

## *J. Englebert Dunphy, M.D.*

*Professor of Surgery & Chairman of the Department from 1964 to 1975.*

*Dr. Dunphy graduated from Harvard Medical School and completed his surgical residency training at the Peter Bent Brigham Hospital in Boston. He then joined the faculty at Harvard until assuming the Chairmanship of the Department of Surgery at the University of Oregon before coming to San Francisco. Dr. Dunphy was president of the Society of University Surgeons, the American Surgical Association, and the American College of Surgeons. He received honorary fellowships in six foreign colleges of surgeons as recognition of his international stature. Dr. Dunphy was renowned for excellence in many aspects of surgery, with a special interest in the gastrointestinal tract. He was one of the leading surgical educators of his day and was greatly admired and respected by his colleagues and residents. Dr. Dunphy conducted research in wound healing at a basic level. Dr. Dunphy strongly believed that prospective academic surgeons should become grounded in basic science, and he was one of the first surgical leaders in the United States to obtain an NIH training grant supporting residents in the laboratory.*



### ***Martin Elliott, MB, BS, MD, FACS***

*Martin Elliott* is Professor of Paediatric Cardiothoracic Surgery at University College London and Co-Medical Director at The Great Ormond Street Hospital for Children NHS Trust (GOS) where he has worked since 1984. He established and leads the National Service for Severe Tracheal Disease in Children at GOS. He developed modified ultrafiltration, helped establish paediatric heart and lung transplantation at GOS, started the European Congenital Heart Defects Database for outcomes analysis and leads the chest wall reconstruction team at GOS. The Tracheal Service at GOS is the largest in Europe, and the Team has pioneered a number of innovative techniques, including slide tracheoplasty, tracheal homograft patch transplantation, the development of absorbable stents and, most recently, the world's first stem cell supported tracheal transplantation in a child. Previously Chairman of the Cardiorespiratory Division at GOS, he was appointed Medical Director of GOS in 2010. Actively interested in teamwork in healthcare, he has been engaged in the redesign of specialist services in the UK, Austria and Australia, and has become fascinated by how hospital care might need to be delivered in the coming years and economically straightened times. He has worked with many other industries to improve safety and teamwork, including with F1, the airline and hotel industries. He teaches on management courses in health care, government and the private sector. He has over 260 peer reviewed publications to his name, has delivered more than 350 invited lectures, and he operates and teaches throughout the world.

## *Past Visiting Professors*

**Bernard Langer, M.D.**

Professor and Chairman of Surgery, University of Toronto  
February 5-6, 1988

**William Silen, M.D.**

Professor of Surgery, Harvard Medical School  
February 3-4, 1989

**James Thompson, M.D.**

Professor and Chairman of Surgery, University of Texas, Galveston  
February 2-3, 1990

**Murray Brennan, M.D.**

Professor and Chair of Surgery, Memorial Sloan-Kettering Cancer Center  
February 3-4, 1991

**Richard Simmons, M.D.**

Professor and Chairman of Surgery, University of Pittsburgh  
January 31-February 1, 1992

**Stephen F. Lowry, M.D.**

Professor of Surgery, Cornell University Medical College  
February 4-5, 1993

**Jared Diamond, Ph.D.**

Professor of Physiology, UCLA School of Medicine  
February 4, 1994

**Samuel A. Wells, Jr., M.D.**

Professor and Chairman of Surgery, Washington University  
February 17, 1995

**Jonathon E. Rhoads**

Chief of Surgical Oncology, University of Pennsylvania, Philadelphia  
February 16, 1996

**Patricia K. Donahoe, M.D.**

Chief, Pediatric Surgical Services, Massachusetts General Hospital  
February 27, 1997

**David L. Dunn, M.D., Ph.D.**

Professor and Chairman of Surgery, University of Minnesota  
February 27, 1998

**Ori D. Rotstein, M.D.**

Professor of Surgery, Toronto Hospital  
February 26, 1999

**Olga Jonasson, M.D.**

Director of Education and Surgical Services Department  
American College of Surgeons  
March 17, 2000

**Glenn Steele, Jr., M.D. Ph.D.**

Dean, School of Medicine, University of Chicago  
March 9, 2001

**Alexander W. Clowes, M.D.**

Professor of Surgery and Chairman, University of Michigan  
March 7, 2002

**Michael Mulholland, M.D., Ph.D.**

Professor of Surgery and Chairman, University of Michigan  
March 7, 2003

**Christian Larsen, M.D., Ph.D.**

Professor of Surgery, Emory University  
March 19, 2004

**Danny O. Jacobs, M.D., M.P.H.**

Chair, Department of Surgery, Duke University Medical Center  
March 4, 2005

**Steven D. Leach, M.D.**

Chief of Surgical Oncology, Johns Hopkins University  
March 3, 2006

**M. Judah Folkman, M.D.**

Professor of Pediatric Surgery & Cell Biology, Harvard Medical School  
Director, Vascular Biology Program, Children's Hospital, Boston  
February 15-16, 2007

**Sir Peter Morris, AC, FRS, FRCS**

Director, Centre for Evidence in Transplantation  
Royal College of Surgeons of England  
April 4, 2008

**George K. Gittes, M.D.**

Chair of Pediatric Surgery, University of Pittsburgh  
April 3, 2009

**Joseph P. Vacanti, M.D.**

Chief, Pediatric Surgery, Massachusetts General Hospital  
March 12, 2010

**Maria Bertagnolli, M.D.**

Professor of Surgery, Harvard  
Chief, Surgical Oncology, Brigham and Women's Hospital  
April 1, 2011

**Michael Harrison, M.D.**

Director Emeritus, Fetal Treatment Center, Professor of Pediatric Surgery,  
University of California, San Francisco  
April 13, 2012

## *2012 Award Recipients*



*Pictured from left to right: Peter Stock, MD, PhD, Eric Kubat, MD, Cristina Thorsen, MD, Michael Harrison, MD, Nancy Ascher, MD, PhD, Jack Harbell, MD, and Kenneth Loh, MD.*

- **2012 BEST PRESENTATION:** **The Aggregate Cost of Mammography in The United States in 2010.** *Presented by Cristina Thorsen, MD.*
- **RUNNER UP:** **Spingosine-1-Phosphate Enhances Satellite Cell Activation in Dystrophic Muscles Through an S1PR2/STAT3 Signaling Pathway.** *Presented by Kenneth C. Loh, MD*
- **RUNNER UP:** **Acinar Cell Secretory Defects Secondary to Corticotropin-Releasing-Factor Receptor 2 (CRF<sub>2</sub>) Deficiency Leads to Exacerbation of Experimental Acute Pancreatitis: A Defect That is Rescued by Urocortin 1 Administration.** *Presented by Eric Kubat, MD*
- **BEST “QUICK-SHOT” PRESENTATION:** **Hepatocytes derived from parthenogenetic embryonic stem cells provide normal liver function and can reverse liver failure in mice.** *Presented by Jack Harbell, MD.*

9:00 AM	Opening Remarks by the Department Chair	<b>Nancy Ascher MD, PhD Professor &amp; Chair</b>
<b>SESSION 1: "Trauma, Inflammation &amp; Development"</b>		<b>Moderator: Rochelle Dicker, MD</b>
9:05 AM	Factors Leading to Surgical Intervention in Pierre Robin Sequence Patients	<b>Beamy Sharma, MD</b>
9:10 AM	Corticotropin-Releasing Factor (CRF) Receptor Activation Causes Necrotizing Enterocolitis (NEC) in Formula Fed, Neonatal Rats	<b>Robert Bell, MD</b>
9:25 AM	Resolvin Attenuates Microvascular Leak during Inflammation	<b>Arturo Garcia, MD</b>
9:40 AM	Identifying Predictors of Poor Prognosis for Prenatally Diagnosed Sacrococcygeal Teratoma to Change the Paradigm for Fetal Surgery	<b>Eveline Shue, MD</b>
9:55 AM	The Relative Contributions of Fibrinogen and Platelets to Clot Strength Over Time In Injury	<b>Lucy Kornblith, MD</b>
10:10 AM	Hospital-Based Violence Intervention: Risk Reduction Resources That Are Essential for Success	<b>Randi Smith, MD</b>
10:25	<i>15 minute break</i>	
<b>SESSION 2: "Global Surgery, Public Health, Outcomes &amp; Education"</b>		<b>Moderator: Lan Vu, MD</b>
10:45 AM	Unanticipated Thyroid Cancer In Patients With Substernal, Multinodular Goiters: Are We Underestimating The Risk?	<b>Leah Candell, MD</b>
10:50 AM	In-Hospital Outcomes After Extracranial-Intracranial Bypass In The United States, 2000-2009: The Effect Of Hospital And Surgeon Volume	<b>Victoria Trinh, MD</b>
10:55 AM	Vitamin D Deficiency Is Associated With Mortality And Adverse Vascular Access Outcomes In The ESRD Population	<b>Joy Walker, MD</b>
11:00 AM	Expression of Apolipoprotein E in Patients with Primary Hyperparathyroidism Before and After Parathyroidectomy	<b>Carolyn Seib, MD</b>
11:05 AM	Peritoneal Dialysis in China; Using Human Centered Design to Identify Barriers to Adoption and Opportunities for Expansion	<b>Amanda Sammann, MD MPH</b>
11:10 AM	Cost-Effectiveness Analysis of Intraoperative Radiation Therapy for Early-Stage Breast Cancer	<b>Cristina O'Donoghue, MD</b>

