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<table>
<thead>
<tr>
<th>Research area</th>
<th>Specific disease/condition</th>
<th>Contact information (name, phone number, and e-mail address)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma and pulmonary disease</td>
<td>Chronic obstructive pulmonary disease, asthma (adult)</td>
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<tr>
<td>Cancer</td>
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<td>Gastroenterology</td>
<td>Crohn’s disease</td>
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</tr>
<tr>
<td>Heart and vascular disease (Dallas)</td>
<td>Aortic aneurysms, coronary artery disease, hypertension, poor leg circulation, heart attack, heart disease, congestive heart failure, angina, carotid artery disease, familial hypercholesterolemia, surgical renal denervation for hypertension, diabetes in heart disease, cholesterol disorders, heart valves, thoracotomy pain, stem cells, critical limb ischemia</td>
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<td>Heart and vascular disease (Fort Worth)</td>
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</tr>
<tr>
<td>Heart and vascular disease (Plano)</td>
<td>Aneurysms; coronary artery disease; surgical renal denervation, or stent, for uncontrolled hypertension; poor leg circulation; heart attack; heart disease; heart valve repair and replacement; critical limb ischemia; repair of AAA, TAA, and dissections with endografts; thoracic surgery leak repair; atrial fibrillation; carotid artery disease; congestive heart failure; left atrial appendage and stroke; gene profiling</td>
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<tr>
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<tr>
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<td>Stroke</td>
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</tr>
<tr>
<td>Women’s health (Fort Worth)</td>
<td>Endometriosis and endometrial ablation; interstitial cystitis/bladder pain syndrome</td>
<td>Theresa Cheyne, RN 817-922-2579 <a href="mailto:theresa.cheyne@BaylorHealth.edu">theresa.cheyne@BaylorHealth.edu</a></td>
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</table>

Baylor Research Institute is dedicated to providing the support and tools needed for successful clinical research. To learn more about Baylor Research Institute, please contact Kristine Hughes at 214-820-7556 or Kristine.Hughes@BaylorHealth.edu.
Safety of rapid intravenous infusion of acetaminophen

Steven M. Needleman, MD

Intravenous acetaminophen, Ofirmev®, is approved for management of mild to moderate pain, management of moderate to severe pain with adjunctive opioids, and reduction of fever. The product is supplied as a 100 mL glass vial. As stated in the prescribing information, it is recommended to be infused over 15 minutes. This recommendation is related to the formulation propacetamol, the prodrug to acetaminophen, approved in Europe, which caused pain on infusion, and data from the clinical development of acetaminophen. The objective of this retrospective chart review study was to show the lack of side effects of rapidly infusing intravenous acetaminophen. Charts of American Society of Anesthesiology (ASA) Class I–III ambulatory surgical patients who received only acetaminophen in the preoperative setting were reviewed for any infusion-related side effects. Using standard binomial proportion analyses and employing SAS/JMP software, all vital signs were analyzed for statistically significant changes between pre- and postinfusion values. One hundred charts were reviewed. Only one patient had pain on infusion, which lasted 10 seconds. No reported side effects or erythema was seen at the injection site. No infusions had to be slowed or discontinued. The median infusion time was 3:41 minutes. Of the vital signs monitored, only the systolic ($P < 0.0001$) and diastolic ($P < 0.0099$) blood pressures had statistically significant changes from pre- to postinfusion; however, they were of no clinical relevance. Acetaminophen can be administered as a rapid infusion with no significant infusion-related side effects or complications.

Many drug inserts contain instructions for administration. The basis for these instructions is often unclear. Intravenous acetaminophen was approved for use by the US Food and Drug Administration in November 2010 for treatment of mild to moderate pain, treatment of moderate to severe pain with adjunctive opioid analgesics, and reduction of fever. Based on the full prescribing information for intravenous acetaminophen (available at http://ofirmev.com/include/pdf/OFIRMEVPrescribingInformation.pdf), the contents of the vial should be administered over 15 minutes. This stipulation was based on experience with the prodrug, propacetamol, which caused pain when infused in upwards of 49% of patients (1–3). Propacetamol, supplied as a powder that needed to be reconstituted for delivery, had a pH of 3.5 to 4 and an osmolarity of 410 mOsmol/L. Acetaminophen is more isotonic, with a pH of 5.5 and an osmolarity of 290 mOsmol/L, which was achieved by adding a pH buffer and antioxidant through an oxygen-free manufacturing process. This form is closer to plasma, which has a pH of 7.3 to 7.4 and osmolarity of 275 to 290 mOsmol/L (1). A reduced incidence of infusion-site reaction was demonstrated in the pivotal study for intravenous acetaminophen conducted by Sinatra et al, where the proportion of subjects reporting local infusion site adverse events was significantly lower for acetaminophen (2%) than for propacetamol (38%; $P < 0.001$) and not different from that of placebo (2%) (4). No studies have tested the potential side effects of giving acetaminophen via rapid infusion. This study examined whether the acetaminophen formulation could be given via rapid intravenous infusion without any infusion-related side effects or complications.

METHODS

This retrospective study was completed at Baylor Medical Center at Grapevine and Baylor Surgicare at Grapevine after approval by the Baylor Research Institute institutional review board. Approval for administering acetaminophen as a rapid infusion was obtained as a change in practice at Baylor Medical Center at Grapevine from the Department of Anesthesiology. This approval was granted only if the patient was monitored by an anesthesiologist during and up to 5 minutes after infusion with standard American Society of Anesthesiology (ASA) monitors (electrocardiogram, blood pressure, respiratory rate, pulse oximetry, skin temperature). Patients with any coexisting liver disease or dysfunction were not candidates for rapid infusion.

An institutional retrospective chart review was performed on 100 patients seen from August 2011 to May 2012, all of whom received rapidly infused acetaminophen in the preoperative setting. This number was arrived at by hypothesizing that the usual mean rate of pain on infusion of propacetamol was 29% (1–3). Of interest was to detect whether a rate of 10% or less...
with acetaminophen would be a significant decrease (assuming statistical type I and II error rates of 0.05 and 0.20, respectively). All patients received acetaminophen in the preoperative holding area prior to being transported to the operating room. The study was limited to ambulatory surgical patients in ASA Class I to III who had not received any other medication (anxiolytics, analgesics, antibiotics, etc.) prior to acetaminophen. Patients with any conditions listed in the warnings and precautions section on the FDA label were not eligible for rapid infusion and thus were excluded from this study. The automated dispensing machine data showing patients who had received acetaminophen were the initial basis for the review.

All patients were closely monitored by an anesthesiologist from the start of infusion up to 5 minutes postinfusion. Acetaminophen was delivered using new, unopened vials, each containing 100 mL with a concentration of 10 mg/mL. The vial was spiked using the standard intravenous tubing set (secondary set 34-inch non-Di(2-ethylhexyl) phthalate, internal diameter 0.100 in; Hospira, Lake Forest, IL) with the roller clamp set at the fully open position. The vial was vented with a blunt 18-gauge needle.

For each study patient, a study data form was completed, which included the date, infusion time (start, stop, and total), site and size of intravenous cannula gauge, reported side effects, and vital signs every 2 minutes from infusion up to 5 minutes postinfusion. Charts were reviewed to determine if any infusion had to be stopped or slowed due to patient complaints and/or side effects reported that resulted from the rapid delivery method. Vital signs were analyzed to determine if any significant changes occurred from preinfusion values to postinfusion values. Data were analyzed by the Baylor Health Care System Quantitative Sciences Department with SAS/JMP statistical analysis software using standard binomial proportion analyses. Confidence intervals and \( P \) values were calculated using the standard \( t \) test with a \( P < 0.05 \) considered statistically significant.

RESULTS

Of the 100 study patients, 89% had the intravenous cannula placed in the hand, and 98% had a 20-gauge cannula placed (Table 1). The mean total time of infusion was 3:45, with a 95% confidence interval of 03:31 to 03:55 (Table 2). There were no reports of erythema at the intravenous site, and no patient reported side effects during or after infusion. One patient reported mild pain on infusion, which lasted approximately 10 seconds, but the pain was self-limited despite the infusion still running at a full uninhibited flow rate. Of the vital signs monitored, only the systolic (\( P < 0.0001 \)) and diastolic (\( P < 0.0099 \)) blood pressures and mean arterial pressure (MAP; <0.0001) had statistically significant reductions from pre- to postinfusion (Table 3). The MAP was calculated using the formula of 2 times diastolic plus systolic divided by 3. There were no clinically relevant deviations (greater than 20%) in MAP (Figure), and no patients had a MAP < 50 mm Hg postinfusion. There were no reported symptoms of hypotension, such as dizziness or lightheadedness, or required intervention for hypotension.

<p>| Table 1. Intravenous site and size for intravenous acetaminophen in 100 patients |</p>
<table>
<thead>
<tr>
<th>Category</th>
<th>Variable</th>
<th>Patients</th>
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<tbody>
<tr>
<td>Intravenous site</td>
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<td>Right antecubital</td>
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<td>Total</td>
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<tr>
<td>Intravenous size (gauge)</td>
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<td></td>
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<tr>
<td></td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
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</tbody>
</table>

| Table 2. Infusion time for intravenous acetaminophen in 100 patients |
|------------------------|---------|
| Percentage | Minutes: seconds |
| 100% (maximum) | 07:19 |
| 99.5% | 07:19 |
| 97.5% | 06:13 |
| 90% | 04:57 |
| 75% (quartile) | 04:22 |
| 50% (median) | 03:41 |
| 25% (quartile) | 02:57 |
| 10% | 02:29 |
| 2.5% | 02:12 |
| 0.5% | 01:31 |
| 0% (minimum) | 01:31 |

| Table 3. Differences in pre- and postinfusion vital signs in 100 patients who received rapid intravenous infusion of acetaminophen |
|------------------------|---------|---------|---------|---------|
| Vital sign | Mean difference | Upper 95% mean | Lower 95% mean | \( P \) value |
| Systolic blood pressure | -4.31 | -2.7804 | -5.8396 | <0.0001 |
| Diastolic blood pressure | -1.92 | -0.471 | -3.369 | 0.0099 |
| Mean arterial pressure | -2.72 | -1.562 | -3.873 | <0.0001 |
| Respiratory rate | 0.00 | 0.0564 | -0.0564 | 1.0000 |
| Heart rate | 0.13 | 0.36004 | 0.84439 | 0.7188 |
| Oxygen saturation | 0.118 | 0.33449 | -0.0985 | 0.2821 |
| Skin temperature | -0.003 | 0.00784 | -0.0186 | 0.7029 |
DISCUSSION

This study demonstrated that no clinically relevant adverse events resulted from administration of intravenous acetaminophen to patients without an infusion time requirement. Only one patient had a complaint of pain at the infusion site, which lasted only 10 seconds. The infusion was not slowed and was completed without further complaints. Most likely, this pain was due to physical reasons such as an intravenous line that was not entirely patent at the start of infusion rather than the medication itself. No other problems were reported by any patients or observed by the anesthesiologist in attendance during the infusion. The infusion time using fully open secondary intravenous tubing was decreased from 15 minutes to a median time of 3 minutes and 41 seconds. Two potential confounding variables in the infusion time that were not controlled for in this study were cannula gauge and site (5, 6). However, our preoperative nursing staff protocol indicates that a 20-gauge cannula and a hand site are preferred. Approximately 90% of the patients in this study received a 20-gauge intravenous line in the hand.

