Dear John,

Thank you for registering for the MGH Department of Radiology's 47th Annual Aubrey O. Hampton Lecture. Following is some helpful information for planning your evening:

**Friday, March 21, 2014**
5:30 pm Cocktails & Hors d'Oeuvres  
6:30 pm Program Begins  
7:30 pm Dinner Service & Dancing
Driving Directions

Place:  [Boston Harbor Hotel, the Wharf Room]

Hotel Staff will be available to guide you to the beautiful Wharf Room, with a panoramic view of Boston Harbor.

Our distinguished Hampton Lecturer this year is:

**John Boice, Sc.D.**
President, National Council on Radiation Protection and Measurements*
Professor of Medicine, Vanderbilt University School of Medicine

"Cumulative Diagnostic Radiation and Cancer Risk"

*National Council on Radiation Protection and Measurements (NCRP). NCRP, located in Bethesda, Maryland, is a Congressionally-chartered not for profit organization that supports the scientific and public aspects of radiation protection through independent analyses by leading scientists throughout the United States.

Please click [here](#) for complete speaker profile.

Please contact Catherine Colt, Administrative Assistant, at ccolt@partners.org or 617-726-3403 if you have any questions.

Sincerely,

James A. Brink, MD
Radiologist-in-Chief

This email was sent to you from mghradiologicalsociety@partners.org because you registered for 47th Annual Aubrey O. Hampton Lecture. Click here if you no longer wish to receive emails about this event.
The 47th Aubrey O. Hampton Lecture at the Massachusetts General Hospital was presented on March 21, 2014 by Dr. John Boice, President of the National Council on Radiation Protection and Measurements (NCRP) and Professor of Medicine at Vanderbilt University. The title of Dr. Boice’s lecture was “Cumulative Diagnostic Radiation and Cancer Risk.”

Aubrey O. Hampton (1900–1955) was born in Copeville, Texas and received his medical degree from Baylor University in 1925. His association with the Massachusetts General Hospital (MGH) began in 1926 as a resident in radiology. He was also a member of the faculty of Harvard Medical School. Dr. Hampton then became the radiologist-in-chief in 1941, but he was granted a leave of absence in 1942 for military service. As a member of the medical corps, Dr. Hampton held the rank of major and served as the chief of radiology at Walter Reed Hospital in Washington, D.C. After the war, Dr. Hampton resigned from his position at the MGH to become the chief radiological consultant for the Veterans Administration and the chief of the radiological department at Garfield Hospital.

Dr. Hampton was a fellow of the American College of Radiology and the Radiological Society of North America. He was also a past president of the New England Roentgen Ray Society. The Aubrey O. Hampton Lecture at MGH was created in his honor. Dr. James A. Brink, Radiologist-In-Chief at the MGH introduced Dr. Boice.

Dr. Boice was the first chief of the Radiation Epidemiology Branch at the National Cancer Institute. His seminal discoveries and over 460 publications have been used to formulate public health measures to prevent radiation-associated diseases. Previous honors include the Harvard School of Public Health Alumni Award of Merit; the E.O. Lawrence Award from the U.S. Department of Energy; the Gorgas Medal from the Association of Military Surgeons of the United States; the outstanding alumnus award from the University of Texas at El Paso (UTEP); and the Distinguished Service Medal from the U.S. Public Health Service. His current studies include atomic veterans who participated in nuclear weapons tests and over a million radiation workers in the United States to examine the lifetime risk of cancer. He studies the children of cancer survivors to assess possible genetic risks from curative radiation treatments.
Cumulative Diagnostic Radiation and Cancer Risk

John D. Boice, Jr.
Vanderbilt University Medical Center
National Council on Radiation Protection and Measurements
john.boice@vanderbilt.edu
March 21, 2014
“And it was so typically brilliant of you to have invited an epidemiologist.”
Views of a Radiation Epidemiologist

Personal views are presented and not necessarily those of the:

NCRP (Report No. 171, 2012)
UNSCEAR (Annex B, 2013)
ICRP
Vanderbilt University
et al.
Outline

Introduction – Boston Heros
TB Fluoroscopy for Pneumothorax
Scoliosis – Spinal X-Rays
CT Epidemiologic Studies
Examples of Reverse Causation
Aubrey Otis Hampton
Copeville, Texas
Population ~ ???