11:15 AM	Task-shifting and the Scope of Surgical Care in Pwani Region, Tanzania	Jessica Beard, MD MPH
11:30 AM	Lower Extremity Revascularization in Nursing Home Residents in the United States	Lawrence Oresanya, MD
11:45 AM	Teaching Basic Surgical Skills In The Skills Lab Vs. Computer-Based Video Training (CBVT): A Randomized Controlled Trial	Emily Huang, MD

12:00 PM Lunch- Faculty Alumni House, 745 Parnassus Avenue

<b>SESSION 3: "Stem Cells, Transplantation, Immunology &amp; Innovations"</b>	<b>Moderator: Tara Karamlou, MD</b>
---	-------------------------------------

1:30 PM	Magnagrasp: Development Of An Innovative, Magnetically Controlled Surgical Retractor For Minimally Invasive Surgery	Matthew Swisher, MD
1:35 PM	Characterization of Human Muscle Stem Cells For Muscle Regeneration	Xiaoti Xu, MD
1:40 PM	Multidisciplinary Initiative Identifies And Targets Five Greatest Barriers To Safe And Efficacious Autologous Fat Grafting For Breast Reconstruction	Chetan Irwin, MD
1:45 PM	Extrathymic Aire-Expressing Cells in Autoimmunity and Transplantation	James Gardner, MD
2:00 PM	Generation of Induced Hepatocytes for Autologous Liver Cell Therapy	Jack Harbell, MD

2:15 PM 15 minute break

2:30 PM	Keynote Presentation: "Developments in Tracheal Reconstruction and Replacement in Children"	Martin Elliott, MB, BS, MD, FRCS 2013 Dunphy Professor
3:30 PM	Closing Remarks & Awards Presentation	Peter Stock, MD, PhD Research Committee Chair

 = Quick Shot presentations       = Standard presentations

*A special thanks to all who participated in this year's Resident Research Symposium and to the UCSF Department of Surgery Research Committee.*

*This event is sponsored by an Educational Grant from the Howard C. Naffziger Surgical Fund.*



## Factors Leading to Surgical Intervention in Pierre Robin Sequence Patients

Kristina Rosbe, MD, Beamy S. Sharma, MD Department of Otolaryngology- Head and Neck Surgery, UCSF

**Introduction:** Pierre-Robin sequence (PRS) is estimated to affect about 1 out of 8,500 newborns (1). The sequence is defined as micrognathia, glossoptosis and a cleft palate (2). The two most significant problems to overcome are respiratory distress and failure to thrive; the largest causes of mortality in PRS patients (3). The respiratory distress usually results from the obvious obstruction of the airway. However, these patients can also have respiratory issues due to hypotonia, central apnea, laryngomalacia, tracheomalacia and bronchial stenosis, although they occur less frequently (4). Their failure to thrive results from the increased energy expenditures towards work of breathing and feeding difficulties from their abnormal oral anatomy.

Fortunately, we have seen that simply positioning the infant's body can relieve airway compromise in many patients (6-10). However, when patients do not recover spontaneously, there are several interventions that are implemented. For airway, patients can get the lip tongue plication (LTA), mandibular distraction osteogenesis (MDO), and lastly, there is the tracheostomy, which is the gold standard treatment for airway complications in Pierre-robin patients. In terms of improving feeding, the classic interventions have been naso-gastric tube and percutaneous gastric tube placement.

In our study we focused on which factors lead to more invasive interventions, in hopes to lead to a better guide for parents and caretakers.

**Methods:** We performed a retrospective chart review from the patients at the Center for Craniofacial Anomalies at UCSF. Inclusion criteria were any patients that met the criteria for Pierre-Robin Sequence and in which we were able to obtain all necessary data including all interventions received. Patients that were lost to follow-up or received most of their care at another center were excluded. The data extracted were between 1985 to August 2012. We looked at which interventions patients received, and which factors, including sleep apnea, aspiration risk, laryngomalacia, GERD and weight, predisposed patients to receiving an invasive intervention. Dr. Hills, a biostatistician, from the Clinical and Translational Science Institute at UCSF worked with us to calculate the results.

**Results:** The total number of patients included in the study was 72. 47.2% (34) received an LTA, of those 5.9% (2) had to receive an MDO subsequently and 11.8% (4) received a tracheostomy. 2.8% (2) received an MDO as their primary surgical intervention and 2.8% (2) received it as a secondary intervention. 25% (1) of those who received an MDO needed a tracheostomy. 11.1% (8) received a tracheostomy, 37.5% (3) of these patients received it as their primary surgical intervention. 45.8% (33) did not require any surgical intervention. 43.1% (31) patients had a sleep study. Of the 10 (32.3%) with no or mild sleep apnea 30% (3) required an intervention vs. 70% (7) did not. 6 (19.4%) had moderate sleep apnea, 83.3% (5) required an intervention vs. 16.7% (1) did not. Lastly, 48.4% (15) had severe sleep apnea, 66.7% (10) required an intervention vs. 33.3% (5) did not. None of these differences were significant. 19.4% (14) were diagnosed with laryngomalacia. 71.4% (10) with laryngomalacia vs. 50.0% (29) without laryngomalacia required a surgical intervention, however, this was not statistically significant. 22 of the patients received a swallow study. 84.6% (11) of those who had an aspiration risk received an airway intervention vs. 77.8% (7) of those who did not have an aspiration risk. This was not significant. Of these same patients, 84.6% (11) with an aspiration risk needed a G-tube vs. 11.1% (1) with no aspiration risk, which was significant. 19.4% (14) patients had a diagnosis of GERD and 71.4% with this diagnosis received an airway intervention vs. 50.0% of patients without GERD. This was not significant. Furthermore, 57.1% of GERD patients required a G-tube vs. 24.1% without GERD, a significant difference. Weights at any age range (birth weight, 4-8 months, and 8-12 months) did not have any significant correlation with surgical airway intervention or G-tube.

**Conclusion:** There was a positive correlation between worsening sleep apnea, laryngomalacia, GERD and aspiration risk with receiving a surgical airway intervention and g-tube. However, the only significant correlation was between aspiration risk and GERD and receiving a g-tube. It was difficult to obtain significant results because of the small sample size, especially when considering the even smaller sample size of patients who received a sleep study and swallow study.

# Corticotropin-releasing factor (CRF) receptor activation causes necrotizing enterocolitis (NEC) in formula fed, neonatal rats

Robert L. Bell MD<sup>1,2</sup>, Wolfgang Stehr MD<sup>3</sup>, Ginger Withers PhD<sup>4</sup>, Frans Kuypers PhD<sup>2</sup>

1) Department of Surgery, UC San Francisco East Bay; Oakland, CA 94602

2) Children's Hospital Oakland Research Institute; Oakland, CA 94609

3) Division of Pediatric Surgery, Children's Hospital and Research Center at Oakland; Oakland, CA 94609

4) Biology Department, Whitman College; Walla Walla, WA 99362

**Introduction:** The underlying cause of neonatal necrotizing enterocolitis (NEC) remains unknown. We hypothesized that corticotropin-releasing factor (CRF) signaling within the gastrointestinal tract serves as the inciting event in NEC's pathogenesis. In this proof of concept study, we induced necrotizing enterocolitis in neonatal rats to determine the effect of CRF receptor agonist and antagonist administration on the disease's incidence.

**Methods:** Animal experiments were approved by the Animal Care and Use Committee at Children's Hospital Oakland Research Institute (Protocol # 212). Maternal separation, formula feeding, and twice-daily exposure to hypoxia and cold stress were used to induce necrotizing enterocolitis in neonatal Sprague Dawley rats. On postnatal day 3, animals were randomized into one of six treatment groups: dam fed unstressed controls (DF); dam fed stressed controls (DFS); formula fed unstressed controls (FF); formula fed stressed (NEC); formula fed unstressed with subcutaneous administration of a CRF receptor agonist [Corticotropin-releasing factor, 30µg/kg] (CRF); and formula fed stressed with subcutaneous administration of the non-specific CRF-R1/CRF-R2 receptor antagonist [Astressin, 60µg/kg] 15-30 minutes prior to stress sessions (AST). Animals were sacrificed after 72 hours. Terminal ileum specimens were evaluated and assigned histologic mucosal injury scores. Incidence of NEC was determined and compared between treatment groups.

