Medical Management of Internal Contamination with Radioactive Materials

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Terminal Objective

Understand the basics of medical management of internal contamination with radioactive materials

Enabling Objectives

- Review principles of management of internal contamination
- Discuss methods for determining efficacy of medical management of internal contamination
- Discuss in some detail the medical management of the most likely radionuclides to be encountered

Internal contamination is the deposition of radioactive material inside the body

References

- NCRP Report # 65: *Management of Persons Accidentally Contaminated with Radionuclides* (April, 1980) – has been reissued as NCRP Report # 161 – 65 is still a valuable resource
- NCRP Report # 161: *Management of Persons Contaminated with Radionuclides: Handbook* (2009)
- EPA Federal Guidance Report #11: *Limiting Values of Radionuclide Intake and Air Concentration and Dose Conversion Factors for Inhalation, Submersion and Ingestion* (EPA-520/1-88-020, Sep, 1988)

Management Issues

- Major problem: if the magnitude of internal contamination is unknown
- Critical treatment decisions may have to be based on sketchy information about the radiological incident or perhaps even the radionuclide(s) of concern
- In the absence of personal dosimetry, the delay in presentation of clinical findings <u>will</u> cause some difficulties for decision-making

Management Issues

- Alpha-emitting radionuclides present difficulties for detection, identification & quantification
- Instrumentation for identification of radio-nuclides may not be immediately available
- Laboratories for excreta analyses or body counting may not be immediately available

Efficacy of Treatment

- Urine and fecal radiobioassays
- Must identify laboratories capable of the assays in advance
- Whole body, lung or thyroid counting may be needed – must identify laboratories in advance

Management of internal contamination is essentially a medical toxicology issue

Important Factors

- Route of entry
- Physical properties – *e.g.*, particle size, phase (liquid, solid, *etc*.)
- Chemical properties – *e.g.*, solubility, pH

Routes of Entry

- Inhalation
- Ingestion
- Percutaneous or transdermal absorption through <u>normal</u> skin
- Injection/puncture through skin/mucous membranes, *i.e.*, absorption through <u>abnormal</u> skin

Toxicological Terms

- Intake – movement past the 3D confines of the body
- Uptake – transportation inside the body
- Incorporation – inclusion in the metabolism of a critical tissue
- Decorporation – removal from the body or from the metabolism of a critical tissue

Half-life

- Half-life
  - Radiological half-life – the time it takes for a radionuclide to decay to ½ of its activity
  - Biological half-life – the time it takes to eliminate ½ of a substance from the body by ordinary means

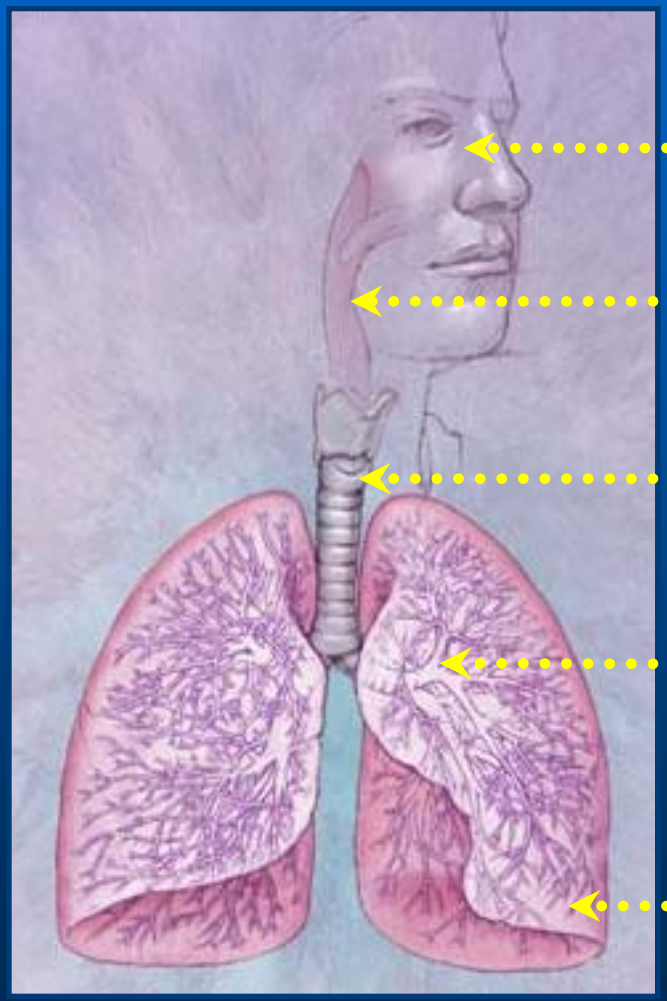
Half-life

- Effective half-life – the time required for the body to eliminate ½ of a substance by combined action of radioactive decay and biological elimination

