Treatment for Internal Contamination

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Objectives

- Describe the issues associated with internal contamination
- Explain the various methods used in decorporation therapy of isotopes involved in internal contamination

Management Issues

- In the absence of personal dosimetry, the **delay in presentation of clinical findings** will cause some difficulties for decision-making

- **Alpha-emitting radionuclides** present difficulties for detection, identification and quantification

Management Issues

- Instrumentation for identification of radionuclides may not be immediately available
- Laboratories for bioassay analysis or body counting may not be immediately available

Definition of Internal Contamination

The deposition of radioactive material inside the body.

Common Routes of Entry

- Inhalation
- Ingestion
- Absorption through wounds or skin
- Injection / puncture

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

Toxicological Terms

- Target organ – the organ that is primarily involved with metabolism of a toxicant
- Critical organ – same as the target organ
- Source organ – an organ that concentrates a toxicant that results in irradiation of other tissues

Important Factors

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

Methods for Assessing Intakes

- Whole Body Counting:
  - Feasible for nuclides that emit penetrating x-ray or gamma rays
  - Useful also for nuclides emitting energetic beta particles
- Bioassay:
  - Urine - most widely used
  - Feces
  - Excised material from wounds

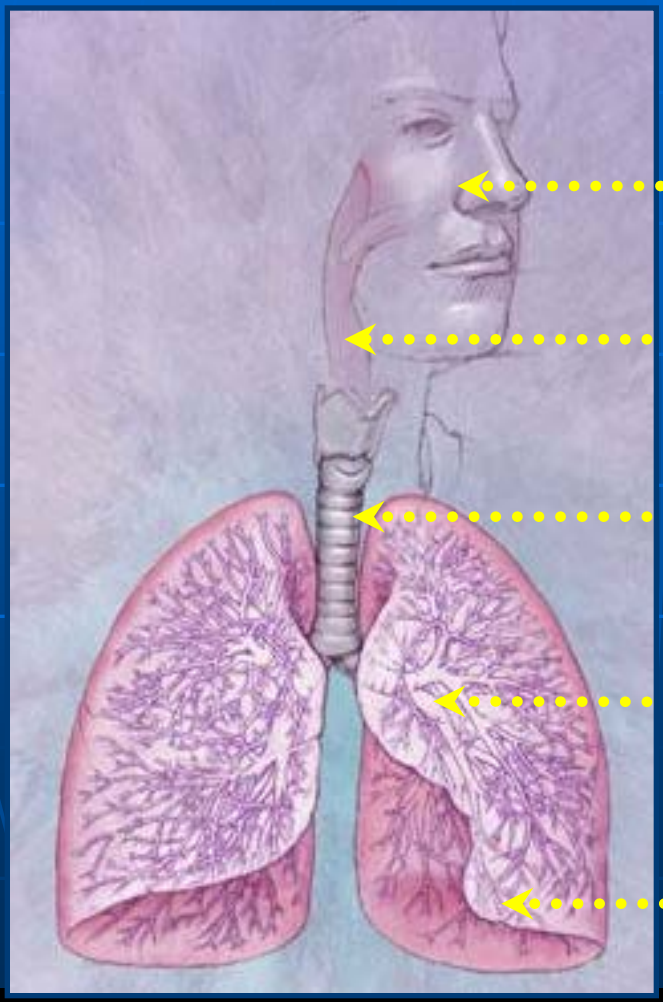
Immediate Diagnosis

- Nasal swabs
- Nasal blows
- Facial surveys
- Sputum
- Spot check urine
- When all else fails - get a good history!

Inhalation Pathway

- **Size** of the particle determines where it's deposited
- **Insoluble** particles remain in the lung for long periods of time
- A small fraction will be transported to the tracheo-bronchial lymph nodes by pulmonary macrophages
- Some cleared through airways, swallowed, and excreted in feces

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

Average stay time in the GIT is 48 hours (1-5 days), so one issue with ingestions is to remove the contaminant or speed up transit time to decrease irradiation of surrounding tissues

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

Major Treatment Methods

1. Reduce and / or inhibit absorption from the gastrointestinal (GI) tract
2. Block uptake to the organ of interest
3. Isotopic dilution
4. Alter chemistry

Major Treatment Methods

5. Displace from receptors
6. Chelation
7. Excision of radionuclide from wound
8. Consider bronchoalveolar lavage (BAL) for insoluble inhaled materials