Aubrey Otis Hampton, famous radiologist
Medical Physics and Imaging

Edward (Ted) Webster

Teacher, friend, and UNSCEAR delegate.
Webster Center for Advanced Research and Education in Radiation

Thanks – Fred Mettler
Professors at Harvard School of Public Health

Brian MacMahon
Head of Epidemiology

Richard Monson
Professor of Epidemiology
Advisor

George Hutchison
Professor of Epidemiology
Thesis Committee

Jack Little
Professor of Radiobiology
Thesis Committee, ICRP, NCRP
Mentor

Shields Warren

Pathologist, HMS, Deacones. First director of biology and medicine, AEC. Examined atomic-bomb survivors. Warren and Gates – 2nd Cancer

He recommended that I study children with Tuberculosis treated at the North Reading State Sanatorium – doctoral thesis.
Scientific Mentors and Collaborators

Hermann Lisco
Professor, Harvard Medical School, Dean Student Affairs, Radiation Pathologist

William (Bill) Moloney
Chief, Hematology, Professor of Medicine at Harvard Medical School and served as Chief of Hematology, 1966 - 1976
National Council on Radiation Protection and Measurements

Jim Brink, Chair of NCRP
Committee on Medicine

REFERENCE LEVELS AND ACHIEVABLE DOSES IN MEDICAL AND DENTAL IMAGING: RECOMMENDATIONS FOR THE UNITED STATES
No frills, volunteer organization, boots on the ground, even the Boston heros pump their own gas …

Thanks – Fred Mettler
Studies of Low-Dose Exposures Accumulating to High Dose

Lung collapse therapy for tuberculosis and associated multiple chest fluoroscopic x rays (1930 - 1954)
# Breast Cancer
## TB - Fluoroscopy, Massachusetts

<table>
<thead>
<tr>
<th></th>
<th>Exposed</th>
<th>Nonexposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of women</td>
<td>2,573</td>
<td>2,367</td>
</tr>
<tr>
<td>No. chest fluoroscopies, ave</td>
<td>88</td>
<td>—</td>
</tr>
<tr>
<td>Dose (ave) [Dale Trout]</td>
<td>790 mGy</td>
<td>—</td>
</tr>
<tr>
<td>Breast cancers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observed (O)</td>
<td>147</td>
<td>87</td>
</tr>
<tr>
<td>Expected (E)</td>
<td>114</td>
<td>101</td>
</tr>
<tr>
<td>O/E</td>
<td>1.29</td>
<td>0.86</td>
</tr>
</tbody>
</table>

29% Excess

---

Estimation of Breast Doses and Breast Cancer Risk Associated with Repeated Fluoroscopic Chest Examinations of Women with Tuberculosis

JOHN D. BOICE, JR., MARVIN ROSENSTEIN, and E. DALE TROUT

Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts 02115

Breast Cancer After Exposure to External Radiation: A Pooled Analysis of Seven Studies

Preston et al., 2002

Adapted from Art Schneider, 2011
Dose Response - Pooled Analysis of Breast Cancer Studies