Reducing the infusion time offers potential advantages for both the patient and the hospital staff. Faster achievement of peak plasma levels can lead to better pain control. Previous studies have shown that the intravenous route of administration leads to earlier and higher plasma peaks than the oral and rectal routes (7). Even earlier plasma peaks could potentially be reached with a faster infusion time, although this was not determined in this study. No existing data indicate that speed of infusion has any relation to liver toxicity. Full, uninhibited flow for acetaminophen may obviate the need for expensive infusion pumps. It also decreases medical errors related to the set up of infusion pumps (8). The extra equipment and time needed for the pumps may deter health care providers from using acetaminophen in the preoperative setting, leading to an increase in narcotic use and reduction in patient safety.

Acetaminophen has been shown to be an effective drug in pain control in outpatient surgical patients (9–11) as well as in major orthopedic surgery (4, 11, 12). The ASA guidelines on acute pain management in the perioperative setting endorse the use of acetaminophen as a component of multimodal analgesia (13). Though the primary reason for a 15-minute infusion time was pain at the infusion site with propacetamol, the prodrug of acetaminophen, and clinical data from the development of intravenous acetaminophen, all vital signs were monitored during the infusion for any possible changes. No patients had their infusion stopped or slowed due to a change in vital signs. Upon statistical analyses, the only significant changes were seen in the patients’ lower systolic, diastolic, and calculated MAP after infusion. However, the mean difference for all three was low. No MAP changes were considered clinically relevant (20%).

Importantly, no patient had any reported symptoms of hypotension, such as dizziness or lightheadedness, or required medical treatment for a drop in blood pressure. A factor that may have contributed to the drop in blood pressure could be an abnormally elevated starting blood pressure. Patient stress or “white coat syndrome” can lead to an initial high blood pressure reading. All other vital signs showed no significant changes from pre- to postinfusion.

This study was limited to ASA Class I to III ambulatory surgical patients. It was not determined if more complicated surgical patients, or patients with complex medical problems, would react in the same manner. The possibility of hepatotoxicity from rapid infusion was not examined. All patients received only intravenous acetaminophen, and it was not determined if infusion-related side effects would have been avoided if the study drug were combined with opioids and/or anxiolytics.

This study can benefit hospitals in efforts toward cost-effective pain control. By showing that the FDA-mandated infusion time is not supported by scientific evidence, hospitals can reduce the personnel time and expense of infusion pumps. Further, the infusion time requirement may have led some healthcare providers to avoid intravenous acetaminophen, resulting in increased narcotic use. The results of this study can be an incremental contribution to patient safety, as reduction in narcotic use improves patient safety.

4. Sinatra RS, Jahr JS, Reynolds LW, Viscusi ER, Groudine SB, Payen-Champenois C. Efficacy and safety of single and repeated administration

Figure. Distribution of percentage change in mean arterial pressure (MAP). The minimum change in MAP percentage was –17.31; maximum change, 13.59; median change, –3.07; and 95% confidence interval, –3.87, –1.56.

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Effect of postoperative course on midterm outcome after esophageal resection for cancer

Themistokles Chamogeorgakis, MD, Faiz Bhora, MD, Ioannis Toumpoulis, MD, Andy Nabong, MA, and Cliff Connery, MD

Esophageal resections are challenging procedures often associated with postoperative complications and a prolonged hospital stay. This study investigated the impact of postoperative course on midterm survival in 35 patients undergoing esophageal resection for malignancy between January 2002 and November 2007. The impact of preoperative and operative variables, pathology, staging, early postoperative complications, and length of hospital stay on midterm survival was determined with Cox regression analysis. During the follow-up period, 17 (48.6%) patients died. Multivariate analysis identified surgical stage and length of stay as independent predictors of midterm survival; in addition, the total number of complications reached statistical significance. In conclusion, in addition to surgical stage, postoperative course has an impact upon midterm survival after esophageal resection.

Esophagectomies are challenging procedures often associated with postoperative complications and prolonged hospital stay. Stage and radicality of resection have traditionally been reported to predict outcomes in patients with primary esophageal carcinoma (1–4). In addition, other variables such as sex, neoadjuvant treatment, and intensive care unit (ICU) length of stay have been reported to be independent predictors of long-term outcome (4–6). This study identified predictors of midterm survival in such patients and specifically investigated the potential role of postoperative complications in survival beyond patients’ discharge from the hospital.

METHODS

A total of 35 consecutive patients underwent esophagectomy for primary esophageal carcinoma between January 2002 and November 2007 at the Continuum Cancer Centers of New York Thoracic Oncology Program (St Luke’s–Roosevelt Hospitals and Beth Israel Medical Center) affiliated with Columbia University College of Physicians and Surgeons and the Albert Einstein College of Medicine. The mean follow-up was 32 months (range, 1.3–69.2 months).

Data collected as part of the Thoracic Surgery General Thoracic Database (7) were age, sex, any associated comorbidities, American Society of Anesthesiologists (ASA) score, Zubrod score, modeled Thoracoscore (8), the type of the procedure performed, pathology, surgical staging, and postoperative complications (Table 1). Midterm mortality data were obtained from the institution’s cancer registry in July 2008.

Informed consent was not obtained because the data used in this study had already been collected for clinical purposes. Furthermore, the present study did not interfere with the treatment of patients, and the database was organized to prevent the identification of an individual patient.

Cases were evaluated with respect to demographic, surgical, and postoperative variables. Numerical variables were presented as mean ± standard deviation, and discrete and categorical variables were presented as percentages. The impact of preoperative and operative variables, pathology, staging, and early postoperative complications on midterm survival was determined with Cox regression analysis. A score equaling the total number of postoperative complications per patient was entered in the survival analysis. In addition, the modified Thoracoscore of each patient was calculated based on the formula that has been previously published (8): Thoracoscore = −6.975 + [−0.108 if patient age was >55 years and <65 years or 1.057 if patient age was ≥65 years] + [0.402 if patient sex was male] + [1.909 if ASA class was ≥3] + [2.655 if Zubrod score was ≥3] + [0.975 if priority of surgery was urgent or emergent] + [0.063 for esophageal malignancy] + [0.093 if number of comorbidities was ≤2 or 0.761 if number of comorbidities was ≥3]. Variables were evaluated with univariate analysis and subsequently with multivariate analysis. The model selection was performed with a backward stepwise method, starting from all variables with a $P < 0.05$. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Finally, a Kaplan-Meier survival curve was generated for the entire patient population. All analyses were performed in SPSS v 15.0 (SPSS, Inc; Chicago, IL).

From the Department of Cardiothoracic Surgery, Baylor University Medical Center at Dallas (Chamogeorgakis); and the Department of Cardiothoracic Surgery, Continuum Cancer Centers, St. Luke’s–Roosevelt Hospital, New York, NY (Bhora, Toumpoulis, Nabong, Connery).

Corresponding author: Themistokles Chamogeorgakis, MD, Department of Cardiothoracic Surgery, Baylor University Medical Center at Dallas, 3900 Junius Street, Suite 605, Dallas, TX 75246 (e-mail: Themistokles.Chamogeorgakis@BaylorHealth.edu).
RESULTS

Twenty-five patients underwent total esophagectomy: 1 with a left-sided neck anastomosis via a left thoracoabdominal incision; 20 with a combined right thoracotomy and laparotomy; and 4 with a transhiatal approach. Ten patients had a partial esophagectomy for a lower third esophageal tumor: 7 via a left thoracoabdominal incision and 3 via a combined right thoracotomy and laparotomy. Except for the transhiatal resections, a double-lumen endotracheal tube was used to achieve selective ventilation of the contralateral lung. Frozen section analysis of the specimen's margin was performed intraoperatively, and additional resection was undertaken, if necessary, to obtain margins free of tumor. In addition, a pyloromyotomy and a feeding jejunostomy were performed in all cases.

There were no in-hospital deaths. Pulmonary complications were the most common of all complications (n = 4); this complication was defined as pneumonia, prolonged mechanical ventilation, or pulmonary atelectasis requiring bronchoscopy. Other postoperative complications were cardiac dysrhythmias (n = 2), recurrent laryngeal nerve paresis (n = 2), anastomotic leak that was treated medically (n = 2), thoracic empyema (n = 1), and chylothorax (n = 1; Table 1). Five patients required transfusion of blood products perioperatively. No patient developed renal failure requiring dialysis postoperatively.

During the follow-up period, 17 (48.6%) patients died, 16 from esophageal cancer and 1 from unknown cause. The Kaplan-Meier survival curve is shown in the Figure. Univariate analysis identified ASA score, surgical stage, total number of postoperative complications, and length of stay as independent variables for midterm survival (Table 2). Blood product transfusion and operative blood loss were not predictors of midterm survival. Multivariate analysis identified surgical stage and length of stay as independent predictors of midterm survival (Table 2).

