Radiation Toxicity and Syndromes

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March 8, 2012
Sources of Natural Radiation

- Space (Cosmic Rays)
- Breathing (Radon)
- Eating
- Buildings
- Soil
Radiation Unit

Gray (Gy) – unit of physical absorbed dose; 1 Gy = 100 rad

Sievert (Sv) – unit of equivalent dose (Equivalent dose equals physical dose for photons, but may be significantly different from it for other types of radiation.)

A person receives a total of about 200 mSv from all background sources in a lifetime.

3 mSv/year x 70 years = 210 mSv
Why do we need to understand radiation and/or combined injury?

1. Military Requirement
   (Troops and first responders)
2. Terrorism
   • Radiological dispersal device (dirty bomb)
   • Attack or sabotage of a nuclear facility
   • Use of nuclear weapon
3. Accidents
   • Nuclear power generators
   • Medical radiation therapy
   • Industrial radiators
   • Lost/stolen medical or industrial radioactive sources
4. Extended space travel
**Scale of Events**

- Small-scale events are those occurring in laboratories, hospitals, nuclear power plants, etc., involving small amounts of radionuclides with the potential exposure and/or contamination of one or a few individuals.

- Large-scale events are those involving relatively large quantities of radionuclides and the potential exposure or contamination of large numbers of people, e.g., terrorist attacks with radiological weapons, nuclear weapons detonation, and large-scale nuclear power plant disasters.
Ionizing Radiation Types

- **Alpha** particles – cannot travel far; stopped by paper.
- **Beta** particles – can travel only a relatively short distance unless with high energy; stopped by wood.
- **Gamma** rays – high penetrability at high energies; damage to deep organs; stopped by lead.
- **Neutrons** – 2-20 times as much damage to tissue as gamma rays
Common Forms of Ionizing Radiation

- **Alpha Particles**
  - consist of two neutrons and two protons (the equivalent of a helium nucleus)
  - has a +2 charge
  - largest and most massive of the four described
  - can be shielded by a few inches of air

- **Beta Particles**
  - Emitted electron or positron
  - smallest of the particles listed
  - moderate energy betas can be shielded by several inches of plastic

- **Gamma Rays**
  - Electromagnetic waves
  - Has no mass
  - high energy gammas can penetrate several cm of lead

- **Neutrons**
  - Particles
  - No electrical charge
  - high energy neutrons can penetrate thick lead shields, but are stopped by water
Lineal Energy Dose Distributions for $^{60}$Co $\gamma$ rays, X rays, and Neutrons

<table>
<thead>
<tr>
<th>Source</th>
<th>$\bar{y}_D$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\gamma$ rays</td>
<td>1.9</td>
</tr>
<tr>
<td>X rays</td>
<td>4</td>
</tr>
<tr>
<td>Neutrons</td>
<td>65</td>
</tr>
</tbody>
</table>

Stankus et al. (1995)
Wilhelm Conrad Roentgen

- November 8, 1895 – Discovers “a new kind of ray”
- He names them X-rays; X representing the unknown.
- December, 1895 – First radiograph of a living object (His wife’s hand).
- January 23, 1896 – First medical use of x-rays reported in the *Lancet*.
Radiation Exposure Limit (Whole Body)

Member of the public -
1 mSv/year = 100 mrem/year

Minor Occupational Limit –
5 mSv/year = 500 mrem/year

Adult Occupational Limit –
50 mSv/year = 5000 mrem/year

Declared Pregnant Radiation Worker’s Fetus –
5 mSv/term = 500 mrem/term

http://www.lowdose.energy.gov
AFRRI Handbook 2009
Significance and Rationale

• The possibility of exposure to radiation doses significant enough to cause tissue injury is not as remote as it might seem. It is estimated that more than 50% of cancer patients receive radiotherapy at some point during the course of their disease, and these exposures can injure normal tissues.
• Less likely, though still very real, is the possibility of being exposed to radiation after a nuclear power plant accident, either as a plant worker or a citizen who lives in or moves through fallout areas.
• The threat of exposure to radiation via a nuclear or radionuclide-based terrorist device is unfortunately also a real-world scenario.
• For these reasons, it is important to understand more about how radiation affects cells and tissues and learn how to ameliorate radiation injury to them.
## Medical Diagnostics
*(Estimated Maximum Organ Dose)*