Breast Cancer

Consistent with linearity

Boice, Radiology 131:589, 1979
Lung and Leukemia
TB - Fluoroscopy, Massachusetts

<table>
<thead>
<tr>
<th></th>
<th>Lung</th>
<th>Leukemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. exposed</td>
<td>6,285</td>
<td>6,285</td>
</tr>
<tr>
<td>No. unexposed</td>
<td>7,100</td>
<td>7,100</td>
</tr>
<tr>
<td>No. chest fluoroscopies (ave)</td>
<td>77</td>
<td>77</td>
</tr>
<tr>
<td>Dose to lung or marrow</td>
<td>840 mGy</td>
<td>90 mGy</td>
</tr>
<tr>
<td>Observed (O)</td>
<td>69</td>
<td>17</td>
</tr>
<tr>
<td>Expected (E)</td>
<td>86</td>
<td>19</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>0.8 (0.6-1.0)</td>
<td>0.9 (0.5-1.8)</td>
</tr>
</tbody>
</table>

No excess lung or leukemia

Not all tissues respond similarly to fractionation.

Davis et al., Cancer Res 49:6130, 1989
## Lung TB - Fluoroscopy, Canada Compared with Japanese LSS

<table>
<thead>
<tr>
<th>Lung Dose (mGy)</th>
<th>Multiple Fluoroscopy</th>
<th>Atomic Bomb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Lung Cancers</td>
<td>RR (95% CI:)</td>
</tr>
<tr>
<td>&lt;10</td>
<td>723</td>
<td>1.0</td>
</tr>
<tr>
<td>10 -</td>
<td>180</td>
<td>0.87 (0.7-1.0)</td>
</tr>
<tr>
<td>500 -</td>
<td>92</td>
<td>0.82 (0.7-1.0)</td>
</tr>
<tr>
<td>1,000 -</td>
<td>114</td>
<td>0.94 (0.8-1.2)</td>
</tr>
<tr>
<td>2,000 -</td>
<td>41</td>
<td>1.09 (0.8-1.5)</td>
</tr>
<tr>
<td>3,000+</td>
<td>28</td>
<td>1.04 (0.7-1.5)</td>
</tr>
</tbody>
</table>

| ERR/Gy (95% CI) | 0.00 (-0.06–0.07) | 0.60 (0.27–0.99) |

Summary - Cumulative Dose and Risk
TB Fluoroscopy

- Low-dose fractions over many years increase breast cancer risk
- Age at exposure modifies effect
- Linearity fits the breast cancer data
- Low-dose fractions NOT found to increase - lung cancer
- Be cautious when generalizing
Spinal X Rays for Scoliosis During Growth Spurt
# Breast Cancer

## Scoliosis – Spinal Dx X Rays

<table>
<thead>
<tr>
<th>Description</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Female Patients</td>
<td>5,573</td>
</tr>
<tr>
<td>Years Treated</td>
<td>1912 - 1965</td>
</tr>
<tr>
<td>Age, Mean (y)</td>
<td>10.6</td>
</tr>
<tr>
<td>No. X-rays</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0 - 618</td>
</tr>
<tr>
<td>Mean</td>
<td>24.7</td>
</tr>
<tr>
<td>Breast Dose (cGy)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0 - 170</td>
</tr>
<tr>
<td>Mean</td>
<td>11</td>
</tr>
<tr>
<td>Breast Cancer Deaths</td>
<td></td>
</tr>
<tr>
<td>Observed</td>
<td>77</td>
</tr>
<tr>
<td>Expected</td>
<td>45.6</td>
</tr>
<tr>
<td>O/E (95% CI)</td>
<td>1.69 (1.3-2.1)</td>
</tr>
</tbody>
</table>

---

Sensitivity of immature breast

- Hoffman *et al.* JNCI 81:1307, 1989
- Doody *et al.* Spine 25:2052, 2000

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Vanderbilt-Ingram Cancer Center

A Comprehensive Cancer Center Designated by the National Cancer Institute
Breast Cancer Scoliosis

Breast Cancer Radiation Dose Response Among Women with Spinal Curvature, U.S. Scoliosis Cohort Study