Major Treatment Methods

1. ***Reduce and/or inhibit absorption from the GI tract***

2. Block uptake to the organ of interest

3. Isotopic dilution

4. Alter chemistry

Reduce / Inhibit GI Absorption

- Antacid - aluminum containing
- **Precipitation into insoluble salt ($BaSO_4$)**
- Cathartics/laxatives – not with acute abdomen, obstruction, etc.
- **Ion exchange – Prussian Blue**
- Gastric lavage (?)– only if recently ingested, large quantities of material
- Enemas / colonic – may ↓ “stay” time

Reduce or Inhibit GI Absorption

- **Barium sulfate**
  - Same insoluble salt used for GI x-ray contrast studies
  - **Precipitates Radium (Ra) or Strontium (Sr) as insoluble sulfates in the GI tract**
  - Dosage form: liquid
  - Dose: 100-300 g po X1 in 250 ml of water (65: 200-300 ml)
  - Name alert: Ba sulfide or sulfite are toxic

Prussian Blue (PB) Treatment of Radio-Cesium or Thallium

- **Cesium (Cs) and thallium (Tl)** are soluble, are taken to liver then bile and back into small intestine
- PB binds **soluble** cesium or thallium in gut **to become insoluble** and excreted via GI tract (bypasses enterohepatic circulation)
- Removes 70% with each pass through GI tract and shortens half-life

Thallium Poisoning

MSNBC News:

2/9/2011 New Brunswick, New Jersy

Chemist accused of poisoning husband to death.

She allegedly gave him a dose of a highly toxic metal known as thallium

Prussian Blue Therapy

- Dosage form: gelcaps, 500 mg each, bottles of 30
- FDA recommended dosage: 3 gm TID (NCRP 161 – tripled from 1gm TID in NCRP 65)
- Side effects - constipation is one SE that can easily be taken care of with mild laxatives
- Be sure to tell the patient - blue feces

Major Treatment Categories

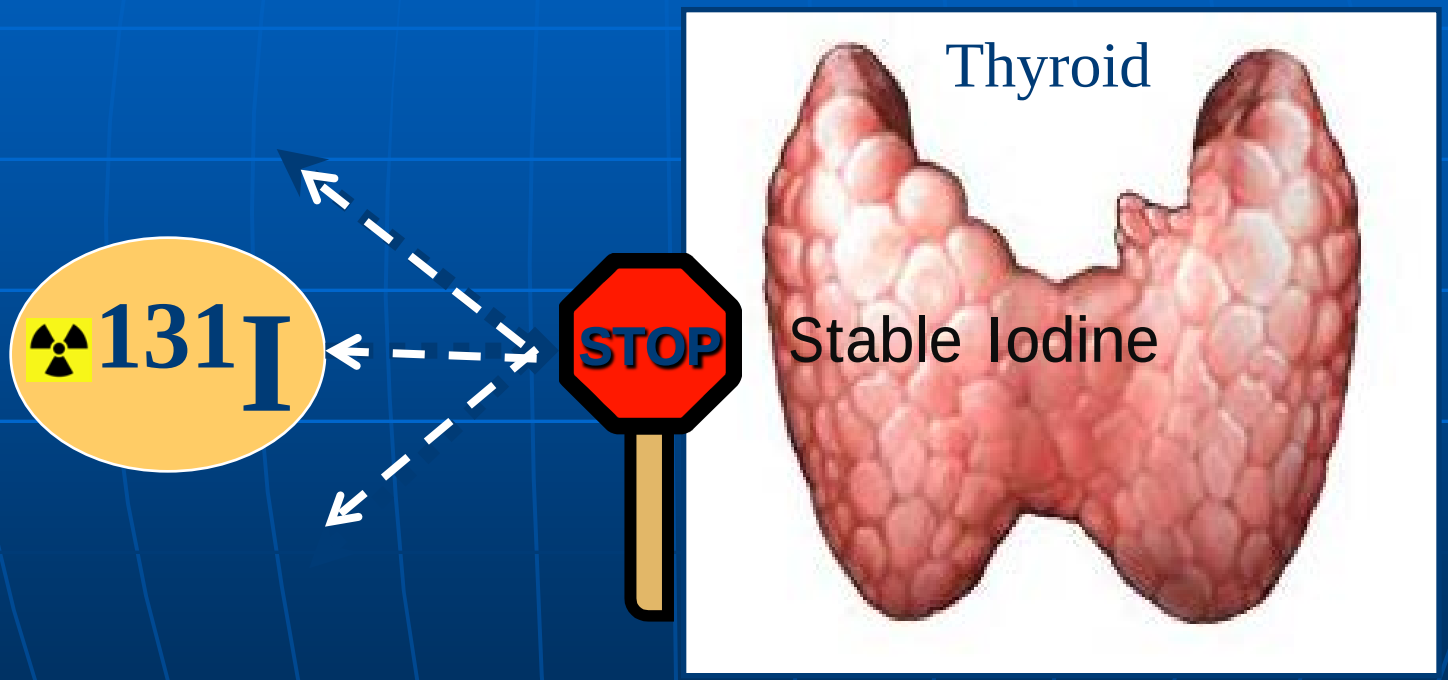
1. Reduce and/or inhibit absorption from the GI tract