DISCUSSION

In this retrospective analysis of patients undergoing curative resection of primary esophageal carcinoma, we identified independent predictors of survival. Despite surgical stage, the

Table 1. Characteristics of 35 patients undergoing esophageal resection for cancer

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency</th>
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<tbody>
<tr>
<td><strong>Preoperative</strong></td>
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<tr>
<td>Mean age (years) (SD)</td>
<td>62.0 (13.5)</td>
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<tr>
<td>Male</td>
<td>22 (63%)</td>
</tr>
<tr>
<td>Female</td>
<td>13 (37%)</td>
</tr>
<tr>
<td>Type of cancer</td>
<td></td>
</tr>
<tr>
<td>Squamous carcinoma</td>
<td>16 (46%)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>19 (54%)</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>I</td>
<td>14 (40%)</td>
</tr>
<tr>
<td>IIA</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>IIB</td>
<td>7 (20%)</td>
</tr>
<tr>
<td>III</td>
<td>11 (31%)</td>
</tr>
<tr>
<td>IV</td>
<td>–</td>
</tr>
<tr>
<td><strong>ASA class</strong></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>–</td>
</tr>
<tr>
<td>II</td>
<td>12 (34%)</td>
</tr>
<tr>
<td>III</td>
<td>22 (63%)</td>
</tr>
<tr>
<td>IV</td>
<td>1 (3%)</td>
</tr>
<tr>
<td><strong>Zubrod score</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>11 (31%)</td>
</tr>
<tr>
<td>1</td>
<td>20 (57%)</td>
</tr>
<tr>
<td>2</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>3</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>4</td>
<td>–</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7 (20%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (51%)</td>
</tr>
<tr>
<td>CAD or HF</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Mean Thoracoscore (SD)</td>
<td>4.1 (1.4)</td>
</tr>
<tr>
<td><strong>Operative</strong></td>
<td></td>
</tr>
<tr>
<td>Total esophageal resection</td>
<td>25 (71%)</td>
</tr>
<tr>
<td>Partial esophageal resection</td>
<td>10 (29%)</td>
</tr>
<tr>
<td><strong>Postoperative</strong></td>
<td></td>
</tr>
<tr>
<td>Pulmonary complications</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Anastomotic leak</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Chylothorax</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Recurrent laryngeal nerve paresis</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Empyema</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Mean length of stay (days) (SD)</td>
<td>19.5 (23.7)</td>
</tr>
</tbody>
</table>

ASA indicates American Association of Anesthesiologists; CAD, coronary artery disease; HF, heart failure.
postoperative course had an impact on midterm outcome; the additive effect of complications and length of stay appears to affect patients’ outcome beyond the immediate postoperative period.

The concept that the postoperative course predicts patient outcome beyond the hospital stay has been shown before in cardiac surgery patients (9). In our patient group, all but one death were cancer related. One can make the hypothesis that a complicated perioperative course may suppress the immune system’s ability to survey and eliminate cancer cells; the exact mechanism, however, can be only speculative at this point.

Although the effect of a prolonged ICU stay on patients’ quality of life has been previously investigated (10), there is a dearth of research on the impact of prolonged postesophagectomy ICU stay on long-term survival. Cense et al, in their analysis of 109 patients undergoing transthoracic esophageal resection, concluded that the length of ICU stay using a cutoff number of 5 days did not influence long-term survival (11). The patients’ median survival was 4.7 years. Two reasons may explain why their results are different: the larger number of patients and the fact that the length of stay was entered as a continuous variable. In our analysis, the hospital length of stay was used as a continuous variable. On the other hand, van Sandick et al showed that ICU length of stay predicts long-term outcome (4). Therefore, an effort to obtain good surgical margins beyond the neoplastic process and add a thorough lymph node dissection in the resection is advisable.

Gender and neoadjuvant treatment have also been reported to affect long-term outcome. Female patients appear to have a better outcome than male patients (5), and neoadjuvant chemoirradiation seems to improve long-term prognosis because it allows curative resection in a greater number of cases due to tumor downstaging (13). The above variables were not independent predictors of midterm outcome in our analysis.

Thoracoscore was first introduced by Falcoz et al as a multivariate model for the prediction of inhospital mortality after general thoracic procedures (14). Furthermore, this risk prediction model can be applied beyond patient discharge (8). This variable was not an independent predictor of midterm survival after esophageal resection for cancer. This survival prediction model is more useful in the whole context of thoracic surgery patients.

Although blood loss and transfusion of packed red blood cells are reported to be independent predictors of survival in gastrointestinal malignancies, this does not appear to be the case in our study, presumably due to the small number of patients included in our analysis; borderline statistics need more patients to reach statistical significance.

There are several limitations in our study. In this retrospective study, possible factors that may have biased the results were not included in the statistical analysis, and the number of patients was small. This study referred to a single-center database, and it is likely that selection of patients for surgery may be an important determinant, which differs widely among thoracic surgery units.

Acknowledgment
The authors wish to thank Kelli R. Trungale, MLS, ELS, for editorial assistance.


Comparison of fluoroscopic operator eye exposures when working from femoral region, side, or head of patient

M. Jordan Ray, MD, Fawzi Mohammad, MD, William B. Taylor, MD, Marco Cura, MD, and Clare Savage, MD

Operator radiation exposure is an important occupational hazard compounded over the course of an interventional radiologist’s career. This study compared operator radiation dose to the eye and head for different positions around the patient. Compared with cases performed from the femoral region, exposures were 1.8 times higher at the side, and 1.6 times higher at the head, using conventional aprons, table shields, and mobile suspended shields. Exposures were 99% lower when using a suspended personal radiation protection system in all positions. In conclusion, standing at the side or head results in higher head exposures in a conventional setup.

Despite improvements in imaging equipment, advances in operator protection have been relatively stagnant, with the eyes and head remaining vulnerable to scatter (1, 2). Interposed shields may be cumbersome and leave gaps in protection, and lead glasses allow scatter to reach the eye from outside the area subtended by the lead lenses, permitting secondary scatter exposure to the lens (1–5). During the wide variety of interventional procedures, operators stand in different positions around the patient where shielding and scatter geometry vary drastically. When standing at the patient’s side, such as during a biliary or nephrostomy procedure, the scatter source is a thick body part in close proximity to the operator, whose hands must reach into the scatter path where interposed hanging shields or attenuating blankets are obstructive to the work effort and are often repositioned, decreasing their effectiveness. Similar problems occur when the operator works at the patient’s head, where the mobile suspended shield can obstruct the hands and must usually remain at least several inches above the patient’s neck. The purpose of this study was to determine how much scatter radiation reached the operator’s head and eyes during procedures performed from the side, femoral, or head position using either a standard lead apron with aggressive shielding or a suspended personal radiation protection system (SPRPS).

METHODS

The study was approved by the institutional review board. Exposure data were collected for three primary operators wearing a dosimeter adjacent to the left eye while performing a variety of procedures. The data were accumulated in one interventional suite to minimize variables related to different equipment design, age, or geometry. The suite included an Artis Zee unit (Siemens, Munich, Germany) equipped with three types of ancillary shields depicted in Figure 1a: a mobile suspended lead-acrylic shield, an under-table lead skirt, and a tableside shield that extended upwards from the under-table skirt (Mavig, Munich, Germany). The SHIELDS method of primary operator radiation protection is depicted in Figure 1b.

The suite also included an SPRPS (ZeroGravity Radiation Protection System, CFI Medical Solutions, Fenton MI) (Figure 1c). This overhead-suspended system had a curved lead-acrylic head shield (0.5 mm Pb) and lead apron (1 mm Pb in front) that extended to the distal calves with flaps hanging over the arms to the elbows, which may be covered with a sterile plastic drape to permit entry and exit. The SPRPS method of primary operator protection involved utilization of the suspended personal radiation protection system with the under-table lead skirt, occasional use of the table-side shield, and nonuse of the suspended lead-acrylic mobile shield. The use of the SHIELDS or SPRPS method was determined by preferences of the primary and secondary operators.

The dosimeter was a recently calibrated electronic direct dosimeter with manufacturer-reported sensitivity to 1 nSv (EDD-30, Unfors, Billdal, Sweden). Dosimetry measurements were recorded at the conclusion of each case using the electronic sensor worn near the left eye as depicted in Figure 1b and 1c. This measurement represents a separate exposure record from the standard monthly dosimeter typically worn on the leaded thyroid collar.

Procedures were performed in the standard manner with the primary operator positioned at the femoral region, the side, or the head of the patient (Figure 2). The method of protection (SHIELDS vs. SPRPS) was constant for each primary operator throughout each individual case. All primary operators at the institution aggressively utilize all three ancillary shields in all procedures when not using the SPRPS, and they practice patient-exposure reduction practices such as reduction of air
Femoral procedures were generally transarterial and transvenous diagnostic and therapeutic procedures in the chest, abdomen, or pelvis. Side procedures included percutaneous nonvascular interventions involving the liver, kidneys, or fluid collection drainages in the abdomen or pelvis. Head procedures generally included transjugular procedures such as transjugular intrahepatic portosystemic shunt placements, inferior vena cava filter placements, and transjugular liver biopsies.

Reported data included operator exposure indicated by dosimeter readings, as well as fluoroscopy duration and patient dose-area-product (DAP) as reported by the fluoroscopy unit. As in other reports of occupational radiation in fluoroscopy suites, operator exposures were standardized to DAP because it is the best correlate for amount of scatter produced in the region of the operator (6, 7). Because our operators routinely exit the procedure area to stand behind a leaded wall during nonfluoroscopic imaging acquisitions, which contribute substantially to total patient DAP, operator exposures were standardized only to the relevant patient DAP corresponding to fluoroscopy. In other words, DAP corresponding to nonfluoroscopic imaging acquisitions, when the operator was not exposed to scatter radiation, was excluded. Standardized operator exposure (SOE) = operator exposure / fluoroscopic DAP and was reported in μSv/[g/cm²].

SOEs corresponding to different operator positions were compared using the two-tailed t test. For each operator position, SOEs for SHIELDS and SPRPS were compared using a two-tailed t test.

