Yale Surgical Society

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SUBSTANCE X: *Uncovering Details of the First Use of Intravenous Chemotherapy*

BY JOHN FENN, MD, FACS AND ROBERT UDELSMAN, MD, MBA, FACS

By 1942, radiation treatments were no longer effective against J.D.'s lymphosarcoma. Yale surgeon **Gustaf Lindskog** had only one option to offer the 47-year-old man, an experimental treatment developed by his colleagues in pharmacology, **Drs. Alfred Gilman** and **Louis Goodman**. J.D. would become the first human being to undergo intravenous chemotherapy for cancer. The historical record of this event has been incomplete, in part because wartime secrecy shrouded the incident. A search led by **Dr. Michael Kashgarian**, professor emeritus of pathology, uncovered J.D.'s medical record earlier this year. We draw upon that information here to offer a fuller understanding of a medical milestone.

The patient, J.D., was born in Poland in 1894 and immigrated to the United States at age 18 along with his father. He never saw his siblings again. One brother was killed in World War I and a second in World War II. His sisters never made their planned voyage to America. J.D. did not marry, lived alone in a four-room house and worked in a ball-bearing factory.

In 1941, J.D. was diagnosed with lymphosarcoma and referred to the Yale Tumor Clinic for x-ray therapy and

From left: Drs. Alfred Gilman, Louis Goodman, and Gustaf Lindskog

management. By his first admission in February, the tumor had grown and was fixed, hard and occupying the right side of the neck beneath the right ear and angle of the mandible. It measured 11 by 9 by 4 centimeters. He could open his mouth only minimally. External beam radiation therapy was initiated, with daily inpatient treatments for the following 16 days.

The tumor was smaller in April. He had a good appetite and was gaining weight. Examination, however, showed two hard, fixed irregular masses in the right cervical region. One measuring 3 by 5 centimeters was excised in June. Microscopic examination showed lymphosarcoma in cervical lymph nodes with marked necrosis and radiation effect.

He was followed by the Yale Tumor Clinic and received outpatient radiation treatment. The cervical masses shrank to the point where they could no longer be palpated. On December 31, 1941, however, several recurrent nodes were apparent. Radiation treatment was resumed, but the tumor was progressively unresponsive. By August 25, he was having respiratory distress, dysphagia and weight loss. There were axillary masses. The recorded entry for that day's tumor conference reads in part: "The patient's outlook is utterly hopeless on the present regimen … Dr. Lindskog will investigate the possibility of obtaining one of the newer chemicals which are lymphocidal."

Those "newer chemicals" were, in fact, nitrogen mustards. Throughout J.D.'s medical records, they are referred to simply as "a lymphocidal" or "substance X." These were wartime precautions. Drs. Gilman and Goodman were working on antidotes to mustard gas, which had been used so devastatingly in World War I. In the course of their experiments, they found that normal lymphoid tissues were extremely sensitive to ß-chlorethyl amine and saw the potential for clinical application.

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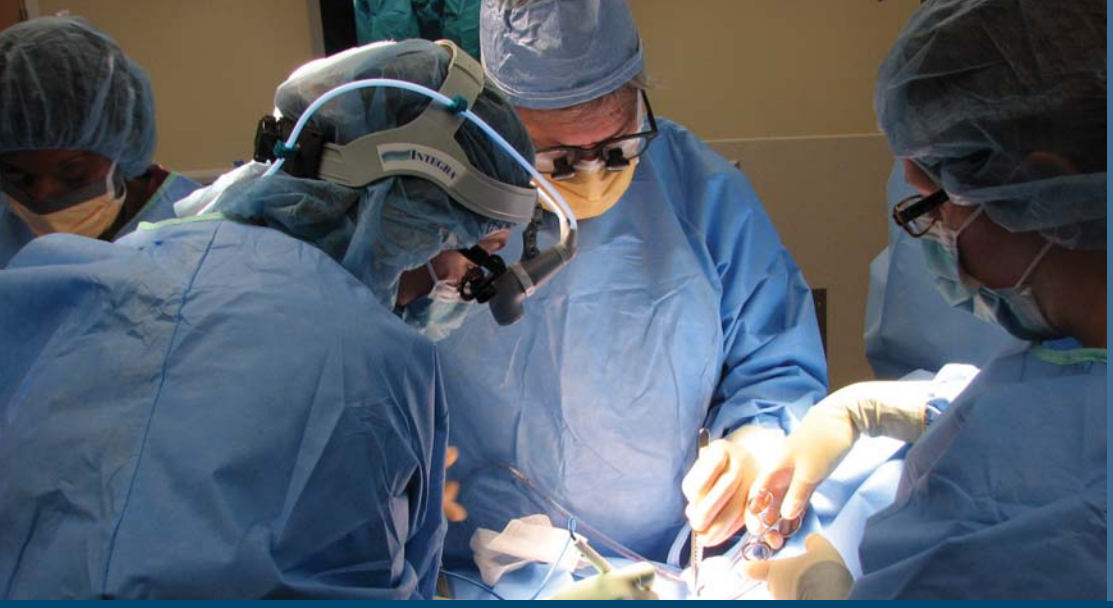
Celebrating the first 200 years

Yale School of Medicine is celebrating its Bicentennial by recalling milestone events at the school.

For more history and upcoming events, visit www. medicine.yale.edu/ysm200.



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PRESIDENT'S COLUMN

DR. MICHAEL O'BRIEN, MD, PHD

This year marks the 200th anniversary of the Yale University School of Medicine. As stated on the Yale University website: *"Founded in 1810, the Yale School of Medicine is among the nation's first medical schools. Over the past 200 years it has grown and evolved to become a world-class institution for research, education, and patient care, as well as a hub of medical innovation and discovery. During the observance of the Bicentennial throughout the 2010–2011 academic year, the school will celebrate its past, present, and future with a variety of special events."* The Department of Surgery is planning three special Grand Rounds in honor of the Bicentennial.

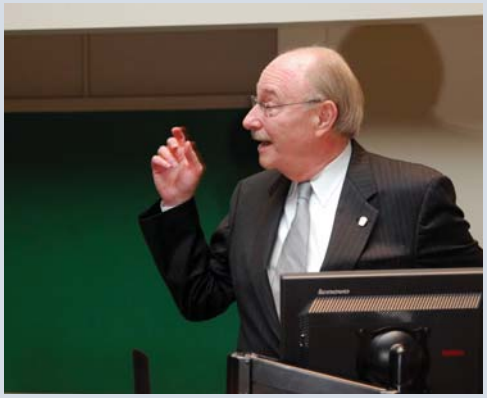
One hundred and eighty three years later, the Yale Surgical Society was founded and is now entering its seventeenth year and is thriving thanks to all of you. As an alumni organization, the Society continues to foster camaraderie and friendship among surgeons who trained, practiced or currently practice surgery at Yale-New Haven Hospital. The monies that you contribute to the society will continue to help provide both the Sam Harvey Award to the outstanding chief surgical resident as well as the Lindskog Award to support international travel opportunities for Yale University medical students. They go toward the YSS Bulletin that provides news and keeps members abreast of current events at Yale-New Haven Hospital and in the Department of Surgery of Yale University. I remain hopeful that many of you will submit updates on newsworthy events in your lives that can be published in the Bulletin and shared with your colleagues.

This past June 2010, the Yale Surgical Society honored **Clarence T. Sasaki**, MD, the Charles W. Ohse Professor and Chief of Otolaryngology at Yale. **Rick Greene**, MD, who trained in surgery at Yale and is now the Chairman of General Surgery at Carolinas Medical Center in Charlotte, N.C., was the guest speaker. The evening was a complete success with many former residents, chiefs and chairs in attendance. Former Chief of Otolaryngology **John Kirschner**, MD, and former Chairs **Arthur Baue**, MD and **Ronald Merrell**, MD, were able to attend and celebrate the accomplishments of Dr. Clarence Sasaki. Next year, June 2011, we will honor **John Elefteriades**, MD, Section Chief and William W.L. Glenn Professor of Cardiothoracic Surgery. Dr. Elefteriades is the Director of the new Aortic Institute at Yale-New Haven Hospital and we look forward to having many of you back to help us celebrate and honor a lifetime of achievements.

In closing, **Andrew Graham**, MD, co-founder and president of Yale Surgical Society from 1994–2009, will be officially retiring in October of 2010. Dr. Graham has provided excellent patient care and contributed to the training of surgical residents and teaching of medical students over the past four decades. He has served as president of the Medical Board and on the Board of Trustees for Yale-New Haven Hospital. Dr. Graham has truly been the inspiration and driving force behind making Yale Surgical Society everything it is today. He will be missed tremendously and always appreciated for his efforts, care, and accomplishments. On behalf of Yale Surgical Society we extend our congratulations and best wishes to Andy and his wife, Simmy, on their time together in his retirement.

A lifetime of achievement

Please join us in June of 2011, when the Yale Surgical Society's reunion will honor **John Elefteriades**, MD, Section Chief and William W.L. Glenn Professor of Cardiothoracic Surgery. Dr. Elefteriades is the Director of the new Aortic Institute at Yale-New Haven Hospital.



Reunion 2010

This year's reunion recognized the outstanding contributions to otolaryngology made by **Clarence T. Sasaki**, MD, the Charles W. Ohse Professor and Chief of Otolaryngology (top). One of the highlights was a talk by **Frederick Greene**, MD, who trained in surgery at Yale and is now the Chairman of General Surgery at Carolinas Medical Center in Charlotte, N.C. (above left). Lindskog Travel Awards went to **Matthew Hornick** (left), pictured with past winner **Jill Rubinstein**, and to **Laura Tom**. The Sam Harvey Award went to Chief Resident **Peter Yoo**, MD (bottom, left), pictured with **Walter Longo**, MD, MBA, professor of surgery.

SUBSTANCE X

CONTINUED FROM FRONT PAGE

They turned to Dr. Thomas Dougherty in the Department of Anatomy, who had developed a lymphoma that grew locally in mice but did not metastasize. In the first animal experiment, a mouse tumor shrank initially after administration of "substance X" and life was extended. The team approached Dr. Lindskog about a suitable human volunteer. "Any drug that gave any promise of controlling the malignancy appeared to me to be worth trying … The patient readily agreed to accept the chance of help, whatever the risk," Dr. Lindskog reflected in the medical record.

J.D. received an injection of "synthetic lymphocidal chemical" on August 27, 1942, and again on August 29, beginning a regimen of 10 daily doses at 0.1 mg/kg. By the 31st, he felt improved. He had been able to sleep in bed four hours, something he had not been able to do for weeks. Eating was becoming easier and regurgitation through his nose had ceased. He could move his head in a wider arc and cross his arms over his chest.

His white count had fallen from 10,000 to 5,000 on September 6 with a decreasing lymphocyte count. With remarkable clinical improvement and clear reduction in the size of the tumor infested lymph nodes, a biopsy of the right axillary node was done on September 9. Fibrous tissue and chronic inflammatory cells, but no tumor tissue, were seen on histologic examination.

By September 12, his white count had fallen to 2,750. Two days later intraoral bleeding was noted. His WBC was 1,300, and within a few days his platelets were 22,000/cmm. A whole unit of blood was transfused on September 21. His petechiae decreased and the gingival bleeding stopped. On September 27, the 31st day of treatment, maximum benefit from the chemotherapy was obtained. Cervical and axillary nodes were gone, leaving only a thickening of subcutaneous tissues.

The patient had intermittent fevers, coughing and a recurrence of petechiae. His WBC diminished to between 200 and 400. An additional transfusion on September 30, however, brought the WBC to 2,200.

His lymphosarcoma was making a vigorous return on October 15, with enlarged cervical lymph nodes and the patient complaining of dysphonia and dysphagia. Chemotherapy was resumed on October 20 for three days. His response was dramatic but short-lived. On November 7, he began a six-day course of chemotherapy. Though he had symptomatic relief and his lymph nodes regressed briefly, there began an inexorable downhill course with profound bone marrow depression, intraoral bleeding and multiple peripheral hematomas. His breathing became more labored and he expired quietly on December 1, 1942.

Autopsy revealed lymphosarcoma with involvement of the cervical and axillary lymph nodes, erosion and hemorrhage of the buccal mucosa, emaciation and extreme aplasia of the bone marrow with replacement fat. No distant metastases were noted.

In this single case, we find proof of efficacy, chemoresistance and chemotoxicity, unfortunately with fatal consequence.

While J.D. was not classified as Dr. Lindskog's private patient, it is clear by the surgeon's continuing and frequent progress notes that he had a special oversight and intense interest in J.D.'s management. Clearly without Dr. Lindskog's initiative, this first use of intravenous chemotherapy would not have taken place.

Putting this historical event into proper perspective, it should be recognized that in 1942 the era of institutional review boards had not arrived. It predated the Nuremberg Code and the Belmont Report. There is little doubt that J.D. understood from Dr. Lindskog what was being proposed and recognized that alternatives were exhausted. His contribution to countless others affected with malignant disease should be acknowledged with profound gratitude.

Adapted with permission from an article by John E. Fenn, MD, FACS, and Robert Udelsman, MD, MBA, FACS, currently in press in The Journal of the American College of Surgeons.

CHAIRMAN'S COLUMN

DR. ROBERT UDELSMAN, MD, MBA
WILLIAM H. CARMALT PROFESSOR
AND CHAIR OF SURGERY

One of the most gratifying things about the practice of surgery is that we make rapid and dramatic improvements in our patients' health. We often have a good idea of whether we've been successful or not by the time we change out of our scrubs. Gauging the success of a department of surgery is more difficult.

We can listen to what others say. For example, this year *U.S. News & World Report* listed Yale sixth on its list of top medical schools. *New York* magazine honored 13 of our faculty with a place on its Best Doctors list: **John Colberg**, **John Elefteriades**, **Harris Foster**, **Sabet Hashim**, **Gary Kopf**, **Walter Longo**, **R. Lawrence Moss**, **John Persing**, **Ronald Salem**, **Clarence Sasaki**, **Bauer Sumpio**, **J. Grant Thompson**, and me.

We can look at the numbers. Our reputation for performing state-of-the-art procedures with excellent outcomes draws a regional, national and even international patient base to New Haven. Clinic visits have risen 63 percent in the past decade, while work RVUs saw a 329-percent increase for the same period. Billings and collections are up more than 300 percent since 2001. Research funding has also increased, as our productive faculty published 507 peer-reviewed articles in the past academic year.

We can look at the structures we build to encourage excellence. I'm particularly proud of the work **John Geibel**, MD, DSC, director of research, and **Chris Breuer**, MD, director of research mentorship and development, are doing to help our residents and medical students develop as investigators. It is our expectation that all residents pursuing a research fellowship will apply for extramural funding. The department supports them with protected time for research and mentorship to help them achieve this important milestone of success.

As many of you know, we're devoted to the education of medical students and to fostering their interest in careers in surgery. We have 37 faculty members participating in a 12-week mentorship with students. This year, 14 medical students are writing their theses with surgery faculty. The Surgical Interest Group hosts many events to draw students into our specialty, including faculty/student socials, a journal club and discussions of surgical grand rounds.

Ironically, with success comes increased demand upon our resources. The full cost of doing leading-edge research, providing excellent patient care and educating our young colleagues to become leaders in medicine can never be covered by NIH grants, insurance payments or tuition. The burgeoning activity within the Department of Surgery would not be possible without supplemental fundraising.

Yale Surgical Society members are among our most loyal supporters. I want to thank you all publicly for your loyalty to this department, which is so critical to our success. Surgery at Yale has a proud tradition and a bright future. You've played an important role in both.

Schedule for Upcoming Grand Rounds

You are all invited. Grand Rounds is held every Wednesday at 7 am in the Fitkin Amphitheater.

DATE	SECTION	PRESENTER	TITLE OF TALK
11/24/10	No Grand Rounds – Thanksgiving Holiday	No Grand Rounds – Thanksgiving Holiday	No Grand Rounds – Thanksgiving Holiday
12/1/10	GI Surgery	**Vikram Reddy,** MD, PHD *Assistant Professor*	Rectal Cancer in the Young
	Trauma Surgery	**Adrianne Maung,** MD *Assistant Professor*	Pulmonary Embolism: Making the Diagnosis in 2010
12/8/10	Oncology	**Julie Sosa,** MD *Associate Professor*	Treatment of Aging Americans with Thyroid Cancer: At What Cost?
	Breast Center	**Brigid Killelia,** MD *Assistant Professor*	The Use of Preoperative MRI in Patients with Newly Diagnosed Breast Cancer
12/15/10	NSQIP Committee – National Surgical Quality Improvement Program	**Larry Moss,** MD *Vice Chairman of the Dept. of Surgery for Surgical Quality Improvement* **Leo Cooney,** MD; **Linda Maerz,** MD; **Marilyn Hirsch,** RN; **Michael O'Brien,** MD, PHD; **Kevin Schuster,** MD	NSQIP Update
12/22/10	Recess	Recess	Recess
12/29/10	Recess	Recess	Recess
1/5/11	Yale New Haven Health Services	**Steven Schlossberg,** MD *Assistant Dean for Clinical Informatics, YSM Chief Medical Information Officer, YMG and YNH*	I. Overview of Physician Payment – CPT And RUC Process II. EPIC, YMG/YNHHS and Meaningful Use
1/12/11	Occupational Medicine – YNHH	**Mark Russi,** MD *Director, Occupational Health and Associate Professor – Medicine & Public Health* **Louise Dembry,** MD *Hospital Epidemiologist*	Bloodborne Pathogen Training
1/19/11	Department of Surgery	**John E. Fenn,** MD *Clinical Professor* **Robert Udelsman,** MD, MBA *William H. Carmalt Professor of Surgery & Oncology; Chairman of Surgery; Chief, Surgery YNHH*	First Use of Intravenous Chemotherapy for Cancer Treatment – The Birth of Medical Oncology Bicentennial Lecture