2. ***Block uptake to the organ of interest***

3. Isotopic dilution

4. Alter chemistry

Block or Saturate the Critical Organ with the Stable Isotope



Iodine

- Dominant initial internal contaminant after a reactor accident, nuclear weapons test, or any incident involving *fresh* fission products is likely to be ^{131}I
- Give 130 mg KI tablet stat (If not given in the first 6-12 hours post-incident, consider other options)

FDA Recommendations for Potassium Iodide

- A daily dose of:
  - 16 mg of KI for infants <1 month
  - 32 mg of KI for children 1 month to 3 years
  - 65 mg of KI for children and teenagers 3 years to 18 years
  - 130 mg of KI for adults including pregnant and lactating women and adolescents over 150 pounds

FDA Recommendations for Potassium Iodide

- 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

Childhood Thyroid Cancer near Chernobyl

- In Gomel region of Belarus, north of Chernobyl, children screened for thyroid cancer by physical exam, ultrasound of the thyroid, and thyroid function tests
- Prior to the accident, thyroid cancer rate = 0.5 / million.
- 1991-1994, rate = 96.4 / million, almost a **200-fold increase**
- BMJ, vol 310, p 801, March 25, 1995

KI Side Effects

- Iodine-induced thyrotoxicosis
  - More common in the elderly
  - More common in iodine-deficient areas
  - Usually require repeated doses

NCRP: 161

KI Side Effects

- Iodine goiter & hypothyroidism
  - More common in iodine-sufficient areas
  - Usually require chronic high doses
  - Treat with caution in patients with multinodular goiter, Graves' disease and autoimmune thyroiditis

KI Side Effects

- Transient hypothyroidism in neonates <1 month of age
  - 214 (0.37%) neonates in Poland after Chernobyl
  - Even transient hypothyroidism can have a profound effect on intellectual development
  - Monitor thyroid function (TSH & T_4) for the first month of KI use in this age group

Alternatives to KI Tablets (Not FDA Approved)

- 5 or 6 drops of Saturated Solution of Potassium Iodide or SSKI (1 g/ml)
- Potassium perchlorate (200 mg) may be used in patients with iodine sensitivity
- Povoiodine (Betadine®) topically
- Anti-thyroid propylthiouracil (PTU), methimazole (MMI) <u>may be effective if given <8 hrs, interferes with oxidation of iodide ion</u> (toxicity issues)

Major Treatment Categories

1. Reduce and/or inhibit absorption from the GI tract
2. Block uptake to the organ of interest
3. ***Isotopic dilution***
4. Alter chemistry

Isotopic Dilution: 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 to tolerance (3-4 litres/d)
- Dilutes the tritium and increases excretion
- Reduces the biological half-life (10 days) to 1/3 to 1/2 of the normal value

Use of Ethanol - NOT FDA APPROVED

Tritium

Major Treatment Categories

3. Isotopic dilution

4. ***Alter chemistry***

5. Displace from receptors

Uranium – Altering the Chemistry

- At normal enrichment of 0.3% ^{235}U, the toxicity of uranium is chemical
- At enrichment >~8%, radiological toxicity to the kidney assumes greater importance
- **In the blood, uranium ionizes**
- The most important ionic form is the **uranyl ion** or **UO_2^{2+}**
- 60% binds with carbonate which is non-toxic

Uranium – Altering the Chemistry

- In **acidic** urine, **uranyl ion** complexes with **tubular 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** (nephrotoxic)