**Results:** The incidence of NEC in each group was: DF = 0/10 (0%); DFS = 0/10 (0%); FF = 1/11 (9.1%); NEC = 5/12 (41.7%); CRF = 7/12 (63.6%); AST = 1/13 (7.7%). Disease incidence was significantly increased over controls in both NEC ( $p < 0.04$ ) and CRF ( $p < 0.01$ ) groups. Compared to the NEC group, disease incidence was significantly decreased in AST animals ( $p = 0.024$ ).

**Conclusions:** These preliminary findings suggest an important role for CRF during the pathogenesis of necrotizing enterocolitis. Peripheral CRF receptors may hold promise as specific pharmacologic targets for NEC's prevention and treatment. Further animal experiments aimed at delineating the relationships between CRF, NEC's major risk-modifying factors, and its known downstream pathophysiological processes are currently underway.

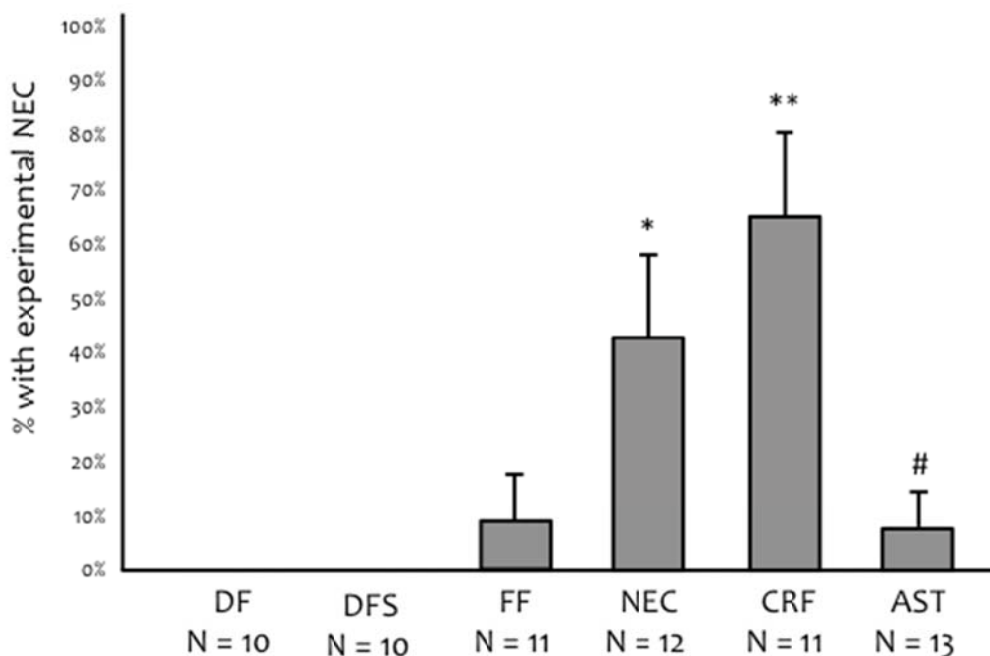


Figure 1: Incidence of necrotizing enterocolitis per treatment group.

Bars represent proportion of animals with NEC  $\pm$  SE. DF = dam fed unstressed; DFS = dam fed stressed; FF = formula fed unstressed; NEC = formula fed stressed; CRF = formula fed unstressed with CRF administration; AST = formula fed stressed with administration of the CRF receptor antagonist Astressin. \*) Statistically different compared to DF, DFS, and FF groups;  $P < 0.04$ . \*\*) Statistically different compared to DF, DFS, and FF groups;  $P < 0.01$ . #) Statistically different compared to NEC group,  $P = 0.02$ .



## Resolvin Attenuates Microvascular Leak during Inflammation

Arturo Garcia MD, Beth Cureton MD, Louise Yeung MD, Emily Miraflor MD, Gregory Victorino MD

**INTRODUCTION:** Counter-regulatory anti-inflammatory mediators are important for the resolution of severe inflammation, especially in trauma and major surgery. Resolvin E1 (RvE1) is an anti-inflammatory, vaso-active mediator from the eicosanoid family of omega-3 polyunsaturated fatty acids and has been shown to arrest neutrophil recruitment, block pro-inflammatory leukotrienes and prostaglandins, and reduce cytokine release. Our hypothesis was that RvE1 reverses the increased microvascular fluid leak observed during inflammation. Our specific aims were: 1) to determine the effect of RvE1 on albumin permeability due to lipopolysaccharide (LPS) *in vitro*, 2) to determine the effect of RvE1 on post-capillary venule leak due to LPS *in vivo*, 3) to determine the effect of RvE1 on post-capillary venule leak due to platelet activating factor (PAF) *in vivo*.

**METHODS:** Aim #1: *In vitro* bovine pulmonary endothelial cell (BPEC) monolayer permeability to albumin was measured by a colorimetric assay at baseline and in response to 100nM RvE1 alone, 0.5mg/mL LPS alone, and 0.5mg/mL LPS + 100nM RvE1. *In vivo* microvascular fluid leak (Lp) was measured in rat mesenteric venules using an intra-vital micro-occlusion technique in Sprague-Dawley rats. Baseline Lp was measured for 30 minutes and control animals underwent a continuous intra-venular infusion of 100 nM RvE1 alone. Aim #2: Lp was measured during systemic infusion of 10mg/kg LPS followed by a continuous intra-venular infusion of 0.5mg/mL of LPS. Results were compared to rats that underwent the LPS infusion as above, plus continuous intra-venular infusion of 100nM RvE1. Aim #3: Lp was measured during a continuous 10 nM PAF intra-venular infusion. Results were compared to animals that underwent the PAF infusion as above plus a continuous intra-venular infusion of 100nM RvE1. Units for permeability are ug/mL of albumin. Units for Lp are  $10^7$  cm-sec/cm-H<sub>2</sub>O.

**RESULTS:** LPS increased BPEC monolayer permeability 2-fold, and this increase was completely attenuated by RvE1 (permeability: LPS=0.53±0.01 vs. LPS+RvE1=0.31±0.01; p=0.005, baseline =0.26±0.1). *In vivo*, RvE1 alone did not affect baseline Lp (Lp-baseline = 1.00±0.03, Lp-RvE1 = 1.09±0.03; p=0.07). LPS-induced inflammation increased Lp over 2-fold (Lp-baseline = 1.00±0.03, Lp-LPS=2.23±0.1; p<0.001). RvE1 administration after LPS decreased Lp back to baseline levels (from 2.23±0.1 to 1.16±0.08; p<0.001). PAF increased Lp 4-fold (Lp-baseline = 1.12±0.07, Lp-PAF = 4.49±0.5; p<0.001). RvE1 administration after PAF decreased Lp 33% compared to PAF alone (from 4.49±0.5 to 3.06±0.2; p=0.02).

**CONCLUSION:** We have found that RvE1 attenuated the increase in microvascular leak during inflammation caused by LPS and PAF. These data support an anti-inflammatory role for RvE1 and suggests a potential pharmacologic role for RvE1 in microvascular dysfunction during inflammation and sepsis.

## Identifying Predictors of Poor Prognosis for Prenatally Diagnosed Sacrococcygeal Teratoma to Change the Paradigm for Fetal Surgery

Eveline H Shue, Marjan S. Bolouri, Vickie A. Feldstein, Lan T. Vu, Doug Miniati, Hanmin Lee

**Introduction:** Sacrococcygeal teratoma (SCT) is the most common congenital germ cell tumor. While some fetuses with SCT are born without complications, between 30-50% develop non-immune hydrops fetalis, and ultimately progress to fetal demise. Currently, fetal intervention is only performed for moribund fetuses, and survival is still dismal. The key to improving survival for prenatally diagnosed SCT is identifying fetuses who may benefit from fetal intervention before hydrops has developed.

**Methods:** A retrospective chart review of fetuses with prenatally diagnosed SCT between 1986 and 2011 was performed. Patients with available outcome data and ultrasound (US) exams performed before 32 weeks gestational age (GA) were included (n=37). Two independent sonologists, blinded to outcome, reviewed sonograms and assessed SCT morphology, tumor volume and estimated fetal weight. Tumor morphology was defined as: 1) >90% cystic; 2) 60-90% cystic; 3) mixed; 4) 60-90% solid; 5) >90% solid. Tumor volume-to-fetal weight ratio (TFR) was calculated using the prolate-ellipse formula. Good outcomes were defined as survival to hospital discharge, whereas poor outcomes were defined as intrauterine fetal demise, termination for hydrops or maternal mirror syndrome, perinatal death, or need for fetal intervention. ROC analysis was performed for TFR, and relative risk of TFR and tumor morphology as predictors of poor prognosis was calculated.

**Results:** Twelve patients (32%) had good prognosis and twenty-five patients (68%) had poor prognosis. All patients with poor prognosis had a morphology score  $\geq 3$ , which is a significant predictor of poor prognosis ( $p < 0.0001$ ). TFR was assessed and a receiver operating characteristic (ROC) analysis identified a cutoff value of 0.12 before 24 weeks GA and 0.11 before 32 weeks GA as predictors for poor prognosis. TFR is a significant predictor of poor prognosis ( $p < 0.0001$ ).

