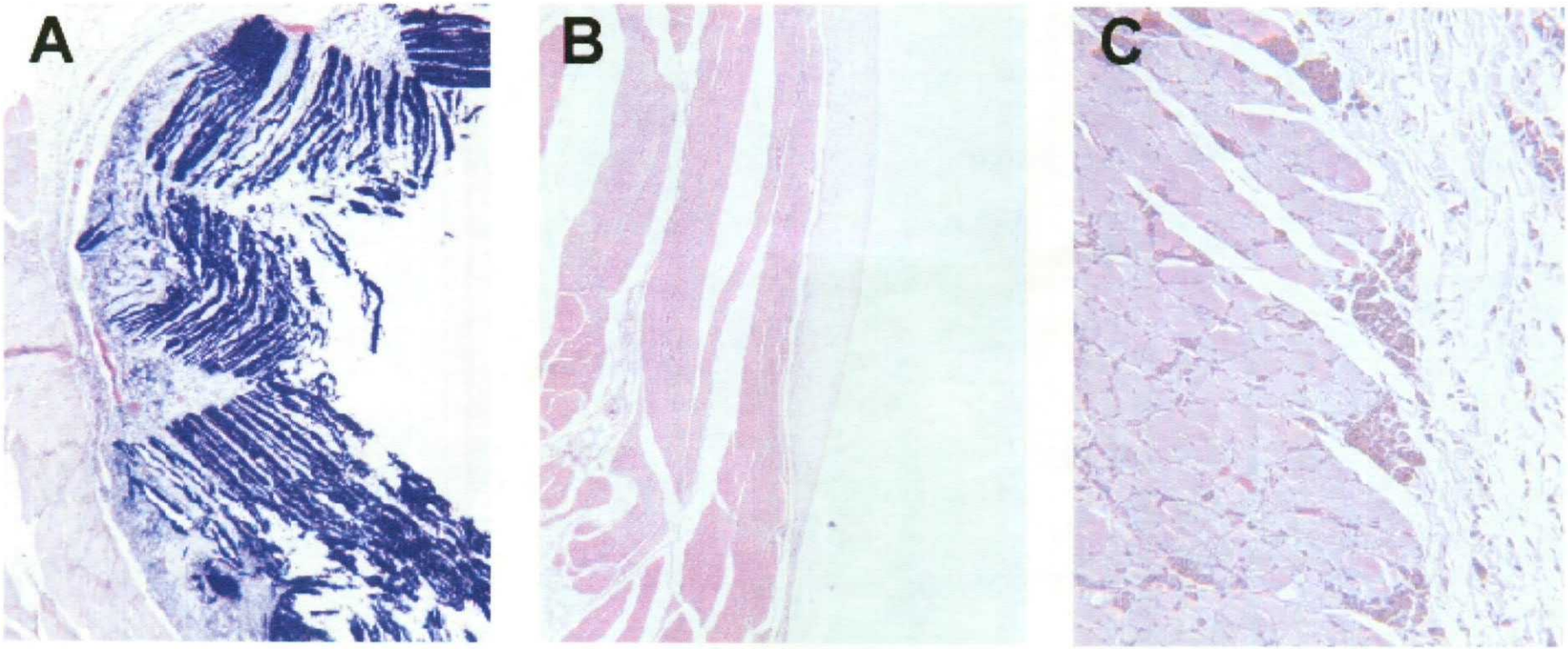
LOCAL WOUND DOSIMETRY

- For alpha particles from DU, a fragment is an infinitely thick source
- By ZnS measurement, surface emits 4240 α dpm cm^{-2}
- Assuming 50-μm tissue thickness → 40 mGy d^{-1}
- As source disintegrates, more cells and tissue is exposed, but at same dose rate
- Thorotrast dose rate about 2.5 x DU; much larger target size because of spreading

Implant-associated soft tissue tumor types

Tumor Types	Thorotrast	DU	Ta	Sham
Benign Tumors				
Fibrous Histiocytoma	0	1	0	0
Fibroma	0	1	0	0
Granular Cell Myoblastoma	1	0	0	0
Malignant Tumors				
Fibrous Histiocytoma	13	7	2	0
Fibrosarcoma	10	2	0	0
Osteosarcoma	1	2	0	0

