Efficacy and Expected Benefit of Currently Available, Medical, Radiation Countermeasures For Nuclear Detonation Scenario

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OBJECTIVES

- Discuss the body’s mechanisms for the internalization of radionuclides.
- Discuss the procedures for diagnosis and treatment of internal contamination with nuclear detonation fission products and methods for assessing the efficacy of those countermeasures.
- The importance of supportive treatment, antibiotics, antivirals, etc., cytokines and stem cell transplants is covered in the talks of others.
XX-12 GRABLE fired on May 25, 1953 at the Nevada Test Site. A 280mm artillery gun fired the 15 kiloton nuclear shell. This was the only time a nuclear artillery shell was ever fired. (Ground Burst, with much fallout)
Radioisotope plume distribution
Internal Contamination Pathways
Following Nuclear Detonation

- An internal dose may occur from inhaling fission products directly from plume or from ground contamination resuspension.

- An internal dose may occur from ingestion of contaminated fission products in food or water.
Early Protective Actions
Available to the Public

- Sheltering /Evacuation (These are the best ways to prevent/reduce internal contamination and avert internal radiation dose.)

- Stable Iodine Prophylaxis

- Other medical countermeasures are also useful for dose mitigation.
Emergency Room Teamwork: Physician And Nurse

REAC/TS stresses the need for the formal integration of the Health Physicist into the team’s response for the diagnosis, triage and treatment of radiologically contaminated patients.
Definition of Internal Contamination

The deposition of radioactive material inside the body.

Common Routes of Entry

- Inhalation
- Ingestion
- Absorption through wounds or skin
- Injection
Internal Deposition

- **Annual Limit on Intake (ALI)**
  - Intake required to deliver 5 rem CEDE or a CDE of 50 rem to any individual organ.

- **Derived Air Concentration (DAC)**
  - $\text{DAC (} \mu\text{Ci/ml} \text{)} = \text{ALI (} \mu\text{Ci})/2.4\times10^9 \text{ ml}$

- **DAC-Hrs**
  - $\% \text{ DAC} \times \text{ Person-hrs worked}$
# Some ALI’s of Interest

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>ALI (inhalation)</th>
<th>ALI (ingestion)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MBq</td>
<td>uCi</td>
</tr>
<tr>
<td>Hydrogen-3</td>
<td>2,960</td>
<td>80,000</td>
</tr>
<tr>
<td>Phosphorus-32</td>
<td>14.8</td>
<td>400</td>
</tr>
<tr>
<td>Cobalt-60</td>
<td>1.1</td>
<td>30</td>
</tr>
<tr>
<td>Strontium-90</td>
<td>0.148</td>
<td>4</td>
</tr>
<tr>
<td>Cesium-137</td>
<td>7.4</td>
<td>200</td>
</tr>
<tr>
<td>Radium-226</td>
<td>0.022</td>
<td>0.6</td>
</tr>
<tr>
<td>Uranium-238</td>
<td>0.0296</td>
<td>0.8</td>
</tr>
<tr>
<td>Plutonium-239</td>
<td>0.0002</td>
<td>0.006</td>
</tr>
</tbody>
</table>
Immediate Diagnosis

- Nasal swipes
- Nasal blows
- Facial surveys
- Sputum
- Spot urine***
- When all else fails - get a good history!
Methods for Assessing Intakes

- **Whole Body or Lung Counting:**
  - Feasible for nuclides that emit penetrating x or gamma rays.
  - Useful also for nuclides emitting energetic beta particles - can be detected by their bremsstrahlung radiation.

- **Bioassay:**
  - 24 hour Urine collections - most widely used.
  - 24 hour Feces collections
  - Excised material from wounds.

- **Cytogenetic Biodosimetry** (? FISH, micronuclei)
The intent and goals of decorporation and other forms of medical countermeasure therapy are:

- To reduce the residence time and the absolute amount of internalized radionuclides.
- And, consequent reduction of delivered radiation dose to the whole body and/or organs.
- In order to reduce stochastic and/or deterministic risks.
Particle Size Distributes in the Respiratory Tree (Physiology Acts as Countermeasure!)