**Conclusion:** Patients with cystic SCT all had good prognosis. TFR  $>0.12$  was validated as a sonographic predictor of poor prognosis. TFR and tumor morphology can be used identify fetuses at risk for poor prognosis and identify those who may benefit from fetal intervention before hydrops has developed.

# THE RELATIVE CONTRIBUTIONS OF FIBRINOGEN AND PLATELETS TO CLOT STRENGTH OVER TIME IN INJURY

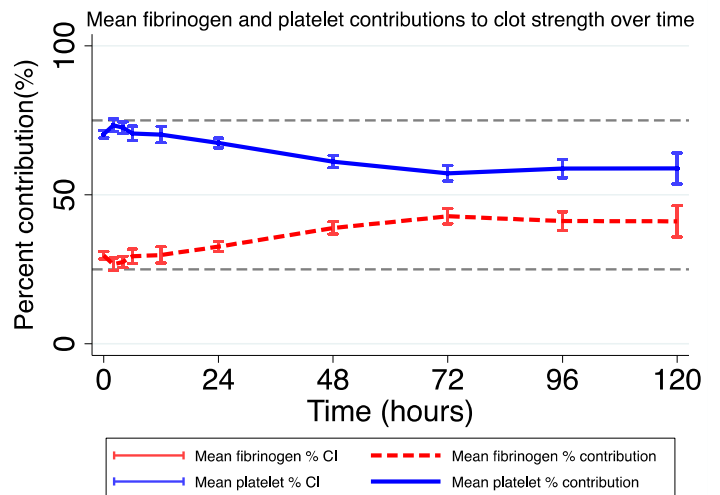
**Lucy Kornblith MD, Matthew Kutcher MD, Brittney Redick BA, Ryan Vilardi BS, Mitchell Cohen, MD**

**Introduction:** Acute traumatic coagulopathy (ATC) is a well-defined entity present in a quarter of trauma patients who present to the emergency department after severe injury and shock. Thromboelastography (TEG) allows real time functional viscoelastic examination of clot formation and lysis, and is of particular use in diagnosing ATC. Together platelets and fibrinogen comprise the key components of ultimate clot strength, however until now the relative contributions of each to clot strength are not known. Recently, functional fibrinogen (FF) testing allows measurement of the fibrinogen component and (by subtraction) the platelet contribution to clot strength. Recent data shows that functional fibrinogen levels (FLEV) correlate better with fibrinogen than alpha angle and kinetic time, which were previously used as a proxy for fibrinogen function. We hypothesized that low admission FLEV are associated with ATC, increased transfusion requirements, and worse outcomes. In addition, we sought to determine for the first time the relative contributions of fibrinogen and platelets to clot strength over time.

**Methods:** Longitudinal citrated plasma samples were prospectively collected from 165 highest-level activation trauma patients on arrival and serially for 120 hours. Demographics and outcomes for all patients were prospectively collected. In addition, thromboelastography (TEG), functional fibrinogen (FF), von Clauss fibrinogen, and standard coagulation measures were performed. Calculation of the platelet contribution to clot strength was performed with the equation  $MA_{TEG} - MA_{functional\ fibrinogen} = MA_{platelets}$ . Correlations were assessed with linear regression, and an alpha of 0.05 was considered significant.

**Results/progress:** From the 165 patients, 402 FF samples from time points 0-120 hours were obtained. FLEV correlated strongly with von Clauss fibrinogen ( $R^2=0.58, p=0.00$ ). However, admission FLEV correlated weakly with admission TEG alpha and kinetic time (K) values ( $R^2=0.18 p=0.00$ , and  $R^2=0.27 p=0.00$ ), but correlated better with admission TEG maximum amplitude (MA) and clot strength (G) values ( $R^2=0.58 p=0.00$ , and  $R^2=0.54 p=0.00$ ). The patients in the lowest admission FLEV percentile had lower pH, higher percentage with coagulopathy (INR  $\geq 1.5$ ), lower fibrinogen, lower platelet counts, lower percent fibrinogen contribution to clot, and required more transfusion in 24 hours (all  $p < 0.05$ ). In addition, the percent contribution of platelets to clot strength was higher than the percent contribution of fibrinogen to clot strength at all time points (Figure).

**Conclusions:** The recent addition of FF testing to standard TEG allows for analysis of the contribution of fibrinogen to ultimate clot strength. We show here that FLEV levels do correlate with standard von Clauss fibrinogen levels, as well as MA and G values. We also demonstrated that patients with lower admission FLEV levels are more coagulopathic and require more blood products. Lastly and perhaps most importantly, our data indicates that platelets play a more significant role than fibrinogen (thrombin induced clot) in clot formation after trauma, suggesting that consideration of an antiplatelet drug may be more appropriate for DVT prophylaxis in trauma patients.



# Hospital-Based Violence Intervention: Risk Reduction Resources That Are Essential for Success

Randi Smith, MD, MPH, Sarah Dobbins, MPH, Abigail Evans, BS, Kimen Balhotra, BS, Rochelle Dicker, MD  
University of California San Francisco

**Introduction:** Hospital-based violence intervention programs (VIPs) aim to reduce violent injury and recidivism. The aim of this study was to determine the most significant risk reduction variables associated with success in our VIP. We hypothesized that our recidivism rate declined since our VIP's inception and that we could identify risk reduction variables that were independent determinants of program success.

**Methods:** We analyzed our prospectively collected data for 2005-2011 from our VIP database. Success was defined as >50% needs met without recidivism or attrition. Impact Analysis was performed per a model promoted by the CDC. Impact measures include rates of risk reduction and injury recidivism rate. Case management time spent per client (dose) was defined as *low* (0-1 hrs/wk), *medium* (1-3 hrs/wk), *moderate* (3-6 hrs/week) and *high* (> 6 hrs/wk). Correlation coefficients and logistic regression were used to examine associations between variables and success in the VIP.

**Results:** 260 clients received services. Need for risk reduction resources were identified in 176 (75%) clients. Meeting needs in two key categories proved significantly associated with success ( $p < .05$ ) (TABLE). The 6-year program recidivism rate was 4% vs. historical control of 16% ( $p < .05$ ). Moderate and high exposure to intensive case management in the first 3 months was also significantly associated with success ( $p < .05$ ). Success in our VIP was not associated with age, gender, education level, prior incarceration, probation status or length of time in program. Lack of success was associated with being a recidivist *prior* to VIP, (OR=.31 [95% CI: 0.14-0.72;  $p < .01$ ).

	Need met N (%)		Significance	
	Successful	Not Successful	p-value	Odds Ratio: (95% CI)
Housing	40 (75)	13 (25)	.772	1.12: (0.49 - 2.57)
Education	38 (72)	15 (28)	.288	0.625 : (0.263 – 1.486)
Mental Health*	71 (86)	12 (14)	<.001	5.967: (2.723 - 13.075)
Family Counseling	16 (80)	4 (20)	.222	2.257: (0.611 - 8.344)
Court Advocacy	38 (76)	12 (24)	.566	1.286 (0.544 - 3.042)
Vocational/ Professional Training	35 (70)	15 (30)	.484	.692: (0.246 – 1.941)
Employment*	44 (86)	7 (24)	.005	4.407: 1.559-12.457)
Driver's License	17 (89)	2 (11)	.124	3.531: (0.708 – 17.618)
Substance Abuse	1 (50)	1 (50)	.830	.699 (0.027 – 18.265)
Other	34 (66)	17 (34)	.309	1.481: (0.695 – 3.156)

\* Significant Predictors of Success in our VIP

**Discussion:** Over 6 years, our recidivism rate has decreased 4-fold compared to the rate prior to VIP inception. For startup and maintenance of a VIP, it is essential to know where to focus collaborative efforts in communities to target the most critical risk reduction resources. This study provides guidance: Securing education, mental health care and employment for our clients appears to be predictive of success. The value of early “high dose” intensive case management is also essential for reducing recidivism.

## UNANTICIPATED THYROID CANCER IN PATIENTS WITH SUBSTERNAL, MULTINODULAR GOITERS: ARE WE UNDERESTIMATING THE RISK?

Leah Candell, Michael J. Campbell, Jessica Gosnell, Quan-Yang Duh, Orlo Clark, and Wen T. Shen.

**Introduction:** Traditionally, the rate of unexpected cancer found in substernal and cervical multinodular goiters (MNG) is thought to be similar, around 5-15%. In our practice we have found that the difficulty of imaging and biopsying a substernal MNG leads to a higher than expected rate of unexpected thyroid cancers at the time of thyroidectomy. The purpose of this study was to compare the rates of unexpected cancer found in substernal versus cervical MNG patients.

**Methods:** We conducted a retrospective review of all patients undergoing thyroidectomy for MNG from 2005 to 2012. Patients met inclusion criteria if they were 17 years or older and did not have a preoperative diagnosis of thyroid cancer. Our primary outcome was the rate of unexpected thyroid cancer ( $\geq 1$  cm) in substernal versus cervical MNG.