RESULTS
Detailed results are depicted in Table 1 and Figure 3. One hundred and thirty procedures were performed using a total of 1148 minutes of fluoroscopy time with total fluoroscopic patient DAP of 423,290 cGy/cm². When using conventional shielding (SHIELDS), SOE was highest when working at the patient’s side, where it was 1.80 times the exposure when working at the femoral region. SOE when working at the patient’s head was 1.62 times the SOE when working at the femoral region. These differences were both significant (P < 0.001 and <0.05, respectively).

When using SPRPS, SOE was greatly reduced in all positions, with a mean of 0.45% (P < 0.0001) of SOE for SHIELDS. These differences between SHIELDS and SPRPS were significant for all operator positions.

Although duration of fluoroscopy is a less suitable parameter than patient DAP for standardization of operator exposure, use of pulsed fluoroscopy, collimation, minimization of fluoroscopy times, and minimization of severely oblique or lateral receptor angles.
DISCUSSION

Shielding of interventionalists’ head and eyes during fluoroscopically guided procedures is problematic. Cataract formation is a known side effect with lens opacities occurring at significantly lower doses than previously believed (1, 2, 3, 8). The upward direction of scatter to the head enables a portion of scatter to pass underneath lead glasses, or enter from the side to reach the eye (4, 5). Secondary scattered radiation from the operator’s head contributes substantially to ocular exposure (4, 5). In one study, the best glasses of 32 tested types yielded eye exposures amounting to 44% of the incident radiation, even with the head directly facing the scatter source (5). The findings of another study indicated that lead glasses could reduce eye exposures 2- to 3-fold (4). Although imperfect, such reductions are substantial and lead to recommendations to use lead eyewear in conventional setups lacking a face shield (1, 2).

Operator-supported face shields provide superior protection and obviate the need for lead eyewear but are uncommonly used due to their bulk (5, 9). By protecting much of the head, they also address concerns about neural tumors, which have been associated with even moderate doses of radiation (10).

When using SHIELDS, there are always gaps in the shielding, most notably at the level of the operator’s arms, permitting scatter to pass upwards underneath the mobile suspended lead-acrylic shield to the operator’s upper body and head (Figure 2). The significantly higher exposures for the side position relative to both the femoral and head positions is likely due to the operator’s proximity to the scatter source in addition to the gaps between the shields that are required to permit operator access to the patient. Working at the head or femoral positions provides some additional distance from the scatter sources; however, gaps in shielding persist.

The SPRPS group had substantial reductions in exposure for all operator positions compared with the SHIELDS group, presumably because the SPRPS moves with the operator and is therefore always positioned optimally with regard to scatter geometry. The height of the lead-acrylic head shield provides

Table 1. Fluoroscopy time, patient dose, and operator exposures for 130 interventional radiology cases for different operator stances using both SHIELDS and SPRPS operator protection methods

<table>
<thead>
<tr>
<th>Shielding modality</th>
<th>Operator position</th>
<th>N</th>
<th>Fluoroscopy time (min)</th>
<th>Patient DAP (cGy/cm²)</th>
<th>OE (uSV)</th>
<th>OE/fluoro time (uSV/min)</th>
<th>OE/DAP (SOE) (uSV/[(cGy/cm²)])</th>
<th>SOE/ SOE_FEM_SHIELDS (%)</th>
<th>SOE/ SOE_SHIELDS* (%)</th>
<th>P</th>
<th>SOE/ SOE_SPRS/ SOE_SHIELDS * (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHIELDS†</td>
<td>Femoral</td>
<td>17</td>
<td>127</td>
<td>50,690</td>
<td>412</td>
<td>3.250</td>
<td>0.8137</td>
<td>100.00%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Side</td>
<td>16</td>
<td>86</td>
<td>32,770</td>
<td>479</td>
<td>7.608</td>
<td>1.4631</td>
<td>179.80%</td>
<td>&lt;0.001</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Head</td>
<td>16</td>
<td>145</td>
<td>59,062</td>
<td>781</td>
<td>5.399</td>
<td>1.3228</td>
<td>162.56%</td>
<td>&lt;0.05</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Subtotal</td>
<td>49</td>
<td>357</td>
<td>142,521</td>
<td>1,673</td>
<td>4.686</td>
<td>1.1740</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>SPRPS</td>
<td>Femoral</td>
<td>41</td>
<td>463</td>
<td>150,510</td>
<td>9</td>
<td>0.062</td>
<td>0.0062</td>
<td>0.77%</td>
<td>&lt;0.0001</td>
<td>0.77%</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Side</td>
<td>23</td>
<td>189</td>
<td>50,615</td>
<td>3</td>
<td>0.018</td>
<td>0.0066</td>
<td>0.82%</td>
<td>&lt;0.0001</td>
<td>0.46%</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Head</td>
<td>17</td>
<td>139</td>
<td>79,644</td>
<td>2</td>
<td>0.015</td>
<td>0.0026</td>
<td>0.32%</td>
<td>&lt;0.0001</td>
<td>0.20%</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subtotal</td>
<td>81</td>
<td>791</td>
<td>280,769</td>
<td>15</td>
<td>0.019</td>
<td>0.0053</td>
<td>–</td>
<td>–</td>
<td>0.45%</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>All</td>
<td>130</td>
<td>1,148</td>
<td>423,290</td>
<td>1,688</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*For matched operator position.
†Shields used by this group included a mobile suspended lead-acrylic shield, an under-table lead skirt, and a table side shield that extended upwards from the under-table skirt.
DAP indicates dose-area-product; OE, operator exposure; SOE, standardized operator exposure; SPRPS, suspended personal radiation protection system.
a barrier to scatter to the head while permitting direct, unimpeded line of sight to the monitor over its top. This is possible because the scatter source is lower than the operator’s head, creating a substantial upward vector from scatter source to operator head (3).

Exposures in the SHIELDS arm of this study are in range with previous studies that used rigorous shielding, corroborating our operators’ aggressive shielding technique (11–13). Unfortunately, in some labs, the table side-shield (Figure 1a) may be intermittently or never used since it must be removed for each patient transfer. Likewise, the mobile hanging shield is sometimes neglected. Despite the gaps in protection with these devices, they provide substantial protection, and their rigorous use is strongly advised when not using a more comprehensive system such as the SPRPS or a radioprotective cabin.

Limitations of this study include absence of randomization. Randomization may have improved comparison between standard lead shielding and SPRPS, but remains irrelevant to the position analysis, the primary focus of this manuscript. Due to dramatic differences between conventional shields and SPRPS, randomization was not believed necessary.

Acknowledgments

The authors thank the laboratory technology and research nursing staff for their contributions in data collection.


Development and evaluation of a treadmill-based exercise tolerance test in cardiac rehabilitation

Julie Dunagan, MS, Jenny Adams, PhD, Dunlei Cheng, PhD, Stephanie Barton, BS, Janet Bigej-Cerqua, RN-C, BSN, Lisa Mims, RN, Jennifer Molden, MSEd, and Valerie Anderson, RN, BSN

Cardiac rehabilitation exercise prescriptions should be based on exercise stress tests; however, limitations in performing stress tests in this setting typically force reliance on subjective measures like the Duke Activity Status Index (DASI). We developed and evaluated a treadmill-based exercise tolerance test (ETT) to provide objective physiologic measures without requiring additional equipment or insurance charges. The ETT is stopped when the patient’s Borg scale rating of perceived exertion (RPE) reaches 15 or when any sign/symptom indicates risk of an adverse event. Outcomes of the study included reasons for stopping; maximum heart rate, systolic blood pressure, and rate pressure product; and adverse events. We tested equivalence to the DASI as requiring the 95% confidence interval for the mean difference between DASI and ETT metabolic equivalents (METs) to fall within the range (–1, 1). Among 502 consecutive cardiac rehabilitation patients, one suffered a panic attack; no other adverse events occurred. Most (80%) stopped because they reached an RPE of 15; the remaining 20% were stopped on indications that continuing risked an adverse event. Maximum systolic blood pressure, heart rate, and rate pressure product were significantly \( P < 0.001 \) below thresholds of the American Association of Cardiovascular and Pulmonary Rehabilitation. Two patients’ heart rates exceeded 150 beats per minute, but their rate pressure products remained below 36,000. The mean difference between DASI and ETT METs was \( -0.8 \) \( ( -0.98, -0.65 ) \), indicating equivalence at our threshold. In conclusion, the ETT can be performed within cardiac rehabilitation, providing a functional capacity assessment equivalent to the DASI and objective physiologic measures for developing exercise prescriptions and measuring progress.

Maximal exercise testing on entry into cardiac rehabilitation (CR) offers the opportunity to identify the metabolic equivalents (METs) \( 1 \) that a patient is capable of achieving, which would enable easy determination of a patient’s starting MET level. However, lacking the resources to perform maximal exercise tests, most CR programs must determine the starting MET level from the Duke Activity Status Index (DASI) questionnaire or the 6-minute walk test. The 6-minute walk test is an objective measure of exercise tolerance in patients with lung disease and in low-functioning cardiac patients \( 2 \), but is not the most challenging test for the majority of patients enrolled in CR. And, while METs can be estimated based on a calculation from the patient’s DASI score, our experience shows that some patients overestimate their ability because they were able to perform the tasks queried prior to surgery and, without having attempted that task since surgery, feel that they should still be able to do it, while others underestimate their postsurgery capability. A third alternative, relying on standardized approaches not based on measurements of current exercise capacity to determine exercise intensity \( \text{e.g.}, \ achieving a heart rate of 20 beats per minute above the resting rate \), potentially minimizes the benefit patients derive from exercise training and slows patient progress \( 3 \). We, therefore, concluded there was a need for a test that could be easily performed in most CR settings and would provide both a challenge to the majority of patients and physiologic performance data. We sought to develop such a tool to accurately assess the level at which to start each patient’s exercise program. As the CR patient population covers a wide range of functional levels, it was important that the tool incorporate the flexibility to meet all needs. This was achieved by providing individualized options and concomitant, appropriate goals for completion of rehabilitation. Here, we evaluate the protocol—the Exercise Tolerance Test (ETT)—developed for both exercise prescription outcomes and effectiveness, comparing it to the DASI scale. This study was approved by the Baylor Research Institute institutional review board.