<table>
<thead>
<tr>
<th>Cumulative Breast Dose (cGy)</th>
<th>Number of Breast Cancer Deaths</th>
<th>Number of Comparison Subjects</th>
<th>RR</th>
<th>95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 9</td>
<td>63</td>
<td>3,325</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>10 – 19</td>
<td>23</td>
<td>1,216</td>
<td>1.2</td>
<td>0.7 – 2.0</td>
</tr>
<tr>
<td>20 – 29</td>
<td>14</td>
<td>526</td>
<td>1.9</td>
<td>1.0 – 3.5</td>
</tr>
<tr>
<td>≥30</td>
<td>12</td>
<td>333</td>
<td>2.4</td>
<td>1.2 – 4.8</td>
</tr>
</tbody>
</table>

**P trend** 0.001

CT Exams Are Increasing Each Year

- Over 85 million CT examinations were performed last year in the U.S. This is approximately one for every four U.S. citizens.
Charles Schultz, *Peanuts*

*Figure 2. Estimated Number of CT Scans Performed Annually in the United States.*

The most recent estimate of 62 million CT scans in 2006 is from an IMV CT Market Summary Report. ³
Outline - Epidemiology and CT Studies

- Importance of CT Studies
- UK study (Pearce et al., 2012)
- Reverse Causation
- Australian Study (Mathews et al., 2013)
- Dosimetry Limitations
- Conclusions

NCRP (Report No. 171, 2012)
UNSCEAR (Annex B, 2013)
Walsh et al. (JRP 2014)
United Kingdom CT Study
(Pearce et al., Lancet 2012)

- Record linkage study of leukaemia and brain cancer incidence following CT scans to 178,000 persons at ages 0–21 y.
- Collection of scan data for individual patients was not possible. Average CT machine settings from two national surveys were used.
- Significant dose responses reported

**Leukemia & MDS**
- Excess relative risk per mGy = 0.036
- Excess relative risk per Gy = 36.

**Brain**
- Excess relative risk per mGy = 0.023
- Excess relative risk per Gy = 23.
“Children who receive frequent examinations may have some underlying disability related to the outcome of interest. That is, a child who receives multiple CT exams of the head may have a central nervous system disorder that is prompting such examinations that eventually results in a cancer diagnosis.” – Reverse Causation
“Children who receive frequent examinations may have some underlying disability related to the outcome of interest. That is, a child who receives multiple CT exams of the head may have a central nervous system disorder that is prompting such examinations that eventually results in a cancer diagnosis.” – Reverse Causation – x rays aren’t causing cancers, cancers are causing x rays.
Example of Reverse Causation

- Thyroid cancer following I-131 scans for evaluation of suspected tumor in Sweden among 35,000 adults (ave thyroid dose 0.94 Gy)


We abstracted clinical data for all 35,000 patients, including thyroid size, I-131 activity administered and the reason for the examination.

Holm et al., JNCI (1988)
### Reason for I-131 Scan All Reasons

<table>
<thead>
<tr>
<th>Reason for I-131 Scan (No. Cancers)</th>
<th>RR of Thyroid Cancer by Years After I-131 Scan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2-</td>
</tr>
<tr>
<td>All Reasons (105)</td>
<td>3.1*</td>
</tr>
</tbody>
</table>

- Significant thyroid cancer risk overall (RR 1.8*)

Note that the adult thyroid gland is not considered radiosensitive.
<table>
<thead>
<tr>
<th>Reason for I-131 Scan (No. Cancers)</th>
<th>RR of Thyroid Cancer by Years After I-131 Scan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2-</td>
</tr>
<tr>
<td>All Reasons (105)</td>
<td>3.1*</td>
</tr>
<tr>
<td>Suspicion of Tumour (69)</td>
<td>6.3*</td>
</tr>
</tbody>
</table>

- Risk very high when reason for scan was a suspicion of tumour (RR 3.5*)
### Reason for I-131 Other Than Suspicion of Tumour