Uranium Management

- **Sodium bicarbonate** - Oral: titrate dosage based on urinary **pH of 8-9**; monitoring hourly and continue for 3 days
  - *Adults:* 2 sodium bicarbonate tablets (4g) po then 1-2 g every 4 hours
  - *Children:* 1-10 mEq/kg/day (84-840 mg/kg/day) po given in divided doses every 4-6 hours

Uranium Management

- For high level U intake, consider diuretics
- Consider dialysis for higher levels of internal contamination or in the case of renal failure

Major Treatment Categories

3. Isotopic dilution

4. Alter chemistry

5. ***Displace from receptors***

Displace from Receptors

- Use **Calcium** (calcium gluconate IV) to compete with **radiostrontium**
  - Other treatments- aluminum phosphate, aluminum hydroxide, barium sulfate, sodium alginate
- Use stable iodide to compete with **radiotechnetium** (half-life so short shouldn't need therapy)

Major Treatment Categories

6. ***Chelate***

7. Excise radionuclides from wounds

8. Consider bronchoalveolar lavage (BAL) for insoluble inhaled materials

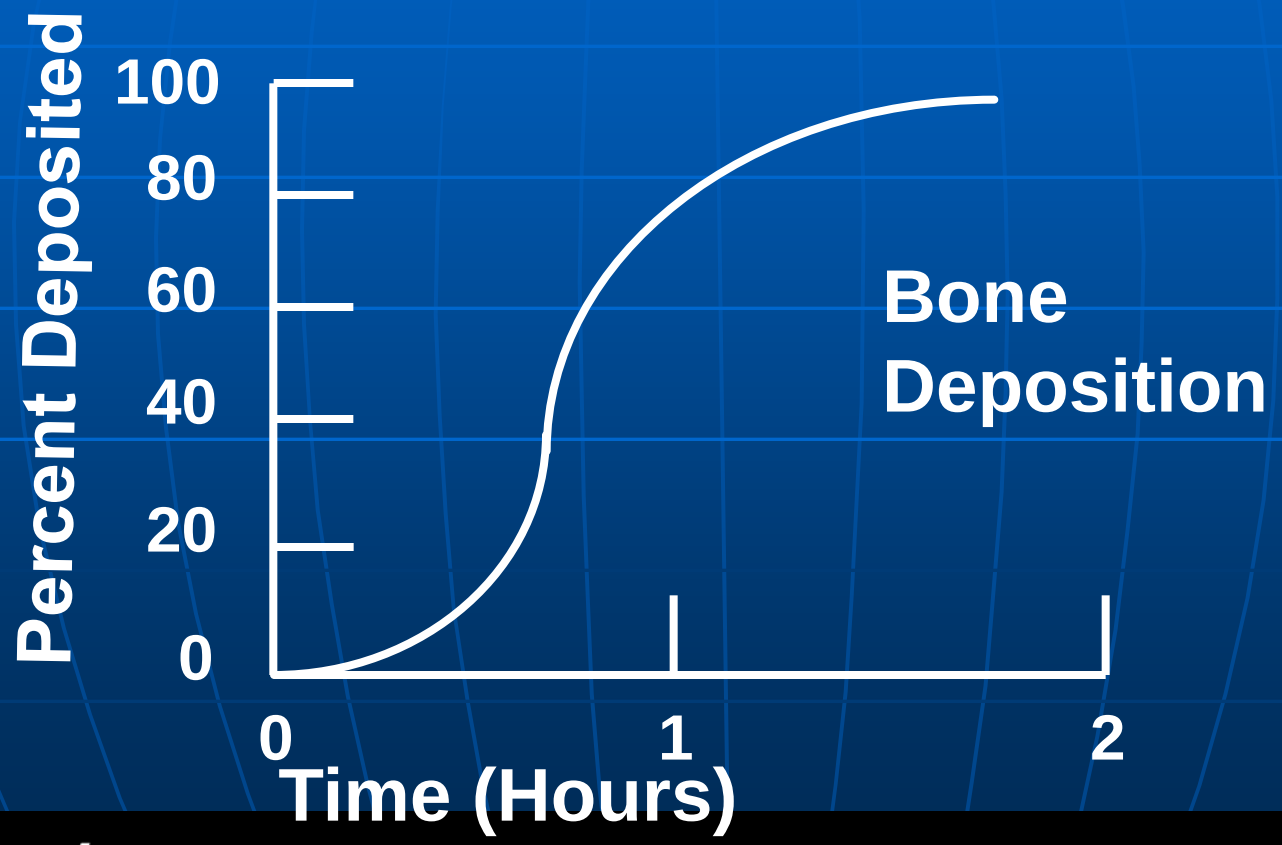
Treatment with Chelation

- ***DTPA - Diethylenetriaminepentaacetic acid***
- EDTA - Versene
- BAL - Dimercaprol
- DFOA - Deferoxamine
- PCA - Penicillamine