<table>
<thead>
<tr>
<th>X-ray films</th>
<th>mSv</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest (PA &amp; Lat)</td>
<td>0.14</td>
</tr>
<tr>
<td>Dental panoramic</td>
<td>0.7</td>
</tr>
<tr>
<td>Lumbar-Sacral Spine</td>
<td>2-3</td>
</tr>
<tr>
<td>Mammogram</td>
<td>2-4</td>
</tr>
</tbody>
</table>

### Radiotracer Imagine

<table>
<thead>
<tr>
<th>Procedure</th>
<th>mSv</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Stress (Tc-99m)</td>
<td>6-12</td>
</tr>
<tr>
<td>Bone (Tc-99m)</td>
<td>4-15</td>
</tr>
<tr>
<td>Dual isotope Stress Test</td>
<td>40-45</td>
</tr>
<tr>
<td>Pet:F-18 FDG (bladder)</td>
<td>55-80</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CT Scans (X-ray)</th>
<th>mSv</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest CT</td>
<td>20-30</td>
</tr>
<tr>
<td>Head CT</td>
<td>30-50</td>
</tr>
<tr>
<td>Abdominal CT</td>
<td>22-60</td>
</tr>
<tr>
<td>Full body CT</td>
<td>50-100</td>
</tr>
</tbody>
</table>

### Fluoroscopy/Procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>mSv</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barium Contrast G.I.</td>
<td>10-22</td>
</tr>
<tr>
<td>Cardiac Catheterization</td>
<td>12-40</td>
</tr>
<tr>
<td>TIPS Procedure</td>
<td>400-1400</td>
</tr>
</tbody>
</table>

[http://www.lowdose.energy.gov](http://www.lowdose.energy.gov)
Examples

**Airport x-ray (whole body scanner)**
0.00007 mSv/scan
(Limit = 0.25 mSv/yr; ≈ 4000 scans/yr)

**Round-trip LA-NY**
≈ 0.037 mSv
(Limit = 1 mSv/yr; ≈ 27 round-trips)

http://www.lowdose.energy.gov
**Organs most sensitive to radiation**

- Bone marrow
- Lymphoid tissues
- Reproductive system
- Gastrointestinal system
- Skin
- Vascular system
Radiation-Induced Skin Injuries
Whole Body Irradiation

- < 1 Gy; no vomit
- 1-2 Gy; vomit > 4 h
- 2-6 Gy; vomit 1-4 h
- > 6 Gy; vomit < 1 h; early erythema, diarrhea, difficult to swallow, (later hair loss)
The pathological effects of radiation are directly related to dose.
A triage score $T$ is assigned as

$$T = \frac{N}{L} + E,$$

$E = 0$ if no emesis; $E = 2$ if emesis
$N/L$ is the neutrophil/lymphocyte ratio. The normal $N/L = 2.1$; further evaluation needed if $T > 3.7$. 