**Results:** We identified 595 consecutive patients that underwent thyroidectomy for MNG and met inclusion criteria. Of these, 148 patients had substernal MNGs and 447 patients had cervical MNGs. The two groups were similar in terms of age, gender, and risk factors including family history of thyroid cancer and history of radiation exposure. On pathologic review, cancer was found in 14.9% of substernal MNG specimens and in 5.6% of cervical MNG specimens ( $p=0.007$ ).

**Conclusion:** The rate of incidentally discovered thyroid cancer is significant in patients with a substernal goiter and increased when compared to patients with cervical goiters. Surgeons should counsel their patients as to the possibility of this unexpected result.

# **In-hospital outcomes after extracranial-intracranial bypass in the United States, 2000-2009: The effect of hospital and surgeon volume**

Trinh VT\*, Davies JM\*, Lawton MT. Department of Neurological Surgery, University of California, San Francisco. *\*These authors contributed equally to this work*

## **INTRODUCTION:**

The extracranial-intracranial (EC-IC) bypass procedure has uncertain standing in evidence-based practice. Although two randomized control trials have called into question its utility in occlusive cervical carotid disease, its role in the management of Moyamoya disease and aneurysms remains unclear. We analyzed utilization and outcomes for United States procedures between 2000-2009 to further elucidate safe practice parameters and to determine if these trends have continued in the new millennium.

## **METHODS:**

The authors performed a retrospective cohort study based on data from the Nationwide Inpatient Sample (NIS). Multivariate regression analysis with the primary endpoints of inpatient mortality, length of stay, and discharge disposition were stratified across patient, surgeon, and hospital characteristics.

## **RESULTS:**

We identified 6,027 patients who underwent EC-IC bypass who were treated at US hospitals, with a mean of 603 patients admitted annually. Of these, 2,456 (40.7%) admissions were for Moyamoya disease, 2,428 (40.3%) were for anterior circulation occlusive disease and 1,143 (19%) were for aneurysms. Mortality rates were lowest for patients with Moyamoya disease (0.2%) and highest for patients with subarachnoid hemorrhage (SAH) (15.2%). The majority (86.4%) of patients with Moyamoya disease were discharged directly to their homes, compared with 28% of patients with SAH. Hospital case-volume was a significant predictor of in-hospital mortality ( $p < 0.001$ ), routine discharge ( $p < 0.001$ ) and median LOS ( $p < 0.001$ ). Several complications of EC-IC bypass occurred less frequently for high-volume providers ( $p < 0.001$ ) for hydrocephalus, placement of ventriculostomy, and mechanical ventilation. In a multivariate analysis in which adjustments were made for age, sex, race, admission type, medical comorbidity score, and infarction/hemorrhage, high-volume hospitals had a lower in-hospital mortality rate ( $p = 0.023$ , OR 0.319). In a multivariate subgroup analysis that adjusted for primary diagnosis, in addition to the previously mentioned parameters, high-volume hospitals had a higher routine discharge disposition ( $p = 0.035$ , OR 1.408).

## **CONCLUSION:**

Primary diagnosis as well as hospital case volume were significant predictors of outcome for in-hospital mortality, discharge disposition, length of stay, and peri-operative complications. In contrast to the previous decade, the results of our analysis demonstrate greater centralization of care and decreased mortality for all diagnosis groups. Bypass for Moyamoya disease is being performed more frequently and with superior perioperative outcomes. Large-volume centers provide superior outcomes and suggest that further centralization of care would be beneficial to patients and may influence the balance of risks and benefits when considering indications for bypass.



*Vitamin D deficiency is associated with mortality and adverse vascular access outcomes in the ESRD population.*

Joy Walker, Jade Hiramoto, Philip Auyang, Hugh Alley, Michael S. Conte, David Lovett, Joseph Rapp, Christopher D. Owens

**Introduction:** Plasma 25 hydroxycholecalciferol (vitamin D) has been associated with adverse cardiovascular outcomes in epidemiological studies. CKD is associated with loss of 1- $\alpha$ -hydroxylase and vitamin D deficiency. We hypothesized that vitamin D deficiency is associated with increased mortality and decreased vascular access patency in patients undergoing permanent vascular access for end stage renal disease.

**Methods:** A cohort of 129 patients undergoing permanent vascular access surgery who also had concurrent plasma vitamin D levels was identified. Vitamin D levels were considered deficient at <20 ng/mL. Mortality and vascular access patency were evaluated using multivariate logistic regression models.

**Results:** The mean age was 66.6, 96.1% were male and 31.8% African American. 61.2% had diabetes mellitus. In the entire cohort 48.8% were vitamin D deficient. Mean follow up time was 2.96 years during which there were 41 (31.8%) deaths and 79(64.75%) vascular access events. Vitamin D deficient patients tended to be younger ( $p=0.002$ ), have lower albumin levels ( $p=.022$ ), higher total cholesterol ( $p=0.0002$ ), and lower calcium levels ( $p=0.032$ ). Despite their younger age, mortality was significantly higher in this group ( $p=0.009$ ) and AVF patency was worse ( $p=0.020$ ). Age, vitamin D deficiency, CAD, HTN, albumin and HgbA1C were associated with mortality. In multivariate analysis vitamin D deficiency OR=5.95; (CI 1.70-20.77)  $P=.005$ , CAD OR=3.56; (CI 1.16-10.85)  $P=.026$ , age OR=1.10; (CI 1.04-1.17)  $P=.001$  and albumin OR=0.27 (CI 0.08-0.90)  $P=.032$  remained significant. Vitamin D deficiency, OR=2.30 (CI 1.02-5.19)  $P=.044$ , previously failed vascular access, OR 5.47 (CI 1.35-22.11)  $P=0.017$  and hematocrit, OR 1.09 (CI 1.01-1.19)  $P=.035$  were independently associated with a loss of vascular access patency in multivariate analysis.

**Conclusion:** Vitamin D deficiency is highly prevalent in patients undergoing vascular access procedures. Patients who are deficient have worse survival and more access related events. Further study is warranted to assess whether vitamin D repletion will improve outcomes in this population.

# Expression of Apolipoprotein E in Patients with Primary Hyperparathyroidism Before and After Parathyroidectomy

Carolyn D. Seib, Jessica E. Gosnell, Quan-Yang Duh, Orlo Clark, Wen T. Shen

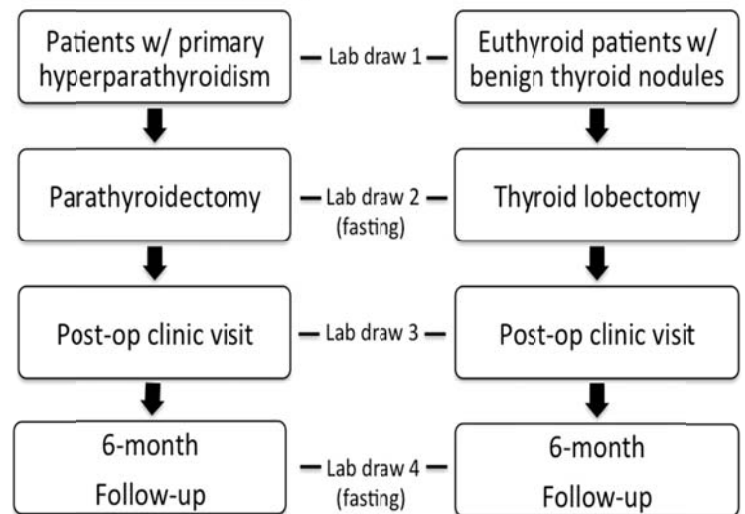
## Introduction:

The association between primary hyperparathyroidism (PHPT) and cardiovascular risk is well established,<sup>1-4</sup> with long-term observational studies in Scandinavia demonstrating increased overall mortality due to cardiovascular disease (CVD) in untreated patients with PHPT, which declines with increasing time following parathyroidectomy<sup>1-6</sup>. The prevention of CVD is not currently an indication for parathyroidectomy because reliable markers of at risk patients are lacking and studies documenting regression of cardiovascular disorders have demonstrated conflicting results<sup>7</sup>. Serum biomarkers are emerging as a promising prognostic tool to better characterize the cardiovascular risks of PHPT, but have not been well studied. Apolipoprotein E (apoE) is a polymorphic gene that modulates the metabolism of plasma lipoproteins and is a well-established genetic risk factor for CVD and dementia<sup>8</sup>. ApoE serum level is a promising biomarker of cardiovascular risk that has not been investigated in patients with PHPT and requires further investigation.

## Methods:

To assess baseline expression of apoE in patients with PHPT and the effect of parathyroidectomy on this expression profile, we are performing a prospective double cohort study in which we will compare apoE serum levels of patients with PHPT before and after parathyroidectomy and euthyroid patients with benign thyroid nodules before and after thyroid lobectomy. Blood is collected at two time points before and after surgery (figure). Serum and lymphocytes will be harvested and stored at -80° C and subsequently analyzed for apoE serum levels and genotype, in addition to full lipid profiles and a panel of biomarkers for inflammation, coagulation, aging, and thrombosis. Estimated sample size based on previously reported changes in apolipoprotein levels in this population is 72. Differences in mean apoE levels at baseline and post-operatively in the two cohorts will be tested with a Wilcoxon rank-sum test. Individual changes in apoE expression after operative intervention will be evaluated with a Wilcoxon signed-rank test for paired data.