METHODS

The CR department at The Heart Hospital Baylor Plano opened in January 2007. The program is primarily staffed by three registered nurses and four exercise physiologists, but chaplains and a registered dietician are also involved in patient education. Patients are typically in the program 6 to 8 weeks following hospital discharge and attend classes on each Monday.
Wednesday, and Friday. In 2012, the outpatient program Phase II volume was just under 6,800 visits. The department also offers inpatient and maintenance programs.

We modified existing stress test protocols to meet the specific needs of the CR setting, developing three different treadmill-based protocols to determine exercise functional capacity (Figure). The ETT was administered in the CR department. The stopping point for all three of the protocols was based on the patient’s rating of perceived exertion (RPE) of 15 on the Borg scale (2) or the occurrence of any abnormal hemodynamic changes such as arrhythmia, chest pain, dizziness, decreased blood pressure with increasing exercise, very high blood pressure, extreme shortness of breath, or any other symptom that outweighs the benefit of continuing exercise. As an added precaution, we also calculated the patient’s maximum “allowed” heart rate using the %HR\text{max} method (4) (with an additional 10 beats per minute subtracted for patients on beta-blockers) and stopped the patient if 90% of this maximum heart rate was reached.

At each stage of the relevant protocol, blood pressure (measured every 2 minutes), heart rate (based on three-lead electrocardiogram tracing), and RPE were documented. Oxygen saturation and peak oxygen uptake were not monitored. The most challenging protocol moved incrementally from 3.0 mph/0% grade to 3.5 mph/15% grade; the least physically challenging went from 1.0 mph/0% grade to 1.3 mph/15% grade.

Patients were assigned METs for every stage for which they completed any portion.

We determined which protocol to use for each patient based on information gathered during the initial patient interview: familiarity with treadmills, age, orthopedic issues, prior/current exercise routine, and height/leg length. From this we chose the most difficult protocol we felt the patient could safely perform for at least 2 minutes. If the interview information was insufficient to make this determination, we started the patient on the treadmill and increased the speed until the patient reported it as a “fast walk” and then started the appropriate protocol from there.

Patients were instructed on the purpose and process of the exercise evaluation test before the protocol was started. The 6-20 Borg RPE scale (5) was reviewed prior to starting the test, and patients were told the test would stop when they reached an RPE of 15 or at any time they felt the need to stop.

For our demonstration of ETT’s validity, we considered all patients who entered our CR program between October 30, 2008, and December 29, 2010, and were able to walk on the treadmill. The institutional review board waived informed consent for this study under 45 C.F.R. § 46.116(d).

We examined the rate pressure products patients reached during the ETT to ensure they remained below the threshold of 36,000 (corresponding to a maximum systolic blood pressure of 240 mm Hg and a peak heart rate of 150 beats per minute, both...
consistent with the American Association of Cardiovascular and Pulmonary Rehabilitation guidelines [2]) (6). The validity of this threshold may be challenged since many CR patients are on beta-blockers, resulting in decreased heart rates. Nevertheless, we believe this endpoint is appropriate: whether a patient’s rate pressure product remains ≤36,000 because the ETT is stopped when it reaches that level or because the beta-blockers prevent the maximum being reached, a potentially hazardous level of myocardial work is avoided.

We also examined the reasons for stopping the ETT protocol to determine what proportion of patients stopped for reasons other than reaching the target RPE of 15. The ability of few to reach this target would indicate a need to revise this aspect of the protocol.

Finally, we compared the patients’ MET levels measured by the DASI test to those measured by the ETT to determine whether the ETT provides an estimate of functional capacity that is at least equivalent to this commonly used measure.

Patient demographic data and primary diagnosis prompting referral to the CR program were obtained from administrative records. The remaining data were collected during the initial patient assessment, with patients completing both a DASI questionnaire and one of the three ETT protocols, administered by exercise physiologists and registered nurses. MET levels were calculated from the ETT protocols as shown in the Figure and from the DASI score using the following formula:

1. Estimated peak oxygen uptake in mL/min = (0.43 × DASI score) + 9.6
2. MET level = 3.5 × estimated peak oxygen uptake in mL/min

Data were prospectively collected but retrospectively analyzed.

Outcomes were examined using one-sample t tests, comparing mean values for maximum systolic blood pressure, peak heart rate, and the rate pressure product to the thresholds (240 mm Hg, 150 beats per minute, and 36,000, respectively). We used a matched pair equivalence test to determine whether DASI and the ETT could be considered equivalent measurements (7). Based on our knowledge of exercise physiology and experience working with METs and the common methods of assessing functional ability in the CR population, we defined the difference interval as “mean DASI MET ±1” (which was expected to translate into a 25% to 30% interval, depending on the exact mean DASI MET level) as the range of equivalence. We then calculated the 95% confidence interval for the observed difference between the DASI and ETT METs. A confidence interval that fell entirely within the (–1, 1) range was considered to demonstrate equivalence. All analyses were done using SAS 9.2 (Cary, NC).

RESULTS

From October 30, 2008, to December 29, 2010, 504 patients entered our CR program. Two patients were missing necessary data for this study and so were excluded, leaving a final study population of 502 patients. Table 1 shows the demographic characteristics of these patients and the primary diagnoses for which they were referred to CR. Most patients were white men, mean age 62 years. Most had had coronary artery bypass grafting, percutaneous coronary intervention, valve surgery, or combinations of these procedures.

We observed mean ± standard deviation values for maximum systolic blood pressure, peak heart rate, and rate pressure product of 143 ± 22 mm Hg, 109 ± 21 beats per minute, and 15,717 ± 4308, respectively, in our study population. All mean values were significantly lower than their respective threshold (P < 0.001), and the maximum systolic blood pressure (220 mm Hg) and rate pressure product (31,020) likewise fell below the thresholds of 240 mm Hg and 36,000. Although we did observe heart rates higher than the threshold of 150 beats per minute in two patients (the highest was 160 beats per minute), peak rate pressure products for both these patients were below the 36,000 threshold.

Table 2 shows the reasons patients stopped the ETT protocols. For 80% of the patients, the protocol was stopped because they had reached the target endpoint of an RPE of 15. With the exception of one patient, who suffered a panic attack, the protocol was stopped for the remaining 20% when warning signs indicated that continuing the protocol carried a risk of triggering an adverse event. Other than the panic attack, we observed no adverse events.

The mean ± standard deviation MET levels in our population were 6.5 ± 1.8 METs as measured by DASI and 5.7 ± 1.8 METs as measured by the ETT protocols. The mean difference (95% confidence interval) in MET score between the two tests was –0.8 (–0.98, –0.65). Since both the lower and upper confidence bounds were within our predefined equivalence interval (–1, 1), by our criteria, the ETT and DASI are statistically equivalent tests.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>Percentage</th>
<th>Male</th>
<th>383 (76.3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>White</td>
<td>428 (85.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hispanic</td>
<td>15 (3.0%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Black</td>
<td>13 (2.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Asian</td>
<td>13 (2.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other</td>
<td>33 (6.6%)</td>
</tr>
<tr>
<td>Primary diagnosis</td>
<td></td>
<td></td>
<td>Coronary artery bypass graft</td>
<td>243 (48.4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Percutaneous coronary intervention</td>
<td>120 (23.9%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Valve surgery</td>
<td>107 (21.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Myocardial infarction</td>
<td>18 (3.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other</td>
<td>14 (2.8%)</td>
</tr>
</tbody>
</table>

Table 1. Characteristics of the study population (N = 502)
The second major aspect of our evaluation of the ETT was to compare it to the DASI as a measure of functional capability in CR patients. We chose the DASI for this evaluation both because it was the method previously used in our program and because the DASI score can be readily converted to a MET level (2) (to which we could compare the ETT results) and has previously been shown to be at least modestly correlated with METs achieved during exercise testing in cardiac patients \((r = 0.31, P = 0.0002)\) (8) and with peak oxygen uptake during exercise testing \((r = 0.58, P < 0.0001)\) (9). Our analysis showed that the ETT was statistically equivalent to the DASI in assessing functional capability, as defined by the equivalence range we chose: the 95% confidence interval surrounding the mean ETT MET level (5.5 to 5.8) fell well within the predetermined range of equivalence (mean DASI MET ±1 = 5.5 to 7.5). While there is room for debate that the (–1, 1) equivalence range we selected was too broad, we believe it to be appropriate—particularly in light of the subjective nature of the questions from which the DASI score (and associated MET level) is calculated. Given that the mean DASI MET in our study population was 6.5, the (–1, 1) equivalence range translated into an approximately 30% interval—i.e., the mean ETT score needed to be less than 15% higher or lower than the DASI mean to be considered equivalent.

One benefit that we have observed working with the ETT is that it enables us to more effectively assess patients’ signs and symptoms, tailoring their exercise prescriptions accordingly. Additionally, since the same protocol can be used at program exit to assess the patient’s gain in functional capability, in the future we can assess our program, which can in turn be used to guide and evaluate initiatives we may implement to increase program effectiveness. Our results, showing a higher mean MET level based on DASI score than ETT protocol, although not significant, also suggest that patients might be overestimating their capabilities on program entry. The ETT can help both patients and CR staff better assess what activities patients can realistically perform and give them confidence in performing these activities so that they neither endanger their own safety nor impose needless limitation on themselves.

One limitation of our study was our inability to compare the ETT to the gold standard of a full exercise stress test. Such an evaluation would be valuable and, assuming positive results, would increase confidence in our method. Some might also consider the use of an RPE of 15 as a termination point for the ETT to be a limitation, as it is both a subjective measure and makes the ETT to the gold standard of a full exercise stress test. However, for our purposes—using a protocol that provides the desired physiological measure for development of a beneficial exercise prescription yet does not require physician involvement, insurance charges, or equipment not typically found in CR programs and demonstrating that this protocol is feasible and provides at least equivalent information to commonly used alternatives—neither comparison to a full exercise stress test, nor a maximal stress test, was necessary. Perceptually regulated exercise testing has been shown to be a valid means of producing consistent, acceptable, and recommended increments in intensity in healthy individuals (10).
Future research should investigate its validity in the CR patient population, as CR is a good example of a context in which maximal testing is not always feasible or appropriate, but a valid measure of exercise intensity is needed.