AFRRI Handbook 2009
Sensitivity to Radiation

Quality
Species
Age
Gender
Mortality in Mice (without support)

Elliott et al., IJRB 68:311,1995
Mortality in Mice (without support)

Elliott et al., IJRB 68:311, 1995
## Sensitivity to Radiation Indicated by LD50

<table>
<thead>
<tr>
<th>Species</th>
<th>LD50 (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheep</td>
<td>1.55</td>
</tr>
<tr>
<td>Pig</td>
<td>1.95</td>
</tr>
<tr>
<td>Goat</td>
<td>2.30</td>
</tr>
<tr>
<td>Dog</td>
<td>2.65</td>
</tr>
<tr>
<td>Rabbit</td>
<td>8.40</td>
</tr>
<tr>
<td>Mouse</td>
<td>9.00</td>
</tr>
<tr>
<td>Rat</td>
<td>9.00</td>
</tr>
<tr>
<td>Hamster</td>
<td>9.00</td>
</tr>
<tr>
<td>Guinea-pig</td>
<td>2.55</td>
</tr>
<tr>
<td>Monkey (according to the species)</td>
<td>3.5-5</td>
</tr>
<tr>
<td>Man</td>
<td>4.5-5</td>
</tr>
<tr>
<td>Turtle</td>
<td>15</td>
</tr>
</tbody>
</table>
Synergistic Effects

• Radiation interacts synergistically with trauma. Therefore, sensitivity to radiation increases.
• Patients with medical or traumatic injury who also have whole-body or significant partial-body irradiation have a substantially worse prognosis.
Consequences after Irradiation

- DNA breaks
- Inflammation
- Activation of cell death
- Induction of bone marrow aplasia
- Infection / sepsis
- Multi-organ dysfunction and failure
DNA Breaks

- Gamma-H2AX increase
- Dicentric chromosome formation
- Micronucleus formation
- Premature chromosome condensation (good for detecting partial-body exposures and small localized exposures)
Dicentric Chromosome

Image courtesy of B.D. Loucas and M.N. Cornforth.
The coefficients $\alpha$ and $\beta$ with estimates of SE for dicentric calibration curves

<table>
<thead>
<tr>
<th>Radiation type</th>
<th>$\alpha \pm \text{SE}(\text{Gy}^{-1})$</th>
<th>$\beta \pm \text{SE}(\text{Gy}^{-2})$</th>
<th>$\alpha/\beta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>60Co gamma rays</td>
<td>0.059 ± 0.0136</td>
<td>0.029 ± 0.0046</td>
<td>2.03</td>
</tr>
<tr>
<td>250-kVp x rays</td>
<td>0.098 ± 0.0209</td>
<td>0.044 ± 0.0093</td>
<td>2.23</td>
</tr>
<tr>
<td>Fission neutrons</td>
<td>0.687 ± 0.003</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Human lymphocytes
Premature Chromosome Condensation

Human lymphocytes

Graph showing the relationship between radiation dose (Gy) and the number of excess PCC fragments/cell. Two lines are plotted: one for neutrons with the equation $y = 1.29 + 5.23D$, and another for x-rays with the equation $y = 2.16 + 2.18D$.
Micronuclei

Number of micronuclei per 100 cells

V79 cells
Neutrons

V79 cells
X-ray

Dose (Gy)
**Gamma-H2AX in Lymphocytes**

A. 30 min after irradiation

B. 2 Gy

Redon et al., PLoS one 5: e15544, 2010
Molecular Biomarkers

- CBC kinetics
- Serum amylase – ↑
- Serum Flt-3 ligand – ↑ Hematopoietic damage
- Serum citrulline – ↓ Gut damage
- Serum IL-6 – ↑
- Serum G-CSF – ↑
- Serum CRP – ↑
# Multiple Parameter Biodosimetry

<table>
<thead>
<tr>
<th>Dose Gy</th>
<th>% emesis</th>
<th>Median onset of emesis (h)</th>
<th>Absolute lymphocyte count; % of normal in first 24 h</th>
<th>Relative increases in serum amylase, day 1</th>
<th>Number of dicentrics per 50 metaphases</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>-</td>
<td>100</td>
<td>1</td>
<td>0.05-0.1</td>
</tr>
<tr>
<td>1</td>
<td>19</td>
<td>-</td>
<td>88</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>35</td>
<td>4.6</td>
<td>78</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>54</td>
<td>2.5</td>
<td>69</td>
<td>6</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>72</td>
<td>1.7</td>
<td>60</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>86</td>
<td>1.3</td>
<td>53</td>
<td>13</td>
<td>51</td>
</tr>
<tr>
<td>&gt;6</td>
<td>90-100</td>
<td>1</td>
<td>&lt;47</td>
<td>&gt;15</td>
<td>-</td>
</tr>
</tbody>
</table>