$$T_e = \frac{t_b \times t_r}{t_b + t_r}$$

Physical Properties

Particle Size & Distribution in the Respiratory Tract



Mass Median Diameter [microns]

18-20

15-18

7-12

4-6 (bronchioles)

1-5 (alveoli)

Clearance Time Nasopharynx

	Time to Swallowing
Anterior Nares	60 min.
Nasopharnyx	10 min.
	[10 mm/min.]

Clearance Time Respiratory Tract

	Time
Trachea	0.1 hours
Bronchi	1 hours
Bronchioles	4 hours
Terminal Bronchioles	10 hours
Alveoli	100 Days +

Clearance Time - GI Tract

	Occupancy Time [hours]
Stomach	6
Small Intestine	14
Upper Large Intestine	18
Lower Large Intestine	22

Chemical Properties

General Principles

- Insoluble substances tend to be excreted via the GI tract
- Soluble substances tend to be excreted via the renal system
- Route of internalization dictates methods for removal

PERIODIC TABLE OF THE ELEMENTS

http://www.ktf-split.hr/periodni/en/

GROUP NUMBERS IUPAC RECOMMENDATION (1985)

GROUP NUMBERS CHEMICAL ABSTRACT SERVICE (1986)

ATOMIC NUMBER — 5 — 13 IIIA

10.811 — RELATIVE ATOMIC MASS (1)

SYMBOL — B

BORON — ELEMENT NAME

PERIOD	1 IA	2 IIA	3 IIIB	4 IVB	5 VB	6 VIB	7 VIIB	8 VIIIB	9 VIIIB	10 VIIIB	11 IB	12 IIB	13 IIIA	14 IVA	15 VA	16 VIA	17 VIIA	18 VIIIA
1	1 1.0079 H HYDROGEN																	2 4.0026 He HELIUM
2	3 6.941 Li LITHIUM	4 9.0122 Be BERYLLIUM											5 10.811 B BORON	6 12.011 C CARBON	7 14.007 N NITROGEN	8 15.999 O OXYGEN	9 18.998 F FLUORINE	10 20.180 Ne NEON
3	11 22.990 Na SODIUM	12 24.305 Mg MAGNESIUM											13 26.982 Al ALUMINIUM	14 28.086 Si SILICON	15 30.974 P PHOSPHORUS	16 32.065 S SULPHUR	17 35.453 Cl CHLORINE	18 39.948 Ar ARGON
4	19 39.098 K POTASSIUM	20 40.078 Ca CALCIUM	21 44.956 Sc SCANDIUM	22 47.867 Ti TITANIUM	23 50.942 V VANADIUM	24 51.996 Cr CHROMIUM	25 54.938 Mn MANGANESE	26 55.845 Fe IRON	27 58.933 Co COBALT	28 58.693 Ni NICKEL	29 63.546 Cu COPPER	30 65.39 Zn ZINC	31 69.723 Ga GALLIUM	32 72.64 Ge GERMANIUM	33 74.922 As ARSENIC	34 78.96 Se SELENIUM	35 79.904 Br BROMINE	36 83.80 Kr KRYPTON
5	37 85.468 Rb RUBIDIUM	38 87.62 Sr STRONTIUM	39 88.906 Y YTTRIUM	40 91.224 Zr ZIRCONIUM	41 92.906 Nb NIOBIUM	42 95.94 Mo MOLYBDENUM	43 (98) Tc TECHNETIUM	44 101.07 Ru RUTHENIUM	45 102.91 Rh RHODIUM	46 106.42 Pd PALLADIUM	47 107.87 Ag SILVER	48 112.41 Cd CADMIUM	49 114.82 In INDIUM	50 118.71 Sn TIN	51 121.76 Sb ANTIMONY	52 127.60 Te TELLURIUM	53 126.90 I IODINE	54 131.29 Xe XENON
6	55 132.91 Cs CAESIUM	56 137.33 Ba BARIUM	57-71 La-Lu Lanthanide	72 178.49 Hf HAFNIUM	73 180.95 Ta TANTALUM	74 183.84 W TUNGSTEN	75 186.21 Re RHENIUM	76 190.23 Os OSMIUM	77 192.22 Ir IRIDIUM	78 195.08 Pt PLATINUM	79 196.97 Au GOLD	80 200.59 Hg MERCURY	81 204.38 Tl THALLIUM	82 207.2 Pb LEAD	83 208.98 Bi BISMUTH	84 (209) Po POLONIUM	85 (210) At ASTATINE	86 (222) Rn RADON
7	87 (223) Fr FRANCIUM	88 (226) Ra RADIUM	89-103 Ac-Lr Actinide	104 (261) Rf RUTHERFORDIUM	105 (262) Db DUBNIUM	106 (266) Sg SEABORGIUM	107 (264) Bh BOHRIUM	108 (277) Hs HASSIUM	109 (268) Mt MEITNERIUM	110 (281) Uun UNUNNILIUM	111 (272) Uuu UNUNUNIUM	112 (285) Uub UNUNBIUM		114 (289) Uuq UNUNQUADIUM				