Acknowledgments

The authors thank the staff of the Baylor Heart and Vascular Hospital cardiac rehabilitation program for their contributions in developing the testing protocols, the staff of The Heart Hospital at Baylor Plano cardiac rehabilitation program for their work collecting data used in this study, and Briget da Graca, MS, ELS, for her help with the literature review and writing this paper.

Application of cranial bone grafts for reconstruction of maxillofacial deformities

Reza Movahed, DMD, Lecio P. Pinto, DDS, PhD, Carlos Morales-Ryan, DDS, MSD, Will R. Allen, DDS, and Larry M. Wolford, DMD

This retrospective study evaluated outcomes with the use of calvarial bone grafts (CBGs) in maxillofacial reconstruction as well as donor and recipient site complications. The records of 50 consecutive patients from a private practice were reviewed; there were 34 women and 16 men, with an average age of 32.4 years (range 16 to 66 years). Among the 50 patients, CBGs were placed in 63 sites: the ramus (10), nasal dorsum (14), maxilla/alveolar ridge (12), glenoid fossa/temporal bone (14), mandibular body/symphysis (3), and orbitozygomatic complex (10). The longest follow-up averaged 22.4 months (range 12 to 48 months). An outer-table CBG harvest technique was utilized. All subjects were evaluated for infection, dehiscence, loss of graft, and any other complications. Three complications occurred (5%) at the recipient sites. Two grafts became infected requiring removal, and one nasal dorsal graft was mobile but remained in position. At 50 donor sites, 2 complications (4%) occurred, resulting in dural tears in two patients that were immediately repaired with no untoward consequence. In conclusion, CBGs are an effective bone source for maxillofacial reconstruction with low donor and recipient site complications.

Autogenous bone grafts are the gold standard for reconstruction of maxillofacial defects. Autogenous bone becomes osseointegrated and vascularized at its site of implantation, which decreases the chances of infection, displacement, and foreign body reaction compared with alloplastic implants. The drawbacks are the harvest time, donor site morbidity, graft resorption, modeling changes, and harvest volume limitations (1).

The clinician has to choose the site of bone harvest wisely, taking into account the nature of the reconstruction and volume requirements. Autogenous bone can be harvested from multiple sites, including the calvarium, tibia, anterior ileum, posterior ileum, rib, sternoclavicle, zygoma, mandible, and so forth. The use of calvarial bone grafts (CBGs) was first reported in 1670, when Van Meekren reconstructed a Russian soldier’s calvarial defect utilizing a CBG from a dog (2). Other early contributors were Konig (3) and Muller (4) in 1890, reporting on human CBGs for the correction of posttraumatic cranio-maxillofacial defects. In the 1980s, Tessier popularized the technique as an aid in the correction of craniofacial deformities (5). Pensler and McCarthy (6) published a study on the thickness and specific anatomy of the calvarium for safe and predictable harvesting.

CBGs have been utilized in reconstruction of the mandible (7), maxilla (8, 9), orbital floor (10, 11), orbital roof (12), malar region (13), and as a strut for nasal reconstruction (14). In craniofacial surgery, the CBG can be used to reconstruct advancement gaps resulting from Lefort I, II, and III procedures.

Outer-table CBGs can be taken from the parietal region of the skull, posterior to the coronal suture, where the skull is the thickest. CBGs can usually be harvested with minimal morbidity at the donor site, with a scar hidden in the hair-bearing region. The geometry and convexity of the CBG makes it suitable for most maxillofacial reconstructions. Due to its cortical nature, the CBG can be rigidly fixated, providing a stable platform for revascularization and osseointegration. In maxillofacial reconstruction, the proximity of the CBG donor site to the surgical site avoids the need for a second distant surgical field, but may preclude simultaneous bone graft harvest and recipient site preparation.

Postoperative complications are few, and recovery is relatively painless. The donor site defect of the outer table can be reconstructed with a bone cement that solidifies with endothermic reaction. The graft should not be harvested in the midline because of the risk of injuring the sagittal sinus.

METHODS

This retrospective study consisted of 50 consecutive patients (34 women and 16 men), treated from 1996 to 2010 by a single private practice, in whom only cranial bone grafts were used to reconstruct maxillofacial defects (Figures 1–2). This study was exempt from institutional review board approval. Records were reviewed, including operative reports, discharge summaries, progress notes, radiographs, and photographs. Subjects were excluded from the study if they had less than 12 months of follow up or inadequate records.

All subjects underwent bone harvesting and grafting by the same surgeon (Wolford). The outer-table CBG harvest technique...
was utilized in all patients, and the volume of the bone was harvested according to the recipient site defect. The harvest of the CBG was performed following completion of the recipient site preparation. The initial incision was made 2 cm posterior to the hair line and 2 cm lateral to the midline. The incision was made in a curvilinear fashion, superior to the temporalis muscle attachment (Figure 3). Using a #10 scalpel, the incision was carried down to the cranium. Raney clips were placed at the edges of the incision. Minimal use of Bovie cautery and minimized harvest time decreased damage to the hair follicles. The bone to be harvested was outlined using a 701 burr, to correlate to the amount of bone necessary for the recipient site. The site of harvest was usually 2 cm lateral to the sagittal and squamoparietal sutures. The unicortical osteotomies of outer cortex bone to be harvested were connected. The inferior or superior edge of the donor site was beveled using a pineapple burr in order to access the diploë, deep to the outer cortex. Using a combination of slightly curved and straight osteotomies, the bone grafts were dislodged from the diploë. The bone was kept in saline and placed on ice for preservation. Hemostasis was achieved. The Raney clips were removed, and the incision was closed in a single layer using a 2.0 or 3.0 Prolene suture. A compression dressing was placed for prevention of hematoma. Sutures were removed 7 to 10 days after surgery.

The evaluation consisted of the clinical description of any complication at the donor or recipient site during the procedure, immediately after surgery, and at longest follow-up. The healing and integration of grafts were evaluated clinically and radiographically.

RESULTS
Fifty patients with 63 grafted areas were evaluated. The distribution of grafted areas is shown in the Table. The six grafted areas included mandibular body/symphysis, ramus, nasal dorsum, maxilla/alveolar ridge, glenoid fossa, and orbitozygomatic complex. Patients’ average age was 32.4 years (range 16 to 66 years), and the longest follow-up averaged 22.4 months (range 12 to 48 months).

The percentage of complications associated with the recipient sites was calculated from the total number of grafted anatomical locations, while the percentage of complications associated with the donor site was calculated using the total number of patients, since there was a single donor site per patient. At the recipient sites, three complications were noted (4.8%). In one case of a maxillary ridge augmentation with simultaneous osseointegrated dental implants, the graft was lost secondary to infection. The second patient had facial congenital infiltrating lipomatosis and received a unilateral orbitozygomatic reconstruction with a CBG, following extensive resection of the tumor, which involved the orbit, zygoma, and associated soft tissue. There was partial loss of the graft secondary to infection, related to the poorly vascularized recipient bed. In the third case a nasal dorsal reconstruction graft became mobile, failing to integrate and fuse to the nasal bony structure, but it remained in place 3 years after surgery. The rest of the grafts healed uneventfully and at the radiographic evaluation appeared to demonstrate adequate integration between the graft and the host bone at long-term follow-up.

At the donor sites, two complications were identified (4.0%). A dural tear occurred on a 16-year-old patient who had only one cortical plate of the parietal bone. The tear was primarily
repaired. In the second patient the dura tear was also closed primarily. Both patients healed uneventfully.

**DISCUSSION**

CBGs are used for a multitude of maxillofacial reconstructions, with low complication rates (15). The literature has reported clinical observation of minimal to no resorption of the CBG at short-term follow-up (16, 17).

The reconstruction, although technique sensitive in its adaptation to the recipient site, is safer and more cost-effective than alloplastic grafting (18–20). CBGs can be considered the material of choice for maxillofacial reconstruction due to their histocompatibility, anatomofunction, and mechanical properties (21). Additionally, CBGs are fresh live tissue that will revascularize and osseointegrate to adjacent bone, having a low rate of infection (22).

Although CBGs require time for harvest, unlike alloplastic graft materials, the disadvantages associated with CBGs are few. When large bone grafts are harvested, the donor defect can be reconstructed with synthetic substitutes, which have been reported to result in infections and inflammatory reactions (23). The chance of a dural tear exists with outer-table CBG harvesting if the inner table is penetrated (24). In harvesting outer CBGs, the possible complications are intracerebral hematoma, subarachnoid hemorrhage, and cerebrospinal fluid leaks (25), none of which were encountered in this study. Additionally, CBGs are fresh live tissue that will revascularize and osseointegrate to adjacent bone, having a low rate of infection (22).

Although no controlled human studies have measured the exact rate of resorption and retained volume of CBGs, the clinical studies support stable outcomes (26–28). DeLuca et al reported an animal study, where the CBGs had a volume retention rate of 85.1%, and recommended CBGs as the gold standard for craniofacial reconstruction (29).

In our retrospective study, the complication rates at the donor site (4.0%) and the recipient site (4.8%) were relatively low. The outer-table CBG harvest technique is a time-consuming procedure compared with use of alloplastic and tissue-engineered materials. In comparison to bone grafts obtained from other anatomical sites, CBGs benefit the operator with one field of surgical access, eliminating the preparation of a distant second site. The reported complication rates are low. This bone grafting procedure is an effective technique for reconstruction of maxillofacial defects.