Histology of Capsules



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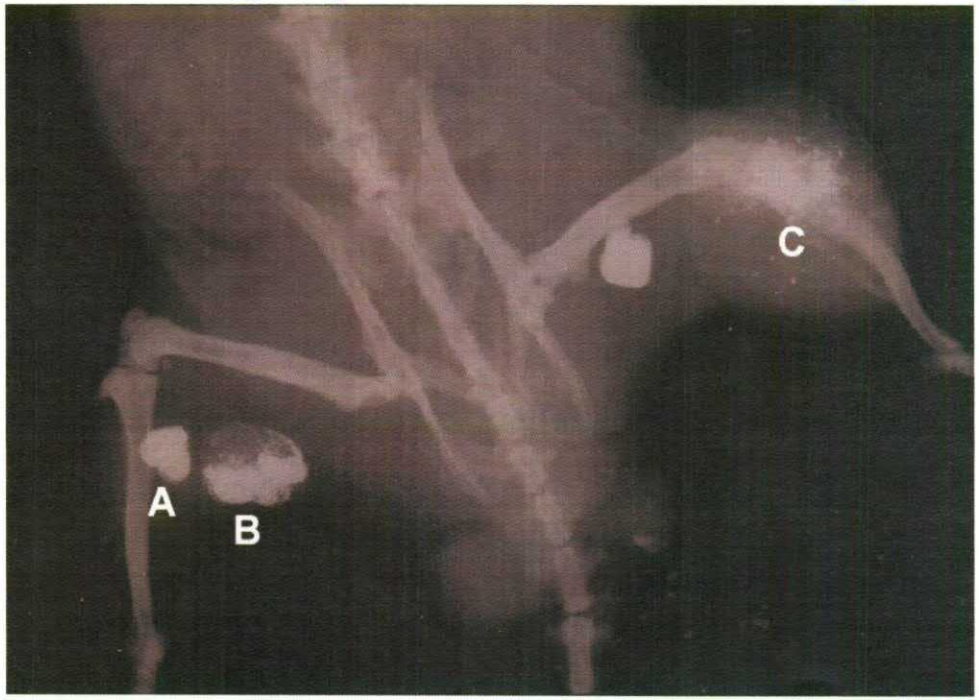
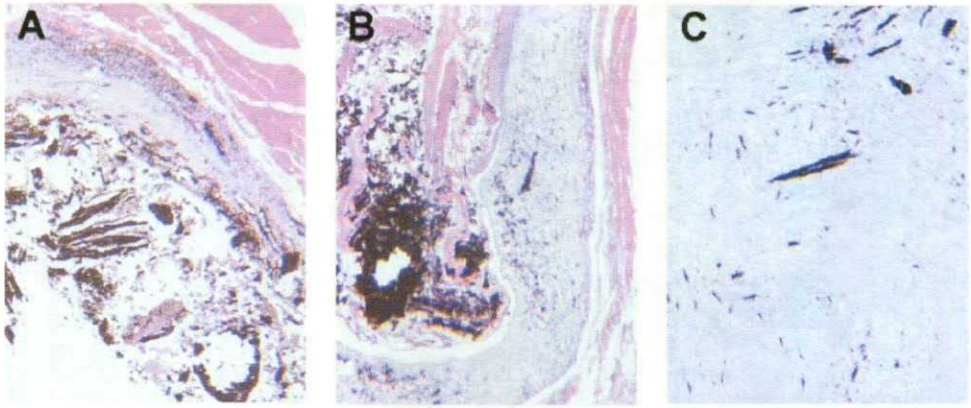
A) DU fragment: 520 days p.i. Thick capsule
(B) Ta fragment: 603 days p.i. Thin capsule
(C) Thorotrast® injection: 792 days p.i. No capsule
-------- = 300 μm

Correlation of Radiographic and Histologic Appearance





(A) thick fibrotic capsule with shards of corroded DU
(B) thick cellular capsule lined by squamous metaplasia, corroded DU
(C) particles and shards of DU in soft tissue sarcoma.