Particle Size (Micron, Mass Median Diameter)

- 18-20
- 15-18
- 7-12
- 4-6 (bronchioles)
- 1-5 (alveoli)
## Absorption of Ingested Radionuclides

<table>
<thead>
<tr>
<th>GROUP</th>
<th>RADIOACTIVE ELEMENTS</th>
<th>%ABSORBED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinides</td>
<td>Pu, Am, Cf</td>
<td>Low, approx 0.1%</td>
</tr>
<tr>
<td>Alkali Metals</td>
<td>Na, K, Rb, Cs, Sr</td>
<td>High, approx 90%</td>
</tr>
<tr>
<td>Group VIII Metals</td>
<td>Fe, Co, Ru</td>
<td>10%, 30-90%, 3%</td>
</tr>
</tbody>
</table>
Simple Meds to Reduce Absorption From Gastrointestinal Tract

1. Aluminium Based Antacids

2. Precipitation into insoluble salts (Barium Sulphate)

3. Catharsis
Dilution Is the Treatment for H-3
KI Saturates the Critical Organ (Thyroid) with Stable Isotope ¹³¹I
Prompt Treatment of $^{131}$I Intake With Oral KI Is Effective

![Graph showing thyroid uptake over time. The x-axis represents time of administration post-exposure in hours, ranging from 0 to 24. The y-axis represents thyroid uptake in percentage, ranging from 0% to 30%. The graph shows a decrease in thyroid uptake as time increases.]
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

- 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.
Uranium Treatment

PROBLEM: Mainly **Chemical** toxicity to kidney, unless enriched U-235

TREATMENT:

- Early Rx is Effective: Sodium bicarbonate to alkalinize urine
- Oral dosage:
  - **Adults**: Initially, 4 g PO then 1-2 g every 4 hours. Titrate dosage based on urinary pH (about 8).
  - **Children**: 1-10 m Eq/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.
Cesium

- $^{137}$Cesium (physical half-life, 30 years; biological half-life 109 days) is the dominant radioisotope in aged fission products.
- Distributes in body fluids similarly to potassium.
- The most effective means for removing radioactive cesium is the oral administration of ferric (III) hexacyanoferrate (II), commonly called Prussian Blue.
- One gram orally three times daily for 3 weeks reduces the biological half-life to about 1/3 of the normal value.
Prussian Blue is Highly Effective in Rx of Radio-Cesium or Thallium Uptake*

- Binds ions in gut
- Reduces biological half life to one third of untreated value
- Not absorbed
- Reduces recycling

*Complete package information available at www.orau.gov/reacts/resources.htm
Prussian Blue is Highly Effective for Treatment of Cesium-137

- Prussian Blue (oral) binds cesium ions in the gastrointestinal tract.
- The Prussian Blue-cesium complex is not absorbed and is excreted in feces.
- Prussian Blue thereby reduces the entero-hepatic recycling and may reduce the cesium biological half-life/dose ~ one third (but more clinical data is needed—there is very limited clinical experience in the United States).
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).
- Calcium-DTPA (trisodium calcium diethylenetriaminepentaacetate) and Zinc-DTPA (trisodium zinc diethylenetriaminepentaacetate) chelation therapy is the treatment of choice.
Uptake of Actinides Can Be Remarkably Rapid

<table>
<thead>
<tr>
<th>Time (Hours)</th>
<th>Percent Deposited</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
</tr>
</tbody>
</table>

Bone Deposition
Prompt DTPA Treatment of $^{239}\text{Pu}$ Intake May Be Very Effective

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>DTPA Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>14.0</td>
<td>0.47</td>
</tr>
<tr>
<td>Skeleton</td>
<td>57.0</td>
<td>5.9</td>
</tr>
</tbody>
</table>
REAC/TS Stockpile/Drug Registry

- Maintains FDA Registries for DTPA and Prussian Blue use in the United States
- Provides a stock of pharmaceuticals at REAC/TS and on site with co-investigators for treatment of internal contamination:
  - Calcium- and Zinc-DTPA
  - Prussian Blue (Radiogardase®)

Through a network of physician co-investigators, special drugs are readily available in the event of radiation emergencies including nuclear terrorism.
647 cases of DTPA treated patients, from 1976 to 2006 in USA (including those under either IND or NDA).

4,704 doses administered (Most cases treated with a single dose).