## Double cohort study design



## Progress:

After 3 months of recruitment, 42 patients have been enrolled in the study and have baseline serum samples stored, including 32 patients with PHPT undergoing parathyroidectomy and 10 patients with benign thyroid nodules undergoing thyroid lobectomy. Of these patients, 24 have undergone surgery and have serum and lymphocytes (obtained in the fasting state pre-operatively) stored for biomarker and genetic analysis, in addition to full lipid panels processed in the UCSF laboratory. We also have serum samples from 16 patients from their post-operative clinic visits. We anticipate completing recruitment in August 2013, at which time we will begin biomarker analysis.

## Conclusion:

With this prospective study of biomarker expression, we hope to show that in addition to preventing the metabolic consequences of osteoporosis, kidney stones, and cognitive decline, definitive treatment of PHPT with parathyroidectomy may also improve the cardiovascular risk profile of patients with the disease.

## **Peritoneal Dialysis in China; Using Human Centered Design to Identify Barriers to Adoption and Opportunities for Expansion**

Sammann, Amanda, MD, MPH; Overmaat, Toby; Zhou, Helen

**Introduction:** End stage renal disease (ESRD), is on the rise in China and has the potential to overburden China's health care system. There are an estimated 670,259 patients living with ESRD in China; however, only 45% of these have access to treatment and of those who do have access, only 79% can afford to pay for dialysis. Of those who do get treatment, hemodialysis (HD) is the predominant modality with only 12% of patients using peritoneal dialysis (PD). With increasing numbers of ESRD patients, limited health care infrastructure and funds to set up HD centers, the Chinese government has begun encouraging the use of PD. The purpose of this research was to conduct human centered, ethnographic research to identify barriers to adoption and opportunities to expand the use of PD in China.

**Methods:** Qualitative ethnographic research was conducted across 5 Tier 1 to Tier 3 cities in China from January to February of 2013. Thirty one in-context, open ended interviews and observations were conducted with a variety of stakeholders in the ecosystem including ESRD and pre-ESRD patients, nurses, nephrologists, Traditional Chinese Medicine (TCM) doctors, hospital administrators and medical distributors. Using the human centered design thinking approach, interactive activities such as journey maps and provocations of sacrificial design opportunities were employed to gain greater insight into the stakeholders needs.

**Results:** Culturally, diagnosis of ESRD is challenging because symptoms are vague and doctors have limited time with patients (reported average of 5 min per visit). Due to the structure of government insurance, patients are suspicious of diagnostic tests because the cost of testing is paid out of pocket, so doctors are discouraged from ordering the chemistry panels or urinalysis that are necessary to diagnose kidney disease. Lastly, there are too few doctors trained in PD, especially in lower tier cities and of those who are trained in PD, they take a more paternalistic approach to treatment counseling and will not offer PD to patients who they believe to be incapable of performing PD or who they presume can not keep a clean treatment environment.

**Conclusion:** There are a number of barriers to expanding the use of peritoneal dialysis in China; however there are also a number of potential solutions that range of awareness campaigns, to the design of new products to improve the subjective and objective cleanliness of in-home treatment. The next steps are to evaluate the different solutions, determine which have the greatest reach and are the most financially viable and technically feasible and begin to pilot test them in select markets in China.

## Cost-Effectiveness Analysis of Intraoperative Radiation Therapy for Early-Stage Breast Cancer

C O'Donoghue, MD Alvarado, R Howe, LJ Esserman, EM Ozanne

**Introduction:** Minority and older women have reduced rates of completing radiotherapy (RT) after breast-conserving surgery (BCS) and higher rates of mastectomy for local breast cancer treatment. For women with early-stage ER positive breast cancer, evidence supports options other than traditional external beam radiation therapy (EBRT) after BCS. This analysis studies whether intraoperative radiation therapy (IORT) is a reasonable, cost-effective alternative to EBRT for African American (AA) women over 55 years with early-stage ER positive breast cancer. We additionally evaluate the option of no RT for AA woman over 70 years.

**Methods:** Using a Markov model, a cost-effectiveness analysis was done to compare BCS with EBRT and IORT for African American women, 55 years old, with ER positive, early stage breast cancer. For the base case, the local recurrence rate (LRR) for IORT was 3.0% and EBRT was 2.4% based on results from the TARGIT-A trial. We additionally performed a subanalysis comparing BCS with EBRT, IORT and no RT for African American women over 70 years. Direct costs used Medicare reimbursements. Utilities and non-medical costs were derived from the literature. Quality adjusted life years (QALY), costs, and the incremental cost-effectiveness ratio (ICER) were calculated over 10 years.

**Results:** For African American women over 55 years with ER positive, early-stage breast cancer, IORT was more cost-effective than EBRT. (Table 1.) With almost identical outcomes in life-expectancy and QALYs, IORT is the dominant cost-effective strategy because it because it saves over \$4,000 per woman when compared to EBRT. For women over 70 years, BCS alone was the most cost-effective strategy. The model was most sensitive to the utilities of radiation therapies.

**Table 1.** Baseline results for 55-year-old and 70-year-old African American woman

	Baseline Results 55 year old AA woman		Baseline Results 70 year old AA woman		
	IORT	6-week EBRT	IORT	No RT	6-week EBRT
Life expectancy in life-years	8.25	8.25	7.57	7.57	7.57
QALYs	7.54	7.54	6.92	6.62	6.92
Cost	\$29,102	\$33,530	\$27,205	\$23,020	\$31,648
ICER	Preferred	Dominated	\$3,929	Preferred	Dominated

**Conclusion:** For African American women over 55 years with early-stage ER positive breast cancer, IORT is the preferred cost-effective RT strategy that may increase compliance with RT and offer an alternative to mastectomy. Additionally, for select women 70 years and older, eliminating all types of radiotherapy is the preferred strategy; however, IORT is also an acceptable cost-effective treatment. There was no situation in which EBRT was a preferred strategy. IORT may have an even greater value for women with barriers to RT, such as travel or limited resources.

## **Surgical Activity of Non-physician Clinicians and Outcomes after Non-obstetric Major Surgical Procedures in Tanzania**

Jessica H. Beard, MD, MPH<sup>1,2</sup> Lawrence B. Oresanya, MD,<sup>1,2</sup> Charles Mkony, MD, MMed,<sup>2</sup> Larry Akoko, MD, MMed,<sup>2</sup> Ally Mwangi MD, MMed,<sup>2</sup> Rochelle Dicker, MD; UCSF<sup>1</sup>

<sup>1</sup>UCSF Department of Surgery

<sup>2</sup>MUHAS Department of Surgery

**Introduction:** Since the 1960s, Tanzania has addressed its shortage of surgeons by task-shifting responsibilities for surgical care to non-physician clinicians (NPCs). Although NPCs deliver the majority of surgical care in Tanzania today, the quality and breadth of care they provide remains relatively unstudied. We aimed to document the scope of surgical practice by level of care provider and to characterize outcomes after major non-obstetric surgical procedures performed by non-physicians at hospitals in one political region in Tanzania.

**Methods:** A retrospective records review of major surgical procedures (MSPs) performed in 2012 was conducted at all seven district and mission hospitals in the Pwani Region, Tanzania. Patient characteristics and level of surgical care provider were documented for all MSPs. Common non-obstetric MSPs were identified and characterized. Rates of post-operative morbidity and mortality were recorded by procedure and level of provider. Outcomes after procedures performed by NPCs and medical doctors were compared.

**Results:** There were 6.5 surgical care providers per 100,000 population in Pwani Region in 2012. A total of 4890 MSPs were performed, making the mean rate of major surgery 461 procedures per 100,000 population per year. Of these cases, 1624 (34.6%) were non-obstetric MSPs. NPCs performed 55.7% of non-obstetric MSPs followed by specialists (28.8%) and medical officers (15.5%). The most common non-obstetric MSPs performed by NPCs were: elective groin herniorrhaphy (23.7%), prostatectomy (16.6%), exploratory laparotomy for acute abdomen (10.4%), hydrocelectomy (8.8%), emergency groin herniorrhaphy (7.9%), hysterectomy (7.2%), and appendectomy (5.0%). Overall post-operative mortality was 1.7% while 18.5% of patients had at least one complication recorded. Leading sources of morbidity were wound infection (8.4%), blood transfusion (6.2%), and re-operation (3.2%). There was no significant difference in outcomes after procedures performed by NPCs and physicians.

**Conclusions:** Surgical output is low and the surgical workforce is limited in Tanzania. Outcomes after non-obstetric major surgical procedures done by NPCs and physicians are equivalent. Task-shifting of surgical care to non-physicians is a safe and sustainable way to address the global surgical workforce crisis and efforts should be made to increase and improve surgical training for NPCs in resource-poor settings.