<table>
<thead>
<tr>
<th>Reason for I-131 Scan (No. Cancers)</th>
<th>RR of Thyroid Cancer by Years After I-131 Scan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2-</td>
</tr>
<tr>
<td>All Reasons (105)</td>
<td>3.1*</td>
</tr>
<tr>
<td>Suspicion of Tumour (69)</td>
<td>6.3*</td>
</tr>
<tr>
<td>Other Reasons (36)</td>
<td>1.3</td>
</tr>
</tbody>
</table>

- No excess risk if scan performed for “other reasons” (RR 0.9), e.g., hyperthyroidism and hypoathyroidism.
Reverse Causation Bias Lasted for More Than 20 y After 131-I Exam

<table>
<thead>
<tr>
<th>Reason for Scan (No. Cancers)</th>
<th>RR of Thyroid Cancer by Years After Scan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2-</td>
</tr>
<tr>
<td>All Reasons (105)</td>
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<td>6.3*</td>
</tr>
<tr>
<td>Other Reasons (36)</td>
<td>1.3</td>
</tr>
</tbody>
</table>

- The “suspicion of tumour” predicted future diagnoses of cancer even 20 y after examination
Thorotrast - Thorium Solution
Contrast Agent
The U.S. study population included patients exposed to Thorotrast during cerebral angiography at the Massachusetts General Hospital in Boston, MA and the Lahey Clinic in Burlington MA (Travis et al., 2001, 2004),
Thorotrast – Brain Cancer
(thorium dioxide solution)

Site-Specific Cancer Mortality Among Thorotrast-Exposed & Nonexposed Patients in the United States

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Thorotrast-Exposed</th>
<th>Comparison Group</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OBS SMR</td>
<td>OBS SMR</td>
<td>RR 95% CI</td>
</tr>
<tr>
<td>Brain &amp; other CNS</td>
<td>21 33.6</td>
<td>6 15.6</td>
<td>1.3 0.6 – 3.7</td>
</tr>
</tbody>
</table>

Patients who have examinations because of a suspicion of tumor usually are more likely to develop the tumor regardless to whether the exam included radiation or not. Travis et al. (2004) Reverse Causation.
Association reported between dental x-rays and meningiomas (Claus et al., 2012) based on interviews. However:

- Meningiomas can cause referred pain to the orofacial region.
- A patient with such pain may receive dental x-rays during the course of their care.
- It may be that radiographs do not cause meningiomas but rather the presence of the tumors triggers the need for radiographs.

White et al., Cancer 2012
Radiation Exposure from CT Scans in “Childhood” . . . <22 y of age

Mother and 21 y old son
Radiation Exposure from CT Scans in “Childhood” . . . <22 y of age

Mother and 21 y old son

- A 21 y old is not a child
Age at Exposure Effect in UK Study: Implausible - Risk Increased with Age

UNSCEAR 2013: “The risk of glioma is highest at < 5 years at irradiation and seems to largely disappear at the age of 20 years or more at irradiation, suggesting that susceptibility decreases as brain development nears completion.”

<table>
<thead>
<tr>
<th>Age at Exam</th>
<th>ERR/Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 -</td>
<td>5</td>
</tr>
<tr>
<td>5 -</td>
<td>28</td>
</tr>
<tr>
<td>10 -</td>
<td>37</td>
</tr>
<tr>
<td>15 -</td>
<td>41</td>
</tr>
</tbody>
</table>
Data Linkages study of 680,000 children (0-19 y) who received CT scans and 10,000,000 with no record of such exposures.

Excesses reported for practically all cancers:
- Digestive organs
- Melanoma
- Soft tissue
- Female genital
- Urinary tract
- Brain
  - after brain CT scan
  - after other CT scan
- Thyroid
- Leukaemia (myeloid)
- Hodgkins lymphoma

But not for:
- Breast Cancer
- Lymphoid Leukaemia
• Data Linkages study of 680,000 children (0-19 y) who received CT scans and 10,000,000 with no record of such exposures.
• Excesses reported for practically all cancers:
  • Digestive organs
  • Melanoma
  • Soft tissue
  • Female genital
  • Urinary tract
  • Brain
    • after brain CT scan
    • after other CT scan
  • Thyroid
  • Leukaemia (myeloid)
  • Hodgkins lymphoma

But not for:
  • Breast Cancer
  • Lymphoid Leukaemia

Cancers not know to be increased after radiation — are increased
Data Linkages study of 680,000 children (0-19 y) who received CT scans and 10,000,000 with no record of such exposures.