- Few side effects in healthy adult human males.
- But, essentially untested in adult females, infants and children in USA. Ca-DTPA is not recommended for use in pregnant women (or children?). This policy is based on animal studies, so human Ca and Zn-DTPA data on women and children and other special populations (people with diseases) is needed before mass casualty Rx decisions are made.
Combined Calcium-DTPA / Zinc-DTPA Therapy Guidelines

- Assure that a credible incident has occurred and that the exposed person(s) at risk has, in all likelihood, become internally contaminated with plutonium, americium, californium, etc.
- Estimate the magnitude of the accident.
- Obtain the patient’s informed consent.
- Obtain base-line Complete Blood Count (CBC) with differential, Blood Urea Nitrogen (BUN), creatinine, urinalysis and urine/fecal radioassay samples.
DTPA

- Trisodium calcium diethylenetriaminepentaacetate (Calcium-DTPA).
- Chelating agent for transuranic elements.
- Calcium-DTPA is approximately 10 times more effective than Zinc-DTPA for initial chelation of transuranics. It is the treatment of choice for initial patient management. Must be given as soon as possible after accident.
- After 24 hours, Calcium-DTPA and Zinc-DTPA are essentially equally effective.
- Repeated dosing of Calcium-DTPA can deplete the body of zinc, magnesium and manganese.
REAC/TS Guidelines for DTPA Rx

- Decision must be made by qualified medical personnel.

- No official guidance on Rx: 1-10 ALI

- Risks from treatment (if any) need to be balanced against radiological risk without treatment.

- Consider the patient’s entire health profile, including psychological.
Guidelines for Use of DTPA*

- IV injection of DTPA (1 gm/4ml) with 6 ml saline over 5-10 minutes

- IV Piggyback (1 gm DTPA in 100ml saline), 20 min.

- Aerosol: 1 gram undiluted via hand-held nebulizer; inhalation takes 10-15 minutes

- IM injection (painful, use with procaine)

- Initially use Ca-DTPA, unless <18 YOA or question of pregnancy, then use only Zn-DTPA

*Ck renal function; monitor Mg, Mn

*Complete package information available at www.orau.gov/reacts/resources.htm
Bioassay Monitoring Guidelines
(depends on chemical form, particle size, radionuclide)
For example:

<table>
<thead>
<tr>
<th>EMENENT</th>
<th>Feces</th>
<th>Urine</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plutonium</td>
<td>24 hours</td>
<td>2-3 weeks</td>
<td>24 hr excretion</td>
</tr>
<tr>
<td>Uranium</td>
<td>24 hours</td>
<td>24 hours</td>
<td>24 hr excretion</td>
</tr>
<tr>
<td>Tritium</td>
<td>N/A</td>
<td>12 hours</td>
<td>single voiding</td>
</tr>
</tbody>
</table>
Example: Special Considerations in Rx of Internal Contamination

- There are special medical issues associated with the treatment of internal contamination; and there are special bioassays for assessing the efficacy of such treatment.

- There are often important psychological issues involved in the management of patients with internal contamination.

- A case study example from the REAC/TS registry will demonstrate these issues.
Am-241 Inhalation, Case Study

- Two workers were transferring $^{241}$Am from a shipping barrel to a disposal container.
- The workers were wearing respiratory protection.
- But, a supervisor was also present, and not wearing respiratory protection.
On exit, all three workers were noted to have facial contamination – and room air samples were positive for alpha.

Lung count bioassay was advised and performed the next day - all 3 patients were positive.

24 hr urine /fecal bioassay begun.
Day 1 Bioassay results

- Patient #1 (supervisor, male):
  - Lung content: 400 Bq
  - Urine: 1 Bq per day

- Patient #2 (female):
  - Lung content: 200 Bq
  - Urine: 0.12 Bq per day

- Patient #3 (male):
  - Lung content: 50 Bq
  - Urine: 0.06 Bq per day
Intakes and Effective Doses

- Patient #1: 1.8 kBq, 210 mSv
- Patient #2: 0.63 kBq, 73 mSv
- Patient #3: 0.15 kBq, 17 mSv (?Stop DTPA?).

- Chelation Tx begun on day 2 with Ca-DTPA for the males and Zn-DTPA for the female, continued for 5 days.