AFRRI Handbook 2009
# Physician Guidance on Choice of Biodosimetry Methods

<table>
<thead>
<tr>
<th>Dose range (Gy)</th>
<th>Dosimetry method</th>
<th>Clinical symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 - 1</td>
<td>Dicentric/PCC</td>
<td>None to slight decrease in blood count</td>
</tr>
<tr>
<td>1 - 3.5</td>
<td>Lymphocyte depletion kinetics/Dicentric/PCC</td>
<td>Mild to severe bone marrow damage</td>
</tr>
<tr>
<td>3.5 - 7.5</td>
<td>Lymphocyte depletion kinetics / PCC</td>
<td>Pancytopenia, mild to moderate GI damage at 5-6 Gy</td>
</tr>
<tr>
<td>7.5 - 10</td>
<td>Lymphocyte depletion kinetics / PCC</td>
<td>Bone marrow and GI damage</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>PCC</td>
<td>GI, neurological, and cardiovascular damage</td>
</tr>
</tbody>
</table>

AFRRI Handbook 2009
Radiation Syndromes

• Acute radiation syndrome (high dose)
  Hematopoietic syndrome
  Gastrointestinal syndrome
  Neurovascular syndrome
  Cutaneous syndrome

• Chronic radiation syndrome (low dose)
  adaptive effect
  hormetric effect (*i.e.*, homeostatic effect)
Sternum Bone Marrow

A Sham

B Radiation

Kiang et al., 2012
Femur Bone Marrow

Histopathology of Bone Marrow Collected at the 30th Day after Injury

Kiang and Gorbunov, 2014

IR dose 9.75 Gy
Radiation-Injured Small Intestine

A. Sham

B. RI

Kiang et al., Radiat Res 173: 319, 2010
Apoptosis (TUNEL) and Autophagy (LC3 Protein) in Ileum

Apoptotic cells (%) are in green

Sham

7d IR

Autophagy

IgG

LC3-II

Sham

2d IR

7d IR

Gorbunov and Kiang, J Pathol 219:242, 2009
Radiation Delays Wound Healing

Kiang et al., Radiat Res 173: 319, 2010
A1. Numerous petechiae are dispersed over the pial surface of the cerebrum and the cerebellum of a terminally ill animal. A2. Cerebella hemorrhage indicated by arrows, Histopathology, H&E staining, The bar is 500 µm. Experimental conditions: The animal was administered with vehicle following CI. Survival period was 17 d.

B1. Brain of an animal which did not manifest the symptoms of radiation illness during the survival experiment. B2. No hemorrhage. Histopathology, H&E staining, The bar is 500 µm. Experimental conditions: The animal was administered with ghrelin following CI. Survival observation period was 30 d.
Radiation Syndromes

• Hematopoietic syndrome (about 1-8 Gy): neutropenia, lymphocytopenia, etc.

• Gastrointestinal syndrome (about 5-20 Gy): nausea, vomit, diarrhea (hair loss)

• Cutaneous syndrome (any Gy): delayed wound healing

• Neurovascular syndrome (>20 Gy): ataxia, confusion, cerebral edema, hypotension, etc.
Medical Consequences of Acute Radiation Injury

- Hematopoietic (1-6 Gy)
- Gastrointestinal (5-20 Gy)
- Cardiovascular
- Subclinical
- CNS (>20 Gy)

Increasing Dose
Radiation Syndromes

- Sepsis
- Multi-organ dysfunction syndrome (MODS)
- Multi-organ failure syndrome (MOFS)
Bacterial Entry From Lumen to Intestinal Tissue

(Nitric oxide breaks down the GI barrier)

Gorbunov and Kiang, J Pathol 219: 242, 2009
A. CI increases bacterial infection

- Enterococcus sp.
- Staphylococcus sp.
- Bacillus sp.
- Lactobacillus sp.