## **Lower Extremity Revascularization in Nursing Home Residents in the United States**

Lawrence Oresanya MD, Shoujun Zhao, MD, PhD, Michael Conte MD, Emily Finlayson MD,MS

**Introduction:** For patients with peripheral arterial disease (PAD), the main goal of lower extremity revascularization (LER) is to prevent limb loss and allow patients to maintain functional independence. Prior studies suggest that patients who are non-ambulatory and functionally dependent have poor outcomes. In our study we examine the preoperative ambulatory status, postoperative outcomes and changes in functional status following LER in nursing home residents

**Methods:** Using data from a national registry of nursing home residents and Medicare claims, we identified all nursing home residents who underwent lower extremity revascularization procedures in the United States between 2005 and 2008. Based on registry data, patients were classified as ambulatory, non-ambulatory and bed bound. We examined the changes in overall functional status as measured by the Minimum Data Set Activities of Daily Living Summary Score among surviving patients at 3, 6, 9 and 12 months postoperatively. We measured the rates of major adverse limb events (re-intervention and above ankle amputations) and post-operative death (MALE+POD) at one year following LER, and used regression methods to identify the risk factors for adverse outcomes.

**Results:** LER procedures were performed on 10809 nursing home residents in the study period. Prior to surgery, 63% of subjects were non ambulatory and 27% were bed bound. Only 23% of subjects maintained or improved their overall functional status one year following LER. The one year incidence of MALE+POD was 63% among all subjects and 67% in bed bound subjects. Open revascularization procedures (HR 1.09 95% CI 1.04 - 1.14), age >80 (HR 1.39 95% CI 1.24 - 1.54), functional dependence (HR 1.62 95% CI 1.51 - 1.74), >7 Charlson comorbidity score (HR 1.15 95% CI 1.06 - 1.26) and emergent procedures (HR 1.27 95% CI 1.20 - 1.33) were independent risk factors for MALE+POD.

**Conclusion:** Only a small proportion of older long term nursing home residents appear to benefit from LER. Better patient selection and use of alternative treatment strategies may improve outcomes in this vulnerable population.



## Teaching basic surgical skills in the skills lab vs. computer-based video training (CBVT): A randomized controlled trial

Emily Huang, M.D.\*, Hueylan Chern, M.D.\*, Patricia O'Sullivan, Ed.D. °, Edward Kim, M.D.\*

\* Department of Surgery, University of California San Francisco

° Department of Medicine, University of California San Francisco

**Introduction:** Advances in technology, along with time and resource restrictions, have made teaching of basic surgical skills via computer-based video training (CBVT) an attractive option. While it has been shown that novice medical students can improve performance on basic surgical skills with CBVT, its effectiveness for residents, who must achieve greater proficiency, is less clear. We implemented a CBVT curriculum for surgical interns at our institution and examined its effects on performance.

**Methods:** This prospective randomized controlled trial included 22 PGY-1 surgical residents in the general surgery, plastic surgery, urology and otolaryngology programs at UCSF. The interns were randomized to receive a CBVT curriculum (n=11) or instructional sessions at the Surgical Skills Center (n=11). Pre- and post-intervention videotapes of each intern performing basic surgical skills (one- and two-handed knot tying, and subcutaneous suturing) were deidentified and scored by three expert raters using a global rating scale. Additionally, post-intervention, all interns were videotaped performing a task which integrates the basic skills. The same raters scored the integrated task using a modified objective structured assessment of technical skills (OSATS), generating tissue handling (4 items) and technical skill (4 items) scores. We conducted an analysis of covariance for the five outcomes, and calculated effect size (es) of the intervention (necessary due to the small sample size).

**Results:** Our measures showed acceptable inter-rater reliability: one- (.77) and two-handed (.63) knot tying, subcutaneous suturing (.73), tissue handling (.73), and technical skill (.85) scores. Adjusting for pre-intervention score, we found no difference in performance between the two groups for basic surgical skills: one-handed knot tying (p=.21, es= .076), two-handed knot tying (p=.48, es=.028), suturing (p=.11, es=.14) or for integrated skills: tissue handling (p=.77; es=.005), and technical skill (p=.60, es=.014).

**Conclusions:** CBVT is an effective option for teaching basic surgical skills to surgical residents, and does not subsequently limit performance on more complex skills. This easily implemented strategy optimizes the use of training resources, freeing skills lab facilities for more advanced topics, while allowing programs without a skills lab to provide effective teaching to their residents.

## **MagnaGrasp: Development of an innovative, magnetically controlled surgical retractor for minimally invasive surgery**

Matthew Swisher, MD, Sara Pittenger, MD, Jerd Phichitkul, BS, Dillon Kwiat, BS, Michael Harrison, MD

**Introduction:** Despite the widespread adoption of laparoscopic surgery, the need for multiple retractors and difficulty achieving necessary angles of retraction still represent unmet technical challenges. As such, the trend towards progressively less invasive surgery (single-incision laparoscopic surgery) has been hindered by the available surgical instruments, which do not offer easily manipulatable angles of retraction and adequate triangulation. To address these unmet clinical needs, we have designed and started to develop an innovative, magnetically operable surgical retractor (MagnaGrasp).

**Methods:** Computer-aided design (CAD) tools were used to design a novel, fully detachable, and magnetic grasper tip. An initial alpha-prototype was created with 3D printing. An external magnet allowing for variation in the magnetic force was designed to be anchored to the operating room table. Initial proof-of-concept testing was used to simulate the necessary retraction forces needed in a laparoscopic cholecystectomy bench-top model.

**Results:** The initial alpha-prototype was designed with a smaller magnet attached to the distal end. Proof-of-concept testing using our bench-top model showed that the force needed to retract the gallbladder fundus cephalad required a larger magnetic component. The addition of a longer magnetic tip allowed for the necessary retraction force. Manipulation of the external magnet allowed for near limitless retraction of the gallbladder fundus.

**Conclusions:** Our initial prototype confirms that a detachable, magnetically operable retractor can provide the necessary retraction in a laparoscopic cholecystectomy model. Future work includes development of a beta-prototype with a longer magnetic component, optimization of the external magnet, and *in vivo* testing in a porcine model.

## **Characterization of Human Muscle Stem Cells For Muscle Regeneration.**

Xiaoti Xu MD, Robert Hesse BS, Valeria Carcamo-Cavazos BS, Catherine Garland MD, Jason H Pomerantz MD

### **Introduction:**

Satellite cells are endogenous skeletal muscle stem cells that potently regenerate muscle, and are therefore appropriate targets to enhance repair or as building blocks for engineering muscle. In mice, satellite cells are well characterized and transplantable. In humans, although satellite cells have been identified, their heterogeneity and regenerative capacity after transplantation have not been determined. Therefore human satellite cells are unavailable for clinical use. The purpose of this study is to develop approaches to characterize and transplant endogenous human satellite cells to enable regenerative applications.

### **Methods:**

Biopsies are taken from diverse human skeletal muscles during reconstructive procedures at UCSF. The muscle is harvested by longitudinal sharp dissection to preserve architecture. Individual undergo glycerol embedding for fiber dissection as well as enzymatic digestion for liver fiber isolation. Satellite cells are identified using antibodies against transcription factors and surface proteins in conjunction with anatomic localization beneath the basal lamina. Satellite cell frequency is determined by counting cells within 100µm fiber lengths. Live fibers are cultured in growth medium. In conjunction a surgical model of denervation atrophy is being created through transection of sciatic nerves of immunodeficient NSG mice.

### **Progress:**

We have collected 32 human muscle samples from diverse muscles, including rectus abdominis, sartorius, vastus lateralis, pectoralis major, latissimus dorsi and gracilis. Analysis of the fibers show that there is 1.08 satellite cells per 100um of muscle fiber in the rectus abdominis and 0.86 satellite cells per 100um of muscle fiber in the sartorius. While the rectus abdominis has more satellite cells per 100um of fiber length, there is no significant difference between the two groups ( $p=.2$ ). Cells derived from culture of single human muscle fiber shows positive staining for desmin, a human muscle protein, indicating successful isolation of viable fibers capable of producing cells of myogenic lineage. Sciatic nerve transection has been performed on 7 mice and reinnervation has been performed on 3 of them. Analysis of denervated tibialis anterior compared to that of normal shows an average difference of 27.3g ( $p=4.7 \times 10^{-5}$ ).

### **Conclusion:**

Current goals to enable clinical application of human skeletal muscle stem cells include 1) identification of optimal donor muscles for satellite cells, taking into account satellite cell frequency, function and donor site morbidity; 2) Development of transplantation protocols using live fibers and/or purified satellite cells; 3) Testing satellite cell transplantation in relevant preclinical models. Our data confirm that human satellite cells can be quantified in sections and isolated fibers. After reaching sufficient sample size of human muscle specimen we will determine if there is a variation in satellite cell frequency amongst different muscle groups. Our data also confirm that live human muscle fiber is feasible. Last our denervation model shows a significant difference in muscle mass. Our next step would be to analyze the effectiveness of our reinnervation procedures. Establishment of human donor muscles and development of human satellite cell transplantation protocols will enable preclinical studies and clinical translation of muscle stem cell therapeutic approaches.