- Bioassay measurements continued
Bioassay Results - Day 6

- **Patient #1 (supervisor, male):**
  - Lung content: 270 Bq
  - Urine: 22 Bq per day

- **Patient #2 (female):**
  - Lung content: 100 Bq
  - Urine: 1.9 Bq per day

- **Patient #3 (male):**
  - Lung content: 21 Bq
  - Urine: 0.4 Bq per day
Averted Doses

- Patient #1:
  - w/o DTPA Tx: 210 mSv
  - w/ DTPA Tx: 49 mSv

- Patient #2:
  - w/o DTPA Tx: 73 mSv
  - w/ DTPA Tx: 38 mSv

- Patient #3:
  - w/o DTPA Tx: 17 mSv
  - w/ DTPA Tx: 10 mSv
Long term bioassay monitoring of actinides such as Am and other radioisotopes is usually necessary. (In this example, DTPA therapy was discontinued after one week, then resumed administration at day 90, and again at day 270, as a result of effect of DTPA on bioassays.)

No further treatment was recommended for patient #3, additional treatment was at day 635 for patients #1 & #2, then at day 1000 for patient #1

(ie, DTPA continued to be effective even years later in removing Am-241 from liver.)

The patient’s personal assessment of their risk is a real factor.

(Pt. #3 was concerned about discontinuation of treatment – how much DTPA treatment is enough?)

Per this example, questions of “when to start” and “when to stop” medical countermeasure treatments are not easy to answer, even for a few individuals.

Mass casualty scenarios will accordingly require an expert consensus on the development of those clinical decision levels of radiation dose which are effective and safe for all ages, sexes and special populations (ie, people with chronic diseases, etc.).

Conclusion: More clinical data from international DTPA Registries is needed.
Potential Beneficial Stochastic and Deterministic Risk Reductions by DTPA Therapy

- EXAMPLES (animal studies):
  - Pu Dose Dependent, Bone Tumor Rate Reduction (approx 30%), Jones et al.
  - Pu Induced Osteosarcoma Rate Reduction (approx 30%, if DTPA given at 1 hr and 10% at 3 hr), Jones et al.
  - Ce-144 Pulmonary Exposed Survival Time Increased in Beagles (from 500-1000 days), Muggenburg et al.

- Summary:
  - Deterministic effects of internal contamination may rarely occur (ex: Po210, Mayak, Goiania incidents), usually from ingestion—but stochastic risks predominate in most incidents.
# REVIEW: Countermeasures Are SPECIFIC

<table>
<thead>
<tr>
<th>Nuclide</th>
<th>Medication</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Americium-241</td>
<td>Ca and Zn DTPA by IV, Aerosol, IM</td>
<td>Works on liver after long deposition</td>
</tr>
<tr>
<td>Californium-252</td>
<td>Ca and Zn DTPA</td>
<td></td>
</tr>
<tr>
<td>Cesium-137</td>
<td>Prussian Blue</td>
<td>? Charcoal (early)</td>
</tr>
<tr>
<td>Cobalt-60</td>
<td>Penicillamine, DTPA</td>
<td>Gastric lavage (early)</td>
</tr>
<tr>
<td>Fission Products</td>
<td>Depends on time dependent source term, site of detonation.</td>
<td>Run spectrum to identify nuclides; Rx: isotope specific countermeasures</td>
</tr>
<tr>
<td></td>
<td>Usually I, Cs, Sr, Co, Pu, Am, U, Kr</td>
<td></td>
</tr>
<tr>
<td>Hydrogen-3</td>
<td>Forced Water</td>
<td>Diuretics</td>
</tr>
<tr>
<td>Iodine-131</td>
<td>Potassium Iodine or Super Saturated Potassium Iodine (SSKI), betadine</td>
<td>Give KI in first 1-6 hr, K-perchlorate (oral, if allergic to I)</td>
</tr>
<tr>
<td>Strontium 90</td>
<td>Sr lactate (oral), Ca Gluconate (iv)</td>
<td>Alginates, Al Antacids, Ba sulphate (oral)</td>
</tr>
<tr>
<td>Plutonium-239</td>
<td>Ca and Zn DTPA</td>
<td>Rarely lung lavage (PuO)</td>
</tr>
</tbody>
</table>
Internal Contamination

Dx/Rx/Monitoring Summary

- Intakes of radionuclides can be treated successfully.
- The appropriate treatment is element-specific. The contaminant must be promptly identified and Rx monitored by bioassay.
- The sooner treatment is begun, the better.
Other References!

- 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)

- FDA Website

- Google “REMM”
More Good References

- http://orie.orau.gov/reacts for Drug INSERTS and for the Video
- Internal/External DECON TRAINING:
  - Ca/Zn DTPA Package Insert
  - Prussian Blue Package Insert
  - KI Package Insert
QUESTIONS?

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REAC/TS