<table>
<thead>
<tr>
<th>Table. Distribution of grafts and outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reconstruction area</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Mandibular ramus</td>
</tr>
<tr>
<td>Nasal dorsum</td>
</tr>
<tr>
<td>Maxilla/ alveolar ridge</td>
</tr>
<tr>
<td>Glenoid fossa/ temporal bone</td>
</tr>
<tr>
<td>Mandible</td>
</tr>
<tr>
<td>Orbitozygomatic complex</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>


Avocations

*River* by Jay Hoppenstein, MD. Dr. Hoppenstein (e-mail: navigato@aol.com) is a surgeon who was on the medical staff at Baylor University Medical Center at Dallas from 1971 until his retirement in 2005. He also served as chairman of the Department of Surgery at Presbyterian Hospital of Dallas.
Frequency of adoption of practice management guidelines at trauma centers

Justin Sobrino, MD, Sunni A. Barnes, PhD, Nadine Dahr, MS, Rustam Kudyakov, MD, Candice Berryman, BS, Avery B. Nathens, MD, PhD, MPH, Mark R. Hemmila, MD, Melanie Neal, MS, and Shahid Shafi, MD, MPH

Evidence-based management guidelines have been shown to improve patient outcomes, yet their utilization by trauma centers remains unknown. This study measured adoption of practice management guidelines or protocols by trauma centers. A survey of 228 trauma centers was conducted over 1 year; 55 completed the survey. Centers were classified into three groups: noncompliant, partially compliant, and compliant with adoption of management protocols. Characteristics of compliant centers were compared with those of the other two groups. Most centers were Level I (58%) not-for-profit (67%) teaching hospitals (84%) with a surgical residency (74%). One-third of centers had an accredited fellowship in surgical critical care (37%). Only one center was compliant with all 32 management protocols. Half of the centers were compliant with 14 of 32 protocols studied (range, 4 to 32). Of the 21 trauma center characteristics studied, only two were independently associated with compliant centers: use of physician extenders and daily attending rounds (both P < .0001). Adoption of management guidelines by trauma centers is inconsistent, with wide variations in practices across centers.

The trauma center designation process is based on the availability of optimal resources for care of the injured (1). However, availability of optimal resources does not necessarily translate into delivery of optimal care (2). Studies have shown wide variations in risk-adjusted outcomes across designated trauma centers despite availability of optimal resources, suggesting that differences in outcomes are likely related to variations in clinical practices (3). Evidence-based practice management guidelines have improved patient outcomes in several diseases (4). In trauma, many professional societies have developed evidence-based management protocols (5–10). However, presently, use of these management protocols by trauma centers remains unknown. We have previously shown that compliance with guidelines remains inadequate, with less than two-thirds of the indicated care provided (3). Therefore, worse-than-expected outcomes at certain trauma centers may be due to clinical practice patterns. A possible remedy is to emphasize adoption of management protocols and mechanisms to ensure compliance with them. The purpose of this study was to measure adoption of practice management guidelines or protocols recommended by professional societies in a national sample of designated trauma centers. A secondary goal was to identify characteristics of trauma centers that have fully adopted these guidelines by having written protocols and monitoring compliance with them.

METHODS

Data were obtained from the National Trauma Data Bank of the American College of Surgeons (ACS) from 2007 to 2009. We identified 228 ACS-verified Level I and Level II trauma centers that treated ≥50 patients with moderate to severe injuries (at least one Abbreviated Injury Scale score ≥3). A web-based survey instrument was developed and pretested. The survey was then administered to the trauma medical directors and/or trauma program managers of these centers over a 1-year period (2010 to 2011). The centers were contacted multiple times during this period via phone and e-mail and encouraged to complete the survey. A total of 55 centers completed the survey and constituted the study population (response rate, 25%).

The survey was designed to measure compliance with several practice management guidelines developed by various professional societies and to identify quality indicators used by the centers. These included the ACS Committee on Trauma, Eastern Association for the Surgery of Trauma, Society for Critical Care Medicine, the Brain Trauma Foundation, the Glue Grant Consortium, and the Surgical Care Improvement Project (5–9, 11). These guidelines were reviewed to identify 32 clinical practices for which protocols have been promulgated. Staff members completing the survey at the centers were asked if they had a written protocol for each one of the 32 processes. We did not review each center’s...
protocol to determine if it was consistent with existing evidence or actual recommended guidelines. If a center reported having a written protocol for a specific process, it was then asked if compliance with that protocol was monitored. Based on the responses, centers were classified into three groups: noncompliant (no protocols in place), partially compliant (protocol in place but compliance not monitored), and compliant with adoption of management protocols (protocols in place and compliance monitored).

Several center characteristics were also obtained in the survey. Multinomial regression analysis was then used to identify characteristics that were independent predictors of centers that were compliant with adoption of protocols. The characteristics analyzed were number of years served by the trauma medical director in that post, number of trauma activations, number of patients with an Injury Severity Score ≥16, academic affiliation, total number of acute care hospital beds, number of trauma admissions, ownership, surgical residency, Accreditation Council for Graduate Medical Education fellowship in surgical critical care, whether the surgical intensive care unit (SICU) director was board certified or eligible in surgical intensive care, distinct ICU service, in-house attending surgeons in trauma, standardized admission order sets, computerized physician order entry, computerized pharmacy system, physician extenders and mid-level providers, pharmacist presence in SICU rounds, nutritionist presence in SICU rounds, formalized sign-out mechanism, and daily attending rounds. Statistical analysis was carried out using SAS 9.2 and SAS EG 4.2 (SAS Institute Inc.; Cary, NC), with \( P < .05 \) considered statistically significant.

RESULTS
Trauma center characteristics are listed in Table 1. A majority of centers were Level I (58%), and a third had an accredited fellowship in surgical critical care (37%). Centers that did not respond to the survey were similar to responders in terms of their clinical volume and ownership but were more likely to be community-based Level II trauma centers (Table 2).

Table 3 summarizes the experience of the centers with each of the 32 protocols. The most commonly used management protocols were related to use of massive blood transfusion, determination of brain death, prevention of venous thromboembolism, and prevention of catheter-related bloodstream infection. Centers had a written protocol for as few as four processes to as many as all 32 processes that were studied. Half of the centers had a written protocol for only 21 of 32 processes. Only one center was compliant with all 32 management protocols. Monitoring compliance was highest for protocols related to identification of organ donors, prevention of catheter-related bloodstream infection, diversion of incoming patients when resources were overwhelmed, use of massive transfusions, and prevention of venous thromboembolism.

### Table 1. Trauma center characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ownership</td>
<td></td>
</tr>
<tr>
<td>Private for-profit</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Private not-for-profit</td>
<td>37 (67%)</td>
</tr>
<tr>
<td>Public</td>
<td>15 (27%)</td>
</tr>
<tr>
<td>Academic affiliation</td>
<td></td>
</tr>
<tr>
<td>Nonteaching</td>
<td>9 (16%)</td>
</tr>
<tr>
<td>Teaching</td>
<td>46 (84%)</td>
</tr>
<tr>
<td>Surgical residency</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>14 (25%)</td>
</tr>
<tr>
<td>Yes</td>
<td>41 (75%)</td>
</tr>
<tr>
<td>ACGME fellowship in SCC</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>35 (64%)</td>
</tr>
<tr>
<td>Yes</td>
<td>20 (36%)</td>
</tr>
<tr>
<td>Distinct SICU service</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>15 (27%)</td>
</tr>
<tr>
<td>Yes</td>
<td>40 (73%)</td>
</tr>
<tr>
<td>In-house attending in trauma surgery</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>20 (36%)</td>
</tr>
<tr>
<td>Yes</td>
<td>35 (64%)</td>
</tr>
</tbody>
</table>

ACGME indicates American Council for Graduate Medical Education; SCC, surgical critical care; SICU, surgical intensive care unit.

### Table 2. Comparison of responders versus nonresponders

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Respondents</th>
<th>Nonrespondents</th>
<th>( P ) value</th>
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</thead>
<tbody>
<tr>
<td>Tax status</td>
<td></td>
<td></td>
<td>0.17</td>
</tr>
<tr>
<td>Community for-profit</td>
<td>2%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Community not-for-profit</td>
<td>60%</td>
<td>69%</td>
<td></td>
</tr>
<tr>
<td>Public entity</td>
<td>11%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>University for-profit</td>
<td>0%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>University not-for-profit</td>
<td>27%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Trauma or surgical critical care fellowship</td>
<td>33%</td>
<td>25%</td>
<td>0.27</td>
</tr>
<tr>
<td>Teaching hospital</td>
<td>84%</td>
<td>72%</td>
<td>0.08</td>
</tr>
<tr>
<td>Trauma center level</td>
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<td>0.04</td>
</tr>
<tr>
<td>Level I</td>
<td>58%</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td>Level II</td>
<td>42%</td>
<td>58%</td>
<td></td>
</tr>
<tr>
<td>Trauma surgeons take in-house call</td>
<td>56%</td>
<td>63%</td>
<td>0.38</td>
</tr>
<tr>
<td>Average daily census</td>
<td>170%</td>
<td>156%</td>
<td>0.48</td>
</tr>
</tbody>
</table>
### Table 3. Utilization of management protocols