Chelation and Actinides

- **Plutonium, Americium, Curium** (and Californium – not FDA approved)
- All have long biological half-lives
- Inhalation 75% of industrial exposures
- If the compound is soluble (nitrate, citrate, fluoride), it is translocated from the lungs to ultimate deposition sites (bone and liver).
- **Ca-DTPA and Zn-DTPA** chelation therapy is the treatment of choice.

Uptake of Actinides is Remarkably Rapid



Calcium DTPA (Ca-DTPA)

- Trisodium calcium diethylenetriaminepentaacetate
- Approximately ***10 times > effective*** than Zn-DTPA for **INITIAL chelation**
- After 24 hours, Ca-DTPA = Zn-DTPA in effectiveness
- Repeated dosing of Ca-DTPA can deplete the body of **zinc and manganese**, so use Zn-DTPA

Clinical Pharmacology of DTPA

- **Exchanges** calcium or zinc for another metal of greater binding power
  - Complex promptly excreted by the kidneys.
  - The plasma half-life of DTPA is 20-60 minutes
  - **DTPA undergoes only a minimal amount of metabolic change and no accumulation in specific organs**

DTPA Dosing Schedules

- Dosage of Ca-DTPA and Zn-DTPA is **1 gm IV or inhalation in a nebulizer** (1:1 dilution with water or saline)
- Initially: 1 gm Ca-DTPA; repeat 1 gm Zn-DTPA daily up to five days if bioassay results indicate need for additional chelation
- No significant adverse reactions in 25 yrs
- Ca-DTPA - Pregnancy category C
- Zn-DTPA - Pregnancy category B

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** – (leukopenia) clinical judgment.
- **Impaired renal function** - clinical judgment.
- **Children** - no data available.

New for DTPA

- More delineation of its use for wound irrigation
  - 1 g DTPA and 10 mL of 2% lidocaine in 100 mL of 5% glucose solution or sterile isotonic saline
- For lanthanides and actinides
- Either Ca- or Zn-DTPA

Major Treatment Methods

6. Chelate

7. ***Excise radionuclides from wounds***

8. Consider bronchoalveolar lavage (BAL) for insoluble inhaled materials

Wound Excision

- Embedded radioactive foreign bodies or contamination in a wound may translocate to regional lymph nodes, etc.
- Irrigation (remember can use DTPA for Pu) and chelation
- May have to excise – punch biopsy may be enough or may have to have local excision(s)

Wound Excision

- Management is particularly difficult with alpha emitters
- Wound closure depends entirely on medical needs
- **Decontaminate but do not mutilate!**
- Strongly consider surgical consultation

Major Treatment Methods

6. Chelate

7. Excise radionuclides from wounds

8. ***Consider bronchoalveolar lavage (BAL) for insoluble inhaled materials***

Bronchoalveolar Lavage (BAL)

- Consider if large amount of radioactive material inhaled
  - Consider only if estimated lung dose likely to be > 5 Sv (500 rem), within a few weeks
- No new literature (30 years old)

Summary of Treatment NCRP 161

- Americium (Am) → DTPA
- Californium (Cf) → DTPA
- Calcium (Ca) → Strontium therapy
- Cesium (Cs) → Prussian Blue
- Cobalt (Co) → DTPA and EDTA
- Curium (Cm) → DTPA
- Fluorine → Aluminum Hydroxide
- Gold (Au) → BAL

Summary of Treatment NCRP 161

- Iodine (I) → KI
- Thallium → Prussian Blue
- Plutonium (Pu) → DTPA
- Radium (Ra) → Strontium therapy
- Strontium (Sr) → Strontium therapy
- Tritium (H-3) → Water diuresis
- Uranium (U) → Bicarbonate

Good References!

- NCRP 65: Management of Persons Accidentally Contaminated with Radionuclides (April, 1980)
- NCRP 161: Management of Persons Contaminated with Radionuclides (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, Sept., 1988)

More Good References

- www.orau.gov/REACTS
- Ca/Zn DTPA Package Insert
- Prussian Blue Package Insert
- KI Package Insert