LANTHANIDE

57 138.91 La LANTHANUM	58 140.12 Ce CERIUM	59 140.91 Pr PRASEODYMIUM	60 144.24 Nd NEODYMIUM	61 (145) Pm PROMETHIUM	62 150.36 Sm SAMARIUM	63 151.96 Eu EUROPIUM	64 157.25 Gd GADOLINIUM	65 158.93 Tb TERBIUM	66 162.50 Dy DYSPROSIUM	67 164.93 Ho HOLMIUM	68 167.26 Er ERBIUM	69 168.93 Tm THULIUM	70 173.04 Yb YTTERBIUM	71 174.97 Lu LUTETIUM

ACTINIDE

89 (227) Ac ACTINIUM	90 232.04 Th THORIUM	91 231.04 Pa PROTACTINIUM	92 238.03 U URANIUM	93 (237) Np NEPTUNIUM	94 (244) Pu PLUTONIUM	95 (243) Am AMERICIUM	96 (247) Cm CURIUM	97 (247) Bk BERKELIUM	98 (251) Cf CALIFORNIUM	99 (252) Es EINSTEINIUM	100 (257) Fm FERMIUM	101 (258) Md MENDELEVIUM	102 (259) No NOBELIUM	103 (262) Lr LAWRENCIUM

(1) Pure Appl. Chem., 73, No. 4, 667-683 (2001)

Relative atomic mass is shown with five significant figures. For elements have no stable nuclides, the value enclosed in brackets indicates the mass number of the longest-lived isotope of the element.

However three such elements (Th, Pa, and U) do have a characteristic terrestrial isotopic composition, and for these an atomic weight is tabulated.

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Absorption of Ingested Radionuclides

Group	Radioactive Elements of	% Absorbed
Alkali Metals	Na, K, Rb, Cs	High ~90
Group VIII Metals	Fe Co Ru	10 30-90 3

Absorption of Ingested Radionuclides

Group	Radioactive Elements of	% Absorbed
Lanthanides	Ce, Pm, Eu, Tb	<0.1
Actinides	Th, U, Np, Pu	<0.1

Medical Management

General Treatment Methods

- Reduce absorption and internal deposition
- Enhance elimination or excretion

BEGIN TREATMENT AS SOON AS POSSIBLE!

Specific Treatment Methods

- Minimize intake
- Reduce and/or inhibit absorption
- Block uptake
- Isotopic dilution
- Promote excretion
- Alter chemistry of the substance
- Displace isotope from receptors
- Chelate

Treatment Methods

- Minimize intake
  - Control contamination
  - Remove from contaminated environment

GI Treatment Methods

- Reduce or inhibit absorption – standard toxicological management of poisonings
  - Activated charcoal
  - Gastric lavage
  - Emetics
  - Purgatives/laxatives

GI Treatment Methods

- Reduce or inhibit absorption
  - Ion exchange resins
  - Alginates
  - Antacids
  - Barium sulfate
  - Phytates

GI Treatment Methods

- Ion Exchange Resins
  - Prussian Blue (PB, Berlin Blue, ferric III hexacyanoferrate II, ferric ferrocyanide) for radiocesium and thallium
  - Alginates for radiostrontium

*Prussian Blue for Radio-Cs or Tl**

- Salts of cesium and thallium are relatively soluble
- Absorbed easily from the GI tract into blood
- Liver incorporates them into bile which is dumped into the gall bladder then into the gut
- They then have another pass through the GI tract – the enterohepatic circulation

Prussian Blue for Radio - Cs or Tl

- PB binds Cs or Tl ions in the gut – the complex is insoluble so the enterohepatic circulation is interrupted
- Eliminated by the GI tract
- Reduces biological half-life to one third of untreated value
- Complete prescribing information available at www.orau.gov/reacts/resources.htm

GI Treatment Methods

- Barium Sulfate – an insoluble barium salt used as contrast medium for x-ray exams of the GI tract
  - An antidote for radiostrontium and radium
  - Insoluble sulfate salts of Sr and Ra are eliminated via the GI tract
  - Few adverse effects – constipation, occasional fecal impaction – use mineral oil following use to prevent

GI Treatment Methods

- Phytates – from oats and soybean products, found in grains and grain cereals
  - Contain phosphorus as phytic acid phosphorus
  - Combines with Ca, Mg, Zn and Fe to form insoluble salts – eliminated via the GI tract
  - Not commercially available

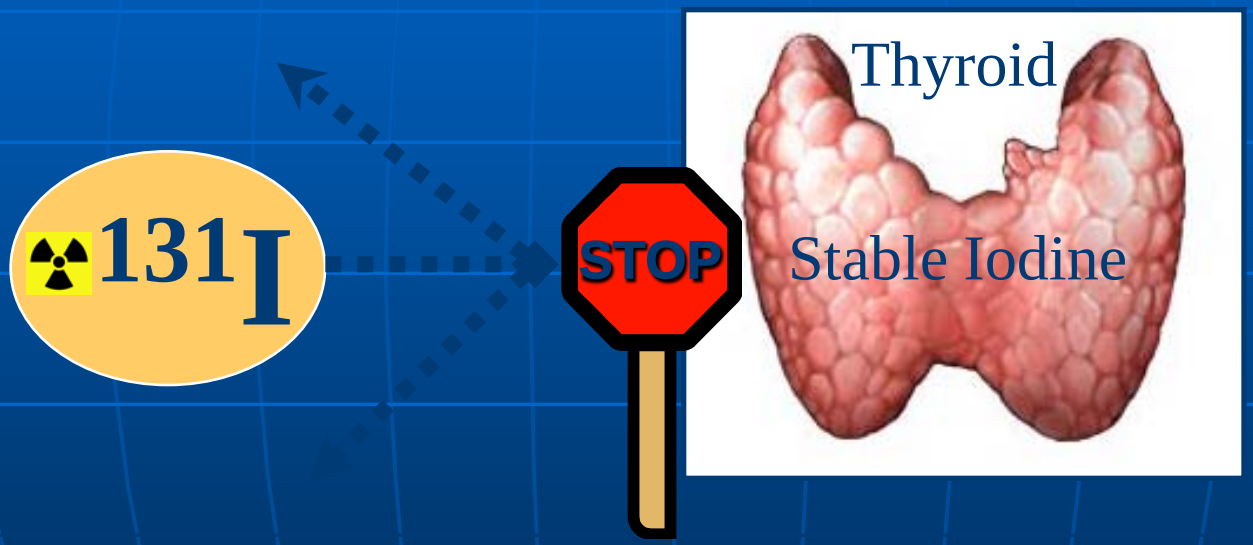
GI Treatment Methods

- Aluminum-containing antacids – reduce GI uptake of radioactive strontium
  - Non-toxic and well-tolerated
  - Aluminum phosphate gel – 100 ml – if given immediately after exposure, can reduce absorption by ~85%
  - Aluminum hydroxide – 60-100 ml – reduce absorption by ~50%

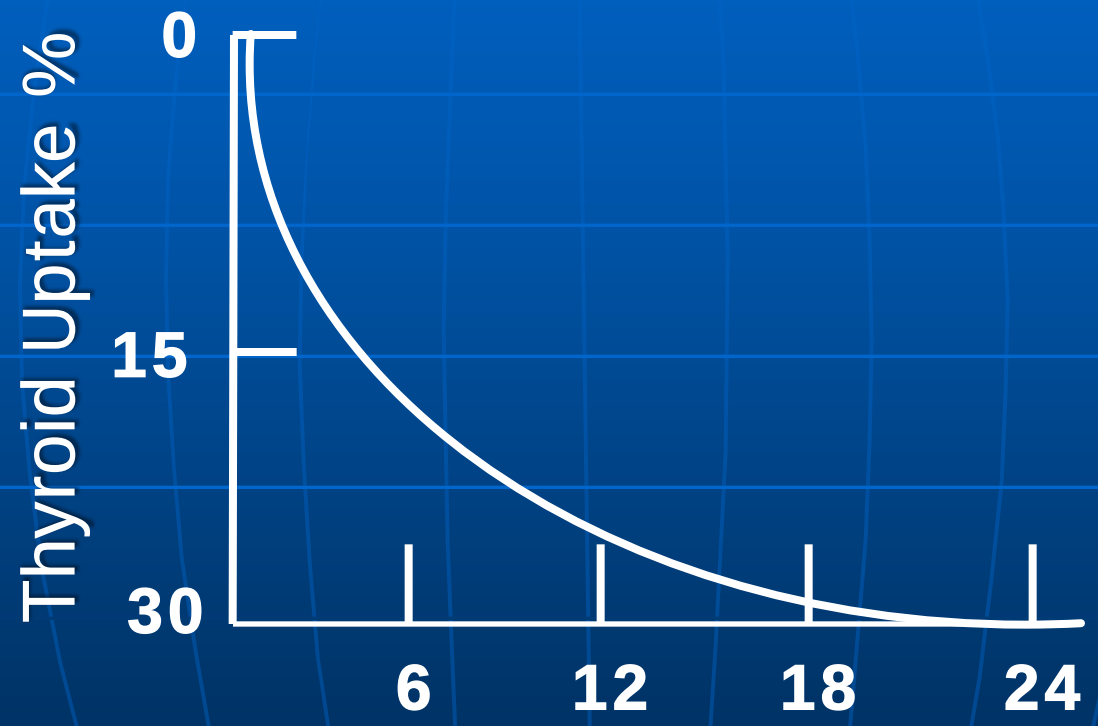
Blocking Agents

- Saturate the metabolic processes in a specific tissue with the stable element
- Reduces uptake of the radionuclide but must be administered in a form that is rapidly absorbed
- Example – use of stable iodine to prevent incorporation of radioiodine in the thyroid

Saturate the Critical Organ with the Stable Isotope



Prompt KI Treatment of ^{131}I Intake is Highly Effective



Time of administration post-exposure, hours

FDA Recommendations for Potassium Iodide

Group	Daily Dose [mg]
Infants <1 month	16
Children 1 month – 3 years	32
Children and teenagers 3 – 18 years	65
Adults (including pregnant and lactating women and adolescents over 150 pounds)	130

Daily dosing should continue until the risk of exposure has passed and/or until other measures (evacuation, sheltering, control of the food and milk supply) have been successfully implemented

Diluting Agents

- Isotopic dilution by administration of large quantities of the stable element so that statistically, the opportunity for incorporation is decreased
  - Example – use of water to reduce the effective half-life of tritium (^{3}H, H-3, radioactive hydrogen)
  - The diluting agent must be at least as readily absorbed and metabolized as the radionuclide

Tritium - ^{3}H

- Follows pathway of water in the body
- Penetrates skin, lungs, and GI tract, either as tritiated water (HTO) or in the gaseous form
- Single exposures are treated by forcing fluids

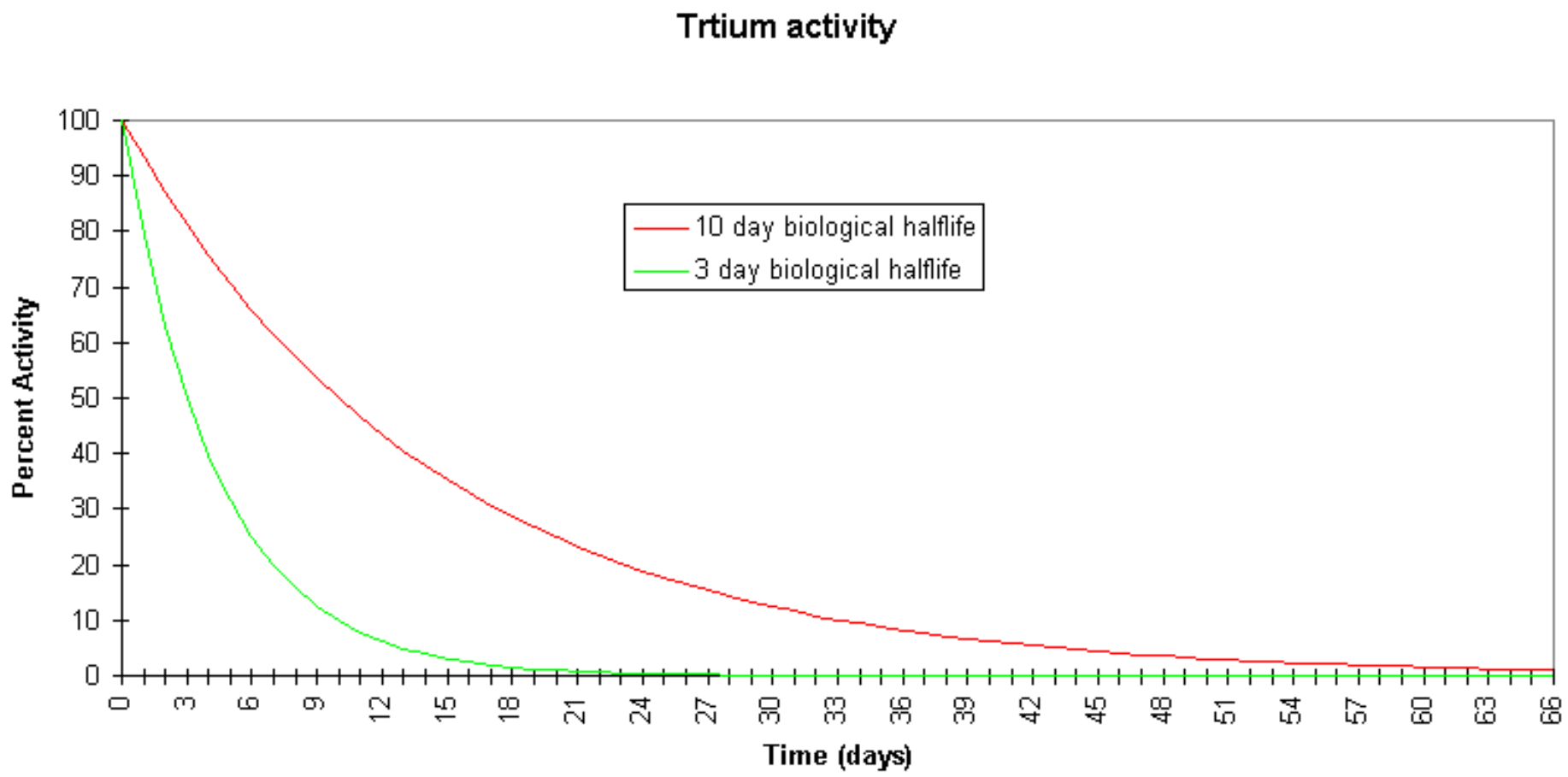
Isotopically Dilute

Tritium

Tritium - ^{3}H

- This has the dual value of diluting the tritium and increasing excretion
- Biological half-life - 10 days
- Forcing fluids to tolerance (3-4 L/d) will reduce the biological half-life to 1/3 to 1/2 of the normal value

Effect of Increasing Water Intake



Displace

- Use calcium to compete with radio-strontium
- Use stable iodide to compete with radiotechnetium

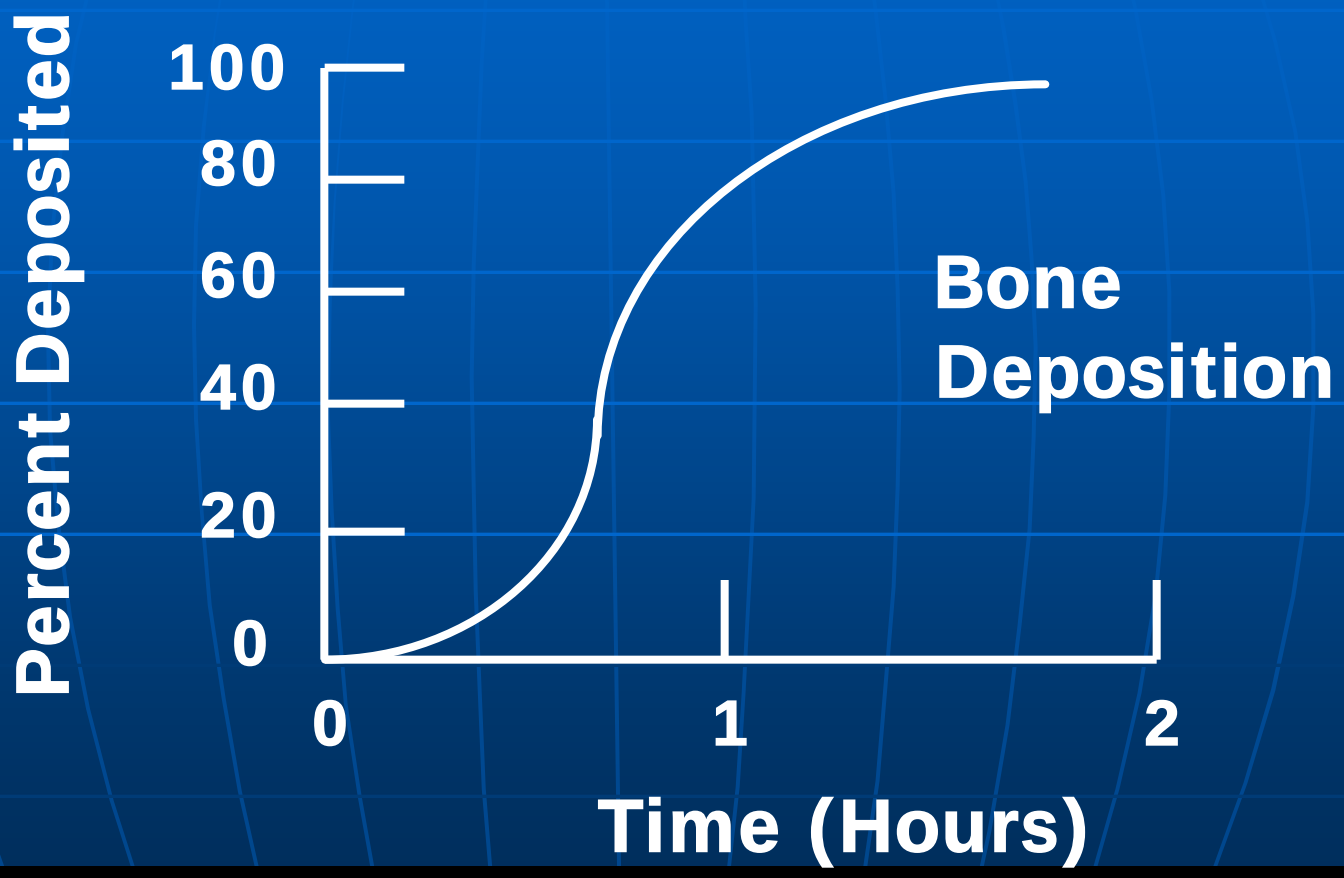
Reduction of Absorption From Gastrointestinal Tract

- Antacid
- Precipitation into insoluble salt
- Catharsis

Chelate

- DTPA – Diethylenetriaminepentaacetic Acid
- EDTA – Versene
- BAL – Dimercaprol
- DFOA – Deferoxamine
- PCA - Penicillamine

Uptake of Actinides is Remarkably Rapid



Prompt DTPA Treatment of ^{239}Pu Intake is Highly Effective

Retention (% of Uptake)

	Control	DTPA Treated
Liver	14.0	0.47
Skeleton	57.0	5.9

DTPA

- Trisodium calcium diethylenetriamine-pentaacetate (Ca-DTPA)
- Chelating agent for transuranic elements
- Ca-DTPA is ~10 times more effective than Zn-DTPA for initial chelation of transuranics
- Treatment of choice for initial patient management

Clinical Pharmacology of DTPA

- DTPA belongs to the group of synthetic polyamino-polycarboxylic acids which form stable complexes (metal chelates) with a large number of metal ions

- DTPA
  - exchanges calcium (zinc) for another metal of greater binding power
  - Chemical complex (the *chelate* is then excreted by the kidneys
  - The plasma half-life of DTPA is 20-60 minutes.
  - DTPA undergoes only a minimal amount of metabolic change

Clinical Pharmacology of DTPA

- No accumulation of DTPA in specific organs has been observed
- Promptly cleared from the body by glomerular filtration
- Ca-DTPA can deplete the body of zinc and, to a lesser extent, manganese with repeated dosing
- Ca-DTPA is approximately 10 times more effective than Zn-DTPA for initial chelation of transuranics

Actinides

- Plutonium, Americium, Curium and Californium
- All have long biological half-lives
- Inhalation is approximately 75% of industrial exposures
- If the compound is soluble (nitrate, citrate, fluoride), compound is ultimately translocated from the lungs to ultimate disposition sites (bone and liver)
- Ca-DTPA and Zn-DTPA chelation therapy is the treatment of choice

DTPA

- Must be given as soon as possible after internalization
- After 24 hours, Ca-DTPA and Zn-DTPA are essentially equally effective
- Repeated dosing of Ca-DTPA can deplete the body of zinc and manganese

DTPA Dosing Schedules

- 1 gm IV or inhalation in a nebulizer (1:1 dilution with water or saline)
- Very safe drug with no significant adverse reactions noted during 25 years of usage
- Initially: 1 gm Ca-DTPA; repeat 1 gm Zn-DTPA daily up to five days if bioassay results indicate need for additional chelation
- Ca-DTPA - Pregnancy category D; Zn-DTPA - Pregnancy category C

DTPA - Relative Contraindications

- Pregnancy - Use first dose as Zn-DTPA instead of Ca-DTPA
- Diabetic on insulin - use Zn-DTPA and monitor glucose levels
- Depressed myelopoietic function - clinical judgment
- Impaired renal function - clinical judgment
- Children - no data available

How to Administer DTPA

- IV injection of DTPA (1 gm/4ml) with 6 ml saline over 5-10 minutes
- IV Piggyback (1 gm DTPA in 100ml saline) over 20 minutes
- Aerosol: 1 gram undiluted via hand-held nebulizer; inhalation takes 10-15 minutes

How to Administer DTPA

- IM injection – very painful
- Under 18 YOA – use zinc-DTPA
- Monitor magnesium and other electrolytes routinely
- Complete package information available at www.orau.gov/reacts/resources.htm

Uranium

- Solubility classes:
  - o UF_6 (uranium hexafluoride): Class D (days)
  - o $UO_2(NO_3)_2$ - Uranyl nitrate: Class D
  - o UO_2 - Uranium dioxide: Class W,Y (weeks, years)
  - o UO_2 - High-fired Uranium dioxide: Class Y
- Inhalation is usual occupational exposure
- Overall biological half-life of 15 days
- 85% of retained U resides in bone
- Kidney toxicity is the basis of occupational exposure limits

Uranium

- In acidic urine, uranyl ion complex with tubule surface proteins
- Some of the bound UO_2^{2+} is retained in the kidney
- Kidney is the first organ to show chemical damage in the form of nephritis and proteinuria
- Oral doses or infusions of sodium bicarbonate are the treatment of choice and should be dosed to keep the urine alkaline by frequent pH measurements

Uranium

Urine Alkalinization:

- Sodium bicarbonate
- IV dosage: 1 mEq/kg/day IV with 10-20 mEq KCl to maintain urine at pH >7.5
- Oral dosage: from the 1979 NCRP 65
- *Adults:* Initially, 1-10 mEq/kg/day or 4 g PO then 1-2 g every 4 hours. Titrate dosage based on urinary pH. *Children:* 1-10 mEq/kg/day (84-840 mg/kg/day) PO, given in divided doses every 4-6 hours. Titrate dosage based on urinary pH.
- May need renal dialysis until renal recovery from injury.

What We've Learned

- Various methods of elimination of radioactive materials from the body
- This is really a toxicological issue, *i.e.*, treatment of poisoning
- There are no specific antidotes or "medical countermeasures" for most internal contaminations

QUESTIONS