<table>
<thead>
<tr>
<th>Management protocol</th>
<th>Written protocol</th>
<th>Monitoring compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Massive transfusions</td>
<td>55 (100%)</td>
<td>47 (85%)</td>
</tr>
<tr>
<td>Brain death determination in patients with massive head injuries</td>
<td>54 (98%)</td>
<td>37 (69%)</td>
</tr>
<tr>
<td>DVT prophylaxis</td>
<td>52 (95%)</td>
<td>44 (85%)</td>
</tr>
<tr>
<td>Prevention of catheter-related bloodstream infection</td>
<td>50 (91%)</td>
<td>45 (90%)</td>
</tr>
<tr>
<td>Diversion of incoming trauma patients if resources are overwhelmed</td>
<td>49 (89%)</td>
<td>45 (92%)</td>
</tr>
<tr>
<td>Alcohol screening/brief intervention</td>
<td>49 (89%)</td>
<td>40 (82%)</td>
</tr>
<tr>
<td>Identification of potential organ donors</td>
<td>48 (87%)</td>
<td>45 (94%)</td>
</tr>
<tr>
<td>Strict glycemic control</td>
<td>47 (85%)</td>
<td>35 (74%)</td>
</tr>
<tr>
<td>Cervical spine evaluation in blunt injuries</td>
<td>47 (85%)</td>
<td>26 (55%)</td>
</tr>
<tr>
<td>Sedation/analgesia</td>
<td>46 (84%)</td>
<td>27 (59%)</td>
</tr>
<tr>
<td>Stress ulcer prophylaxis</td>
<td>43 (78%)</td>
<td>31 (72%)</td>
</tr>
<tr>
<td>Prevention of alcohol withdrawal</td>
<td>42 (76%)</td>
<td>23 (55%)</td>
</tr>
<tr>
<td>Daily spontaneous breathing trial for vent liberation</td>
<td>41 (75%)</td>
<td>24 (59%)</td>
</tr>
<tr>
<td>Obstetric evaluation of pregnant trauma patients in the emergency department</td>
<td>39 (71%)</td>
<td>24 (62%)</td>
</tr>
<tr>
<td>Daily sedation holiday</td>
<td>39 (71%)</td>
<td>23 (59%)</td>
</tr>
<tr>
<td>Reversal of prolonged INR in patients who were on warfarin</td>
<td>37 (67%)</td>
<td>25 (68%)</td>
</tr>
<tr>
<td>Enteral nutrition</td>
<td>35 (64%)</td>
<td>22 (63%)</td>
</tr>
<tr>
<td>Intracranial pressure—directed therapy for closed-head injury</td>
<td>31 (56%)</td>
<td>20 (65%)</td>
</tr>
<tr>
<td>Screening for blunt cerebrovascular injuries</td>
<td>30 (55%)</td>
<td>17 (57%)</td>
</tr>
<tr>
<td>Empiric use of antibiotics</td>
<td>29 (53%)</td>
<td>21 (72%)</td>
</tr>
<tr>
<td>Nonoperative management of blunt liver, spleen, and renal injuries</td>
<td>28 (51%)</td>
<td>20 (71%)</td>
</tr>
<tr>
<td>ARDS: low-stretch ventilation</td>
<td>28 (51%)</td>
<td>19 (68%)</td>
</tr>
<tr>
<td>Indications for resuscitative thoracotomy in the emergency department</td>
<td>26 (47%)</td>
<td>19 (73%)</td>
</tr>
<tr>
<td>Emergent angioplasty for pelvic fractures</td>
<td>25 (45%)</td>
<td>13 (52%)</td>
</tr>
<tr>
<td>Preoperative antibiotics for laparotomy in penetrating abdominal injuries</td>
<td>25 (45%)</td>
<td>20 (80%)</td>
</tr>
<tr>
<td>Prophylactic IVC filter use</td>
<td>21 (38%)</td>
<td>13 (62%)</td>
</tr>
<tr>
<td>Transfusion triggers</td>
<td>19 (35%)</td>
<td>15 (79%)</td>
</tr>
<tr>
<td>Management of suspected blunt cardiac injury</td>
<td>19 (35%)</td>
<td>10 (53%)</td>
</tr>
<tr>
<td>Operative irrigation and debridement of open long-bone fractures</td>
<td>17 (31%)</td>
<td>14 (82%)</td>
</tr>
<tr>
<td>Early use (&lt;7 days) of heparin or LMWH for DVT prophylaxis after intracranial bleed</td>
<td>16 (29%)</td>
<td>11 (69%)</td>
</tr>
<tr>
<td>IVC filter retrieval</td>
<td>14 (25%)</td>
<td>11 (79%)</td>
</tr>
<tr>
<td>Establishment of central venous access if peripheral lines cannot be established</td>
<td>12 (22%)</td>
<td>5 (42%)</td>
</tr>
</tbody>
</table>

ARDS indicates acute respiratory distress syndrome; DVT, deep venous thrombosis; INR, international normalized ratio; IVC, inferior vena cava; LMWH, low-molecular-weight heparin.

### Table 4. Quality indicators

<table>
<thead>
<tr>
<th>Quality indicator or complication</th>
<th>Sites monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma deaths</td>
<td>100%</td>
</tr>
<tr>
<td>Venous thromboembolus prophylaxis</td>
<td>98%</td>
</tr>
<tr>
<td>Missing emergency medical services reports</td>
<td>96%</td>
</tr>
<tr>
<td>Missed injuries</td>
<td>96%</td>
</tr>
<tr>
<td>Unplanned readmission</td>
<td>95%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>95%</td>
</tr>
<tr>
<td>Admission by nonsurgeon</td>
<td>93%</td>
</tr>
<tr>
<td>Infections—surgical site</td>
<td>93%</td>
</tr>
<tr>
<td>Cardiopulmonary arrest</td>
<td>93%</td>
</tr>
<tr>
<td>Diagnosis and treatment delayed &gt;24 hours after presentation</td>
<td>93%</td>
</tr>
<tr>
<td>Infections—device related—line, bladder</td>
<td>91%</td>
</tr>
<tr>
<td>Delayed or inappropriate activations</td>
<td>91%</td>
</tr>
<tr>
<td>Infections— intra-abdominal</td>
<td>89%</td>
</tr>
<tr>
<td>Unplanned procedure</td>
<td>87%</td>
</tr>
<tr>
<td>Unplanned intensive care unit admission</td>
<td>87%</td>
</tr>
<tr>
<td>Reintubation within 48 hours of extubation</td>
<td>85%</td>
</tr>
<tr>
<td>Infections—wound</td>
<td>85%</td>
</tr>
<tr>
<td>Blood unavailability</td>
<td>85%</td>
</tr>
<tr>
<td>Incomplete documentation</td>
<td>85%</td>
</tr>
<tr>
<td>Specialist response time</td>
<td>85%</td>
</tr>
<tr>
<td>Craniorrhhaphy after 4 hours with expanding epidural/subdural hematoma</td>
<td>84%</td>
</tr>
<tr>
<td>Retained foreign body</td>
<td>84%</td>
</tr>
<tr>
<td>Postoperative bleeding</td>
<td>84%</td>
</tr>
<tr>
<td>Adverse effects of procedures</td>
<td>84%</td>
</tr>
<tr>
<td>No intubation if Glasgow Coma Scale ≤8</td>
<td>82%</td>
</tr>
<tr>
<td>Personnel availability</td>
<td>82%</td>
</tr>
<tr>
<td>No laparotomy &lt;1 hour with abdominal injuries and systolic blood pressure &lt;90</td>
<td>78%</td>
</tr>
<tr>
<td>Laparotomy after 4 hours</td>
<td>78%</td>
</tr>
<tr>
<td>No hourly charting of vitals in emergency department</td>
<td>76%</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>76%</td>
</tr>
<tr>
<td>Operation &gt;8 hours after open long-bone fractures</td>
<td>73%</td>
</tr>
<tr>
<td>Emergency department dwell time</td>
<td>73%</td>
</tr>
<tr>
<td>Equipment failure in emergency department</td>
<td>71%</td>
</tr>
<tr>
<td>Registry backlog</td>
<td>71%</td>
</tr>
<tr>
<td>Transfer after &gt;6 hours at the referring hospital</td>
<td>69%</td>
</tr>
<tr>
<td>Nonoperative management of gunshot wound—abdomen</td>
<td>67%</td>
</tr>
<tr>
<td>Abdominal, thoracic, vascular, or cranial surgery &gt;24 hours after presentation</td>
<td>65%</td>
</tr>
<tr>
<td>Organ failure</td>
<td>64%</td>
</tr>
<tr>
<td>Scene time &gt;20 minutes</td>
<td>62%</td>
</tr>
<tr>
<td>Readmission within 3 months</td>
<td>56%</td>
</tr>
<tr>
<td>Progressive neurologic decline</td>
<td>53%</td>
</tr>
<tr>
<td>No head computed tomography if Glasgow Coma Scale ≤14</td>
<td>47%</td>
</tr>
<tr>
<td>Nonfixation of femoral diaphyseal fractures in adults</td>
<td>38%</td>
</tr>
<tr>
<td>Outpatient follow-up rate</td>
<td>22%</td>
</tr>
</tbody>
</table>
Of the 21 trauma center characteristics studied, only two were independently associated with compliant centers: use of physician extenders (89% of centers) and daily attending rounds (90% of centers; both \( P < .0001 \)).

The most commonly used quality indicators are listed in Table 4. All centers reviewed trauma deaths, as this was one of the critical requirements for their designation status. However, there were large variations in use of other quality indicators. Fewer than half the centers monitored nonfixation of long-bone fractures, lack of a head computed tomography scan in patients presenting with Glasgow Coma Scale ≤14, and outpatient follow-up rates.

**DISCUSSION**

There are two major findings of this study. First, adoption of practice management guidelines by trauma centers is inconsistent with wide variations in practices evident across centers. Second, use of physician extenders and hands-on participation of attending surgeons in daily patient care were associated with increased adoption of guidelines.

Previous studies have shown wide variations in clinical practices across trauma centers. However, the causes of this variation remain unknown. Todd et al showed variability in the management of splenic injuries among urban teaching, urban nonteaching, and rural hospitals. Surgeons at urban teaching hospitals were more likely to attempt splenic salvage with nonoperative management (12). We have also shown that trauma centers with lower-than-expected mortality rates were less likely to perform operative interventions in trauma patients than were centers with higher mortality rates (13). Similar variations have been shown in management of other diseases. Cardiovascular disease, for example, has been shown to have wide variations in both diagnostic and therapeutic interventions (14). Inconsistent clinical practices lead to high-cost, inefficient care that may be harmful to patients (15).

Evidence-based management protocols have been promulgated in several medical specialties. Adoption of these protocols has the potential to reduce variations in care, minimize costs, and improve quality of care. However, adoption of these guidelines in routine clinical practices remains suboptimal. The Health Care Quality Improvement Initiative began in 1992 and included the National Cooperative Cardiovascular Project. Despite this, O’Connor et al published results in 1999 indicating that evidence-based care received by cardiac patients varied widely (16). A similar scenario exists in the management of adult respiratory distress syndrome (ARDS) and the adoption of low-stretch ventilation. First published in 2000 by the ARDS Network, this multicenter randomized clinical trial showed that low-stretch ventilation improved survival (17, 18). Yet adoption of guidelines for management of ARDS remains generally low and widely variable a decade after publication of this landmark study (19–23). The findings of the current study are consistent with these previous studies and highlight the gap between knowledge and its translation into routine clinical practice at trauma centers.

There are multiple barriers to adoption of management protocols. Pathman et al developed their model of cognitive steps that physicians take in adhering to protocols, including preawareness, awareness, agreement, adoption, and adherence (24). Berwick identified three clusters of influence on the diffusion rate of innovations: perception of the innovation, characteristics of individuals who adopt the change, and the contextual factors within an organization (25). Cabana et al developed a model of knowledge leading to attitudes and then to behavior and identified barriers in all three areas. These included a lack of awareness, familiarity, agreement, and outcome expectancy; inertