60th Anniversary of the Zollinger-Ellison Syndrome
Critical to the success of any great surgical enterprise is the ability of physicians and surgeons to advance the care of patients with new procedures and innovative therapies that advance the field and improve lives. It is also understood that these innovations are widely disseminated and taught to the next generation as the cornerstone of our academic mission.

Sixty years ago such a discovery and therapeutic innovation was recognized and reported by Drs. Robert Zollinger and Edwin Ellison as they defined the syndrome of a pancreatic tumor secreting gastrin that was responsible for unrelenting peptic ulcer disease. By defining the syndrome that bears their name, the pioneering discovery of the Zollinger-Ellison syndrome opened the door to the science of gastrointestinal physiology and the study of gut hormones. This description moved the care of these patients beyond basic gastric resection to a more sophisticated approach to disease management using pharmacology, diagnostic imaging and therapeutic interventions.

The Department of Surgery at The Ohio State University Wexner Medical Center is proud of the extraordinary legacy of Drs. Zollinger and Ellison and we would like to celebrate their pioneering translational work in this edition of DOSsier. Distinguished Professor of Surgery, Dr. E. Christopher Ellison, reflects on the impact and importance of these seminal reports some 60 years later. We further recognize and outline recent successes in the development of treatments for patients with chronic pancreatitis and burns as extensions of the “bedside to bench to bedside” paradigm of discovery and innovation. We complete the “academic circle” by outlining advances in surgical education and by outlining our efforts here on campus to train the best and brightest surgical residents through NIH funded training grants (ARTIST grant); international collaborations to develop research in India and finally to enhance patient care outcomes through the Center for Surgical Outcomes Research at Nationwide Children’s Hospital.

I believe that Drs. Zollinger and Ellison would marvel at the legacy of discoveries and innovations that their pioneering work has stimulated in the Department of Surgery some 60 years later.

Robert S. D. Higgins, MD, MSHA
On November 6, 1954 Robert M. Zollinger, Sr., MD and Edwin H. Ellison, MD presented Surgery Grand Rounds at The Ohio State University, describing a syndrome of ulcerogenic tumors of the pancreas. By that time more than 100 patients had undergone a radical gastric resection for the control of gastric hypersecretion associated with ulcers resistant to medical therapy. Zollinger and Ellison reported on these gastric patients, evaluated five years after operation, emphasizing the effects of extensive gastric resection on postoperative nutrition.

Dr. Zollinger treated a patient who had two perforations of the jejunum and uncontrollable ulcer symptoms. The patient was found to be secreting 300 mEq of gastric acid during a 12 hour period. She underwent truncal vagotomy and proximal gastrectomy, but despite irradiation a distal pancreatectomy was performed and histology indicated a non-beta islet cell tumor.

In the spring of 1954, Dr. Ellison treated a patient with recurrent ulceration of the jejunum which was resected several times. The patient continued to have excessive acidity despite two gastric resections, and died after a total gastrectomy performed on May 1954. At that operation a distal pancreatectomy was performed and histology indicated a non-beta islet cell tumor.

Zollinger and Ellison presented the report at the annual meeting of the American Surgical Association on April 29, 1955. The paper was discussed by many prominent leaders in gastrointestinal surgery. The manuscript was published in the October 1955 Annals of Surgery in the article titled “Primary Peptic Ulcerations of the Jejunum Associated with Islet Cell Tumors of the Pancreas.” A syndrome was proposed implicating a pancreatic tumor which after a decade of research was shown to produce the potent secretagogue gastrin. In February 1956 Dr. Ben Eiseman proposed that this entity be called the Zollinger-Ellison Syndrome.

E. Christopher Ellison, MD, son of Dr. Edwin Ellison and Distinguished Professor and interim dean of The Ohio State University College of Medicine, explains the significance, “Zollinger and Ellison cared for two patients with ulcer diathesis in 1954 and 1955. They recognized the presence of a non-beta islet cell tumor in both patients and through team science it was discovered these tumors secreted gastrin causing the large amounts of acid secretion observed in this disease. The discovery opened a new era in GI physiology: the study of gastrointestinal hormones in health and disease. Although the initial treatment focused on controlling the ulcer disease necessitating total gastrectomy, the development of effective pharmacologic anti-ulcer medication allowed surgeons to focus on tumor resection. Aided by novel imaging techniques which have improved tumor localization, tumor resection is today more successful than ever. Cure rates of 50% are possible compared to 4% prior to 1980.”

Widely known as “The Big Z”, Robert M. Zollinger, Sr., MD, (1903–1992), was one of the giants of American surgery. He earned his medical degree from Ohio State in 1925. He then completed an internship at Peter Bent Brigham Hospital (PBBH) where he was trained by surgical master Harvey Cushing, MD. Prior to Zollinger’s internship Cushing sent him to Case Western Reserve to work with Elliot Cutler, MD, establishing an association that would span the next twenty years. In 1932 Dr. Cutler succeeded Cushing as chair at PBBH and later Dr. Zollinger was appointed there as associate professor. Zollinger and Cutler published the first edition of the now famous Atlas of Surgical Operations.

In 1946 following service in the U.S. Army during WW II, Dr. Zollinger was appointed professor of surgery at Ohio State with the understanding that he would assume leadership of the Department of Surgery after chairman Dr. Verne Dodd retired. After his appointment as chairman in 1947, Dr. Zollinger reorganized the general surgical service along the lines developed by Drs. Cushing and Cutler. The training program in general surgery was established as a five-year program, in keeping with the Halsted concept. A straight surgical internship was established, and a research program involving the house staff was incorporated into the program.

One of the first faculty members recruited by Dr. Zollinger was Edwin H. Ellison, MD, (1918–1970). Dr. Ellison received his surgical training at Ohio State University College of Medicine under the tutelage of Zollinger. He went on to serve on the OSU faculty from 1944 to 1957 and became a major influence in the development of the academic department. The Department of Surgery could not have grown so rapidly without him. From 1958 to 1969 Ellison was a professor and chairman of the Division of Surgery of the Medical College of Wisconsin, then Marquette School of Medicine. He was an excellent teacher and surgical scientist, making significant contributions to the field of gastrointestinal surgery.

The legacy of excellence continues with sons Robert M. Zollinger, Jr., MD, professor emeritus, Case Western Reserve University and E. Christopher Ellison, MD, Distinguished Professor and interim dean of The Ohio State University College of Medicine, who are co-editors of the Ninth Edition Zollinger’s Atlas of Surgical Operations with the Tenth Edition to be published in 2016.
Patients with chronic pancreatitis often have a very low quality of life and therapeutic options are often limited to long-term narcotic pain medication. This painful, debilitating disease accounts for nearly 60,000 hospitalizations per year in the United States. Over time, inflammation and repeated insults from chronic or acute recurrent pancreatitis creates fibrosis, which destroys normal pancreas cells including islet cells and leads to the loss of endocrine function. This results in permanent diabetes.

The OSU Wexner Medical Center’s total pancreatectomy with islet autologous transplantation (TPIAT) program offers a potential cure for a select group of patients. “The challenge is to find patients with early-stage pancreatitis who have preserved islet cell function,” explains Darwin Conwell, MD, professor of medicine and director, Division of Gastroenterology, Hepatology & Nutrition and Medical Director of the TPIAT Program. “We can greatly increase the quality of life for these patients.”

Dr. Conwell and his colleague Philip Hart, MD profile “at risk” patients based on pancreatitis risk factors, and findings on advanced MRI imaging and endoscopy. In addition, a protocol developed by Dr. Conwell also helps select patients who may best benefit from this procedure. Endoscopy combined with a pancreatic function test (ePFT) has a very high predictive value of 97%. Therefore, it can rule-out patients who do not have evidence of pancreas dysfunction, reducing unnecessary surgical and invasive endoscopic procedures like ERCP. Other selection factors include history of compliance with medical recommendations, avoidance of habits like smoking and alcohol, history of substance abuse and social/psychological factors.

Ohio State has the resources to meet all of the patient’s needs in one convenient location. The multidisciplinary team includes pancreatology, radiology, endoscopy, endocrinology, general and transplant surgery, pain management, psychology, social services and case coordinators. Patients undergo a battery of tests to determine if they are a good candidate, then pre-transplant testing takes place in the Morehouse Center clinic where they are assessed for operability, islet function, genetic mutations, chemical dependency, and psychological issues. Social services and financial counselors are also available. All this information is referred to the selection committee. “Patients can receive all medical and surgical services in the same building on the same day,” states Dr. Conwell.

Patients meet with the surgical team including Amer Rajab, MD, PhD, Pancreas and Islet Transplantation director. Following approval by the multidisciplinary team, the pancreatectomy and islet auto-transplantation are scheduled to occur on the same day. The surgical team resects the pancreas taking care to preserve blood flow to the pancreas for as long as possible to optimize islet perfusion. The operation site is then temporarily closed while Dr. Rajab isolates the islet cells from the explanted pancreas, a process that can take up to five hours. In a state-of-the-art laboratory located in the new James Cancer Hospital, mechanical and enzymatic digestion is used to isolate the islet cells and create a concentrate that is suspended in an albumin solution. Dr. Rajab returns to the OR to complete the transplantation by infusing the islet cells into the liver via portal vein catheterization. “The patient’s liver is the best host for the islet cells,” explains Dr. Rajab.

The early experience at OSUWMC has been very promising. The average length of hospitalization is 15 days. All patients have retained some insulin production. The majority have discontinued narcotic use and there is a universal improvement in quality of life. “We have a national reputation of being a pancreas center because of the leadership of Dr. Christopher Ellison (interim dean of the College of Medicine) and Dr. Conwell,” said Dr. Rajab. “This is a highly specialized, technological procedure requiring an institutional commitment. We are fortunate to have that at Ohio State.”
Teaching tomorrow’s surgeon-scientists

For more than ten years the OSU Department of Surgery has supported the development of academic surgical careers by encouraging its residents to pursue research training through the OSU College of Medicine’s Master of Science in Medical Science degree program (MMSP). This program offers a tailored research curriculum combined with a mentored research experience for residents and fellows in clinical training programs at Ohio State and Nationwide Children’s Hospital. Our mission is aligned with national efforts to support the physician-scientist pipeline. The General Surgery training program aims not only to train superb surgeons but also has the goal to develop future leaders in surgery.

Our residency program is distinguished by its inclusion of a professional development year to complement the five clinical training years. Many residents pursue two full years of mentored research training along with didactics available through the MMSP. These efforts which resulted in outstanding research accomplishments by our high quality surgery trainees, provided a foundation for application to the National Institutes of Health for an institutional training grant (NIH T32 funding mechanism) to further develop and enhance the research education and training momentum achieved over the previous decade.

The goal of the ARTIST program is to train and inspire a unique cadre of surgeon-scientists to translate astute observations at the bedside, in the operating room, and in the clinic into novel hypotheses that can be interrogated through immunology-focused translational research. Ultimately these surgeon-scientist research programs will accelerate the movement of discoveries in immunology for development of immune-based diagnostics, prognostics and/or therapeutics.

“The areas of research supported by this T32 are relevant to surgeons who work with tissues daily in the operating room and who are uniquely qualified to identify the important surgical problems and potential solutions when tissues are insufficient or damaged through disease or surgery,” explains Dr. Bumgardner. These research areas include: immune mechanisms of tissue injury, immune mechanisms of tissue repair & regeneration, and applied immunology: diagnostic/prognostic biomarkers or immunotherapeutics.

Ekene Onwuka, MD, who investigates tissue-engineered vascular grafts in the lab of mentor Christopher Breuer, MD, was the first resident to be appointed to the new ARTIST T32. “The ARTIST grant has already impacted my career,” states Onwuka. “This career development program encouraged me to apply for, and be elected to a leadership position as the candidate member on the Association for Academic Surgeons Global Affairs Committee.”

Starting in July 2015 general surgery residents Eliza Beal, MD (mentors Sylvester Black, MD, PhD and Carl Schmidt, MD), Christopher McQuinn, MD (mentors Greg Lesinski, PhD and Mark Bloomston, MD) and Taehwan Yoo, MD (mentors Cameron Rink, PhD and Mounir Haurani, MD) will begin their ARTIST T32 programs.

Additional resources:
J Clin Invest: http://www.jci.org/articles/view/80933

Above: MMSP candidate Sara Mansfield, MD investigates virology and immunology in the lab of Robert Baiocchi, MD

Left: ARTIST awardees. (L to R) Taehwan Yoo, MD, Ekene Onwuka, MD, Eliza Beal, MD and Christopher McQuinn, MD
Helping burn patients heal sooner

“Giving burn patients access to the best care available – whether inpatients or outpatients – that is our mission,” explains Larry M. Jones, MD, Burn Center director and AEP Foundation Chair in Burn Care. “We have developed a system of burn care at Ohio State that allows patients to go home sooner while at the same time keeping complications in check and readmission rates low.”

A burn injury can be devastating. At the OSU Burn Center, central Ohio’s only adult burn center, our comprehensive care team is dedicated to the needs of patients and their families including the physical, mental, emotional, and social impact of burns.

Outpatient services offered in the Burn Clinic include:

• Physical and occupational therapists to evaluate and treat patients within the Wexner Medical Center, avoiding the need to make additional appointments.
• An on-site, Durable Medical Equipment (DME) licensed company that measures and manufactures pressure garments for our patients, avoiding the need for the patient to make another trip for a garment measurement, then returning again for a garment fitting.
• Dr. Kristen Jackson, burn psychologist, is available to help our patients and families overcome the psychological problems that frequently accompany recovery from a burn injury. In the near future, we hope to also have a hospital social worker available in the outpatient clinic.

Many of our new patients are seen completely on an outpatient basis. New technologies, such as seven day dressings that reduce the need for painful daily dressing changes and tele-burn technology allow patients to recover at home, resulting in much higher patient satisfaction.

We investigate novel ways to improve care by shortening healing times, reduce pain and infection and lessen functional impairment and loss of mobility. The Burn Program was awarded two of the four grants available last year through the OSU Center for Clinical and Translational Science. One of the CCTS grants supports “Safety, feasibility and acceptability of patient-controlled sedation for anxiolysis with dexmedetomidine (PCS-DEX) for burn-care dressing changes” a study involving a four way collaboration with the Department of Pharmacy, the Department of Nursing and the College of Nursing with Dr. Jones as principle investigator. The second CCTS grant supports the investigation of the effect of laser treatment and pirfenidone on hypertrophic burn scar reduction with J. Kevin Bailey, MD, as principle investigator.

The addition of Dr. Bailey to our faculty and his expertise in burn surgery, hand surgery and laser reconstruction affords additional opportunities for us to extend our clinical reach. Most recently, our burn surgeons have begun treating frostbite injuries with tissue plasminogen activator (tPA) that improves blood flow in frozen tissue and helps to avoid amputations.

Our recent re-verification as an adult burn center by the American College of Surgeons and the American Burn Association is a testament to the quality of our patient care, research and our teaching efforts. The OSU Burn Team’s vision is to create the future of burn care. Dr. Jones states, “My dream is for the creation here at Ohio State of a self-contained burn center where our state-of-the-art multidisciplinary care can be delivered to anyone who has suffered a thermal, chemical or electrical injury – a burn center where our research results will positively impact that care and where we can train future generations of burn team members”.

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“The whole concept of a team approach to patient care started with the care of burned patients,” states Dr. Jones. “Our multidisciplinary delivery of care allows all of a patient’s needs to be met under one roof and many times with one visit.”

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International collaboration in India

On January 15-17, 2015, Ohio State’s Office of International Affairs and Wexner Medical Center, as well as many other business and industry partners, hosted the H3C Health Sciences Innovation Conference and Trade Show in Mumbai, India. The conference focus was on building global partnerships in order to share innovative and life-saving medical research, explore new funding opportunities and recruit international students.

The Ohio State University president Dr. Michael V. Drake participated in the conference, along with Ohio State colleagues in the health sciences and other international experts in medicine and science. Conference co-chairs were Chandan K. Sen, PhD, professor of surgery and associate dean in the College of Medicine; and William I. Brustein, PhD, vice provost for Global Strategies and International Affairs in the Office of Academic Affairs. The OSU Global Gateway office in Mumbai, India, directed by Ratnesh Bhattacharya, provide logistical support for the event.

The conference united physicians, scientists and leaders of business and industry. “Bringing these three disciplines together creates a very powerful thing,” explained Sen. Decreasing federal and state funding makes finding new research support critical, particularly for junior investigators. This international collaboration seeks to open new avenues of research funding sources. Dr. Sen states, “My goal is to assist junior research faculty find support so that they can thrive.”

Global collaborations provide excellent educational opportunities as well. Students gain insight by traveling abroad, learning the diversity of other cultures and getting a new perspective and orientation to the world.

“Experiencing how the rest of the world lives is a quintessential element of leadership education,” explains Sen. The conference was held at the historic Taj Palace Hotel, the country’s first Indian-owned five-star hotel, and was sold-out with attendance exceeding capacity. The three-day event hosted forty sessions, over 25 industry sponsors, and more than 100 speakers. “Opening of the main H3C conference by Indian Health Minister Hon’ble J.P. Nadda escalated the event to national prominence,” remarked Sen. “OSU president Dr. Michael Drake made a critical difference with representation by the highest level of Ohio State leadership.” The presence of the highest ranking U.S. government official in Mumbai, Consulate-General Thomas Vajda, demonstrated clear commitment of both governments to support the proposed co-operation between OSU and India.

In the week following the H3C Conference President of the United States Barack Obama visited India as the official “chief guest” at India’s Republic Day parade. President Obama is the first U.S. president invited to attend this event, signaling a growing partnership between India and the United States. During his visit the president pledged $4 billion in investments and loans, calling the partnership between the U.S. and India an “untapped potential.”

A pre-conference meeting was held in the city of Kolkata. “The pre-conferences were instrumental in forging new wound care partnerships with the Peerless Hospital in Kolkata, which is now committed to developing a chronic wound care facility. This opens up new opportunities for business for our visiting industry leaders,” explained Dr. Sen. In the city of Delhi Dr. Sen was honored as the inaugurator of the first National Facility for Regenerative Medicine, established under the framework of AIIMS, India’s premier institution for health care and research.

If you are interested in learning more about the conference please contact Brent.Toto@osumc.edu or visit http://www.india2015.osu.edu/
Led by Katherine J. Deans, MD, MHSc and Peter C. Minneci, MD, MHSc, the Center for Surgical Outcomes Research (CSOR) at Nationwide Children’s Hospital is a clinical research laboratory with the mission of improving surgical outcomes and patient satisfaction. “We aim to incorporate the patient/parent perspective in our work, aligning their preferences with the best treatment options,” remarks Minneci.

The CSOR provides a “toolbox” of research methodologies to practicing clinicians. “Surgeons can come to the CSOR with a clinical question and from it we can create a research question, identify an optimal methodology, execute a study, and assist in reporting results,” explains Deans. Drs. Deans and Minneci currently lead more than 50 ongoing clinical research studies. In addition to NIH and AHRQ funding, Deans and Minneci were awarded a $1.6 million research grant in 2013 from the Patient-Centered Outcomes Research Institute (PCORI) to study the use of technology in improving shared decision-making.

One example of their studies on shared decision-making is with the management of appendicitis. They completed a pilot study demonstrating that antibiotic therapy is a feasible alternative to surgery for children with uncomplicated acute appendicitis. They are now studying the effects of engaging parents in the decision of whether their child should receive antibiotics alone or surgery. Working with local software companies, Deans and Minneci created an iPad app that parents can use to learn more about the diagnosis and treatment options. By incorporating patients as active participants in their care, they hope to improve postoperative outcomes, decisional efficacy, quality of life, and healthcare satisfaction.

Many CSOR projects utilize stakeholder groups which Deans and Minneci believe are impactful in the success and generalizability of surgical research. These groups have vested interests in the design and outcome of the research and consist of patients, families, patient educators, payers, nurses, and physicians of various disciplines. “Involving stakeholders is an invaluable way to broaden your view and shape the research study so that it is patient-centered,” says Deans.

A core area of interest for Deans and Minneci is researching radiation exposure from diagnostic imaging and examining how to quantify the amount of radiation that a pediatric patient receives from CT scans. Deans and Minneci are currently collaborating with Daniel Lodwick, MD, MS, a general surgery resident at Ohio State, who has a Master’s degree in Medical Physics. The team is creating, implementing, and evaluating a novel process that merges clinical patient level data from the electronic medical record with patient and organ specific radiation dose data. This allows the team to measure and monitor radiation exposure long-term. “Patients may receive multiple CT scans during their treatment, and the risk of radiation exposure is additive with repeated scans. Previously, nobody was able to quantify how much radiation patients received,” noted Lodwick. Their method utilizes advanced patient modeling and then simplifies the process by utilizing pretabulated radiation exposures that are scaled to an individual’s imaging parameters. The result is age and gender matched, and scaled to patient body size and composition.

“Ultimately every procedure in medicine comes with risk and we cannot tell families that we have no estimate of that risk. We owe it to them to study the medical use of radiation and quantify the radiation burden to each patient to give our best knowledge of that risk,” states Lodwick. It is their unique combination of knowledge of radiation physics from Dr. Lodwick with the focus on clinical research methodology from Drs. Deans and Minneci that has made this research possible. Of his training at the CSOR Lodwick says, “It’s incredible to be able to work with mentors that understand how to create this system and have the passion and commitment required to build it.”

Learn more by visiting http://www.nationwidechildrens.org/surgical-services-research-innovation
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