B. CI induces early bacterial infection

Kiang et al., Radiat Res 173:319, 2010
<table>
<thead>
<tr>
<th></th>
<th>Hiroshima</th>
<th>Nagasaki</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aug 6, 1945</td>
<td>Aug. 9, 1945</td>
</tr>
<tr>
<td>Little Boy-(U^{235})</td>
<td>(n=5185)</td>
<td>(n= 4107)</td>
</tr>
<tr>
<td>Single injury</td>
<td>60.5 %</td>
<td>57.7 %</td>
</tr>
<tr>
<td>Two injuries</td>
<td>34.5 %</td>
<td>37.1 %</td>
</tr>
<tr>
<td>Three injuries</td>
<td>5.0 %</td>
<td>5.2%</td>
</tr>
</tbody>
</table>

Data from 1946 Joint Commission of USA and Japanese Physicians 20KT fission devices
August 6, 1945…Suddenly, with a tremendous roar, everything went pitch black… I saw one man with hundreds of glass shards piercing his body from the waist up. The skin of another man had peeled off his entire upper body, exposing a mass of red flesh…

http://www.wagingpeace.org/articles/1998/07/00_takahashi_a-bomb.htm
Synergistic effects

- Radiation interacts synergistically with trauma. Therefore, sensitivity to radiation increases.
- Patients with medical or traumatic injury who also have whole-body or significant partial-body irradiation have a substantially worse prognosis.
Combined Injury Increases DNA Breaks More Than Radiation Injury in Bone Marrow Cells

Kiang et al., 2012
Combined Injury Decreases WBC More Than Radiation Injury

A WBC

B Lymphocyte

C Neutrophil

Kiang et al., 2012
Combined Injury Increases IL-6 More Than Radiation Injury

Kiang et al., Radiat Res 173:319, 2010
A. Combined injury increases bacterial infection

B. Combined injury induces early bacterial infection

Kiang et al., Radiat Res 173:319, 2010
Internally Deposited Radionuclides

Alexandra Litvinenko died Nov 26, 2006 from polonium-210 poison
Isotopes

University seven: H-3, C-14, P-32, Co-60, I-125, I-131, and Cf-252

Industrial three: Ir-192, Cs-137, and Co-60

Military four: H-3, U-235, Pu-239, and Am-241

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Treatments

- Anti-emetic drug
  Ondansetron (Zofran®, Zofran ODT®)
  Granisetron (Kytril®)

- Growth factors
  G-CSF (Neupogen®, Neulasta®)
  Gm-CSF (Leukine®)

- Antibiotics
  prescribed

- Psychological support
# Treatment
*(NCRP Report 161, 2009)*

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Am-241 ($\alpha, \beta, \gamma$)</td>
<td>DTPA</td>
</tr>
<tr>
<td>C-14 ($\beta$)</td>
<td>No treatment available</td>
</tr>
<tr>
<td>Cf-252 ($\alpha, \beta, \gamma$)</td>
<td>DTPA</td>
</tr>
<tr>
<td>Co-60 ($\beta, \gamma$)</td>
<td>DMSA, DTPA, EDTA, NAC</td>
</tr>
<tr>
<td>Cs-137 ($\beta, \gamma$)</td>
<td>Prussian blue</td>
</tr>
</tbody>
</table>