# **Multidisciplinary Initiative Identifies And Targets Five Greatest Barriers To Safe And Efficacious Autologous Fat Grafting For Breast Reconstruction**

Chetan Irwin M.D., Laura Esserman M.D., Hani Sbitany M.D.

## **Introduction**

Autologous fat grafting is a promising plastic surgery procedure increasingly being applied to breast reconstruction. At University of California, San Francisco a multidisciplinary fat grafting program has been initiated to coordinate research, clinical and advocacy efforts at safe and efficacious implementation of fat grafting for breast conservation and mastectomy patients. We sought to define the most important knowledge gaps remaining in the literature and the greatest barriers to successful incorporation of fat grafting in daily clinical practice and systematically address each area.

## **Methods**

Qualitative surveys were conducted of nine physicians and nurses to assess concerns and anticipated barriers to success in implementation. We then matched the survey data with the literature and found five key areas requiring attention. Clinical research and advocacy efforts are targeted to systematically address each.

## **Results**

1) Medical oncology: Lack of prospective data on locoregional recurrence and survival in fat grafted patients at five-year follow-up. 2) Radiology: Insufficient data characterizing the mammographic changes that occur in grafted fat and the timeline of those changes. 3) Radiation oncology: Insufficient data regarding the interaction with or impact of radiotherapy on fat graft survival and volume maintenance. 4) Policy: Lack of insurance coverage for fat grafting procedures in breast reconstruction, as it is often deemed an “experimental procedure.” 5) Plastic Surgery: Insufficient data on BRAVA enhanced fat grafting and minimum device wear required to achieve significant fat grafting benefit (volume and take).

## **Conclusions**

Safe and efficacious incorporation of fat grafting into the armamentarium of the breast cancer center requires a multidisciplinary approach with an emphasis on prospectively addressing the most pressing issues by designing an integrated clinical and research program integrating data collection for each of the five areas identified.

# Extrathymic Aire-Expressing Cells in Autoimmunity and Transplantation

James Gardner, MD, PhD; Mark Anderson, MD, PhD

## Introduction:

Educating the adaptive immune system to distinguish self from nonself is a critical component of human health and disease. This self-education has been classically understood to occur in the thymus, where it depends heavily on the function of a single gene, the AutoImmune REgulator (*AIRE*). *AIRE* was identified by positional cloning in families with Autoimmune Polyglandular Syndrome Type I (APS1), a severe, multi-organ autoimmune disease. Thymic *AIRE* expression normally prevents such autoimmunity by endowing specialized “educator” medullary thymic epithelial cells (mTECs) with the ability to express a diverse set of otherwise tissue-restricted self-antigens like insulin, thyroglobulin, and myelin-basic protein. These mTECs express and present such self-antigens to developing T cells in the context of self-MHC, thus exposing them to a more complete picture of the immunologic self and, by exclusion, defining the response against invading pathogens and allogeneic MHC. Previously, immunologic self-tolerance was believed to be established exclusively within the thymus, but recently we described a novel population of extraThymic *Aire*-expressing Cells (eTACs) in the secondary and tertiary lymphoid organs that appear to continue the work of immune self-education in the rest of the organism and to persist throughout its lifespan long after thymic involution. Our work focuses on understanding the fundamental biology of this population in immune homeostasis, and on their therapeutic potential in autoimmunity and transplantation. We believe that by understanding the fundamental mechanisms of immune self-education we will be able to more precisely treat autoimmune disease and achieve donor-specific tolerance in transplantation.

## Methods

We have constructed a series of transgenic mice that afford us precise control over eTACs and the antigens they express. The Aire-driven IGRP-GFP (Adig) mouse allows us to express a GFP-tagged copy of the important islet antigen IGRP in eTACs, with which we can isolate and purify eTACs, study their interaction with IGRP-specific CD8+ T cells, and study the impact of such self-antigen expression in eTACs on autoimmune diabetes. The Aire-driven BDC antigen (AdBDC) mouse allows us to study eTAC interactions with islet-specific CD4+ T cells, and to examine the role of eTACs in the peripheral induction of adaptive regulatory T cells (Treg). The Aire-Diphtheria Toxin Receptor (AireDTR) mouse allows us to selectively delete eTACs, and the Aire-Cre recombinase Estrogen Receptor (Aire-CreER) mouse allows us to selectively turn off and on specific genes in eTACs. We are currently using this latter strain to express allo-MHC on eTACs in an effort to determine whether allo-MHC expression is sufficient to confer donor-specific tolerance in islet transplantation. Together, these tools, along with conventional molecular and cellular biology techniques ranging from two-photon microscopy to immunofluorescence to microarray analysis, give us unique insight into these complex biological systems.

## Results

We have identified and defined eTACs as a unique population of bone marrow-derived antigen presenting cells (APCs) related to dendritic cells (DCs) which are highly potent inducers of immunologic tolerance. Like mTECs, eTACs express a diverse array of self-antigens, although interestingly the *Aire*-regulated TSAs expressed in eTACs are almost entirely distinct from those driven by *Aire* in mTECs. Interaction between eTACs and both CD4+ and CD8+ T cells uniformly causes deletion or repurposing of those T cells into a regulatory phenotype, and transgenic expression of disease-relevant antigens in eTACs entirely prevents T cell-mediated autoimmune disease in a range of model systems. Further, unlike other peripheral APC populations, eTACs are uniquely stable, and resist conversion from “tolerogenic” to “immunogenic” in the presence of inflammatory stimuli; indeed they appear to exclusively suppress immune responses. We can now isolate and purify highly pure populations of eTACs and have begun to cultivate these cells *in vitro*. Finally, we have recently identified populations of human eTACs and demonstrated that they appear functionally and phenotypically equivalent to their murine counterparts. Our current research is focused on three goals: (1) defining the basic mechanisms of eTAC-mediated T-cell tolerance; (2) *in vitro* differentiation and expansion of eTACs from bone marrow precursors; and (3) determining whether exposure to allogeneic eTACs can achieve donor-specific tolerance in a pancreatic islet allograft model.

## Conclusions:

We hope to continue to define the basic biology of this unique population, and to explore therapeutic opportunities for such tolerance induction in autoimmunity and transplantation.

## Generation of Induced Hepatocytes for Autologous Liver Cell Therapy

Jack Harbell, Saiyong Zhu, Milad Rezvani, Aras Mattis, Sheng Ding, and Holger Willenbring

**Introduction:** Hepatocyte transplantation has potential as an alternative to orthotopic liver transplantation for therapy of liver diseases in which mainly hepatocyte function is impaired. Currently, hepatocytes for transplantation are derived from cadaveric donor livers, requiring the recipients to receive life-long immune suppression to prevent rejection of the transplanted cells. A strategy to bypass the need for immune suppression is generating induced hepatocytes (iHeps) from a patient's own readily and safely accessible cells. The development of induced pluripotent stem cell technology has brought the generation of autologous cells for transplantation *in vitro* within reach. However, while many methods of directed differentiation *in vitro* have been shown to generate hepatocyte-like cells from pluripotent stem cells, the functionality of these cells *in vivo* is unproven. Additionally, the intermediate pluripotent state intrinsic to this approach raises the concern of tumorigenicity in therapeutic applications. As a potentially more effective and safer alternative, recent reports have shown that directly converting a terminally differentiated mouse cell into an iHep by overexpressing transcription factors is feasible. In this study, we aimed to test whether such forced lineage conversion is feasible in human somatic cells and whether the resulting iHeps have therapeutic potential in a mouse model of human liver failure.

**Methods:** To create iHeps, lentiviral vectors were used to overexpress transcription factors in human somatic cells, including dermal fibroblasts and adipose-derived stem cells. iHeps were identified *in vitro* by quantitative reverse transcription PCR analysis of hepatocyte-specific gene expression, imaging of indocyanine green uptake, and quantification of albumin secretion into the media. Immune-deficient fumarylacetoacetate hydrolase (Fah)-deficient mice, a model of subacute human liver failure, were used for *in vivo* testing of iHeps. Function of iHeps after transplantation by intrasplenic injection was assessed by measuring human albumin in the recipient mouse serum, and by analysis of expression of FAH and other hepatocyte-specific proteins, including cytochrome P450 enzymes.

**Results:** iHeps showed significant expression of hepatocyte-specific genes *in vitro* and secreted albumin into the media. Some iHep clones could be expanded *in vitro* and were able to engraft in livers of immune-deficient Fah-deficient mice. Engrafted iHeps demonstrated mature hepatocyte functions *in vivo*, including albumin secretion into the mouse serum.

**Conclusions:** Readily accessible human somatic cells can be converted into cells that provide hepatocyte-specific functions *in vitro* and *in vivo*. Further development of this approach may yield an autologous liver cell therapy.