Andrew Graham ends a storied career

With his retirement this year, **Andrew Graham**, MD, wraps up a career that spanned four decades and touched countless medical students and patients. After graduating from Tufts School of Medicine, Dr. Graham completed a surgical residency at Yale under **Gustaf E. Lindskog**, MD. He later became an oncologic fellow under Section Chief **Mark Hayes**, MD, in 1965, when surgeons were still administering chemotherapy. Dr. Graham was deeply involved in many aspects of the care of cancer patients. After a brief stint in solo practice, he was invited by **Richard A. Selzer**, MD, HS '61, and **Bernie S. Siegel**, MD, HS '61, to join their New Haven practice, where he mentored many medical students and residents. Dr. Graham was the founding president of the Yale Surgical Society and led its efforts to honor surgical faculty, support residents and encourage medical students to pursue surgical careers.

"No one has done more to be supportive of surgery at Yale than Andrew Graham," said Chair **Robert Udelsman**, MD. "Dr. Graham is not only a highly respected surgeon in his own right; he has worked tirelessly to encourage our medical students and residents as they pursue surgical careers. His legacy of service is outstanding."

Steering students into the OR

Chikezie Eseonu, MD '11, has had his article, "Attracting Top Medical Students to Neurosurgery," accepted by the *American Association of Neurological Surgeons (AANS) Journal*. The article examines the decline in medical students who opt for a neurosurgical residency, examines the causes behind the numbers and suggests steps to reverse the trend. The article recommends that medical schools address the shortage through mentoring, collaboration with related fields to add neurosurgery into the curriculum, research opportunities for first year medical students, creation of neurosurgery interest groups and an effort to explore curriculum changes.

Yale Surgical Society

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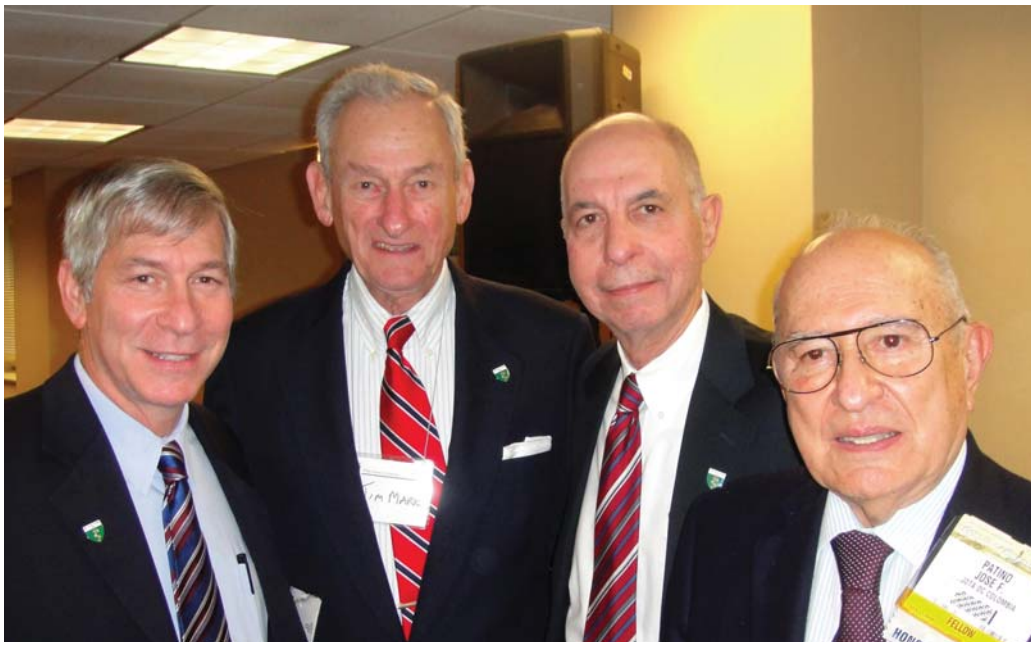

FAR-FLUNG COLLEAGUES

American College of Surgeons Clinical Congress once again provided the opportunity to catch up with former residents around the country and the world. (Left to right) **Dr. Robert Udelsman**, chair of surgery, joins former house staff **Drs. James B.D. Mark**, professor of surgery emeritus at Stanford, **John E. Fenn**, clinical professor of surgery, and **Jose Patiño**, professor of medicine at University of the Andes and a pioneer in advancing surgical practice in South America. We thank everyone who joined us for Yale events at the Washington, D.C. gathering.