Excesses reported for practically all cancers:

- Digestive organs
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- Soft tissue
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- Thyroid
- Leukaemia (myeloid)
- Hodgkins lymphoma

But not for:

- Breast Cancer
- Lymphoid Leukaemia

Cancers know to be increased after radiation — are not increased
Australian CT Study
(Mathews et al., BMJ 2013)

- Data Linkages study of 680,000 children (0-19 y) who received CT scans and 10,000,000 with no record of such exposures.
- Excesses reported for practically all cancers:
  - Digestive organs
  - Melanoma
  - Soft tissue
  - Female genital
  - Urinary tract
  - Brain
    - after brain CT scan
    - after other CT scan
  - Thyroid
  - Leukaemia (myeloid)
  - Hodgkins lymphoma

But not for:
- Breast Cancer
- Lymphoid Leukaemia

Brain cancers increased whether or not the brain was exposed.
The appearance within five years of first CT scan of a significant excess of solid cancers is implausibly early.

The risk estimate for all cancers, excluding brain cancer after brain CT is statistically incompatible with the Japanese study on atomic-bomb survivors (ERR/Sv 27 vs 3)
...there are concerns about the risk estimates because of lack of information about indications for the CT scans and the consequent potential for ‘reverse causation’ (i.e. cancers may have been caused by the medical conditions prompting the CT scans rather than by the CT dose) and lack of individual dosimetry."
Taiwan Head CT and Benign Brain Tumor
Huang et al., Br J Cancer 2014

- 24,000 children with head CT with 4-1 match to nonexposed children. Excluded everyone with cancer or conditions predisposing to brain tumor. Significant association with benign, but not malignant, tumor reported.

- Apparently did not exclude those with benign tumors.

- Small numbers, only 5 malignant and 14 benign tumors

- Risk decreased with time since CT exam

- Youngest not at highest risk

- Reverse causation implies that it is the early symptoms of undetected tumor, or of factors that predispose to tumor, that are the indications for the CT scans, rather than the CT scans per se that are causing the apparent excess risk of cancer.
“Hopefully, CT studies that are now under way, such as the ‘EPI-CT’ study in Europe (see www.epi-ct.iarc.fr), will shed additional light on historical paediatric CT doses, have fewer ‘missed doses’, and be better able to address issues of possible risk factor confounding and reverse causation by, for example, establishing the reason(s) for an examination.” (Walsh et al., JRP 2014).
Summary

Cumulative exposure to high doses of diagnostic radiation may cause cancer later in life.

We’ll never detect cancer increases following a single CT. It may be tiny, it may be zero. But multiple CTs are a concern – thus medical benefit should be clear and dose ALADA (As Low As Diagnostically Acceptable).

Current studies of pediatric CT are not interpretable because of potential for confounding by indication and absence of individual dosimetry.

Good epidemiology could address the reasons for examination, provide individual dosimetry, and attempt to capture “missing doses”.

Meanwhile, it would seem prudent to assume that the low doses of radiation received during a CT scan may produce a small additional risk of cancer, and clinical practice might be guided by this assumption.
Informative References on CT Studies

Critique of Both Studies
UNSCEAR 2013: *EFFECTS OF RADIATION EXPOSURE OF CHILDREN*

Critique of UK Study
NCRP Report No. 171 (2012): *UNCERTAINTIES IN THE ESTIMATION OF RADIATION RISKS*

Critique of Australian Study

Example of Reverse Causation (Confounding by Indication)