AFRRI Handbook 2009
<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-3 ($\beta$)</td>
<td>Forced fluids; Water diuresis</td>
</tr>
<tr>
<td>I-125 and -131 ($\gamma$, $\beta$)</td>
<td>KI, propylthiouracil, methamizole, potassium perchlorate</td>
</tr>
<tr>
<td>Ir-192 ($\beta$, $\gamma$)</td>
<td>DTPA, EDTA</td>
</tr>
<tr>
<td>P-32 ($\beta$)</td>
<td>Phosphorus therapy</td>
</tr>
<tr>
<td>Pu-239 ($\alpha$, $\beta$, $\gamma$)</td>
<td>DTPA, DFOA, EDTA, DTPA+DFOA</td>
</tr>
<tr>
<td>U-235 ($\alpha$, $\beta$, $\gamma$)</td>
<td>Bicarbonate; Dialysis</td>
</tr>
</tbody>
</table>

AFRRI Handbook 2009
Children are particularly susceptible to thyroid cancer following exposure to radioactive iodine. The uptake of radioactive iodine should be blocked by administering oral KI within 4 hours of exposure.
## KI Recommended Doses

<table>
<thead>
<tr>
<th>Category</th>
<th>Thyroid Exposure</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults &gt; 40 years old</td>
<td>≥ 5000 mGy</td>
<td>130 mg d⁻¹</td>
</tr>
<tr>
<td>Adults 18-40 years old</td>
<td>≥ 100 mGy</td>
<td>130 mg d⁻¹</td>
</tr>
<tr>
<td>Pregnant or lactating women</td>
<td>≥ 50 mGy</td>
<td>130 mg d⁻¹</td>
</tr>
<tr>
<td>Children and adolescents 3-18 year old</td>
<td>≥ 50 mGy</td>
<td>65 mg d⁻¹</td>
</tr>
<tr>
<td>Infants 1 month to 3 years old</td>
<td>≥ 50 mGy</td>
<td>32 mg d⁻¹</td>
</tr>
<tr>
<td>Neonates from birth to 1 month old</td>
<td>≥ 50 mGy</td>
<td>16 mg d⁻¹</td>
</tr>
</tbody>
</table>
Psychological Support

Affected people appear to fall into one of three groups

- Distressed
- Behavior changes
- High risk to develop psychiatric illness

Proper treatment of the psychological consequences of nuclear events is crucial to the long-term well-being of communities and their members.
**Delayed Effects**

Cancer Risk

Increased rate: 4-6% per Gy or Sv

Non-cancer effects

Cataract: 2 months – 35 years

Pregnancy

> 0.5 Gy results in growth retardation, mental retardation, etc.

AFRRI Handbook 2009
Radiotherapy for Breast Cancer
Breast Cancers in Connecticut (1935-82)
Second breast Cancer Occurrence (Age)

<table>
<thead>
<tr>
<th>655 cases; 1189 controls</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>1.19</td>
<td>0.9-1.5</td>
</tr>
<tr>
<td>Time after Exposure (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-9</td>
<td>0.99</td>
<td>0.7-1.4</td>
</tr>
<tr>
<td>≥ 10</td>
<td>1.33</td>
<td>1.0-1.8</td>
</tr>
<tr>
<td>Age at Exposure (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 35</td>
<td>2.26</td>
<td>0.9-5.7</td>
</tr>
<tr>
<td>35-44</td>
<td>1.46</td>
<td>0.9-2.3</td>
</tr>
<tr>
<td>≥ 45</td>
<td>1.01</td>
<td>0.8-1.4</td>
</tr>
</tbody>
</table>

Boice et al., ENJM 326:781, 1992
Excess Relative Risk (Gender)

Handbook: Medical Management of Radiological Casualties
www.afrri.usuhs.mil
301-295-0316
MEIR@afrri.usuhs.mil

www.remm.nlm.gov

www.bt.cdc.gov/radiation/
Two upcoming symposia

http://www.usuhs.mil/afrrianniversary/events/mmo/register.html

http://www.usuhs.mil/afrrianniversary/events/combined/register.html
Disclaimer

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Dilber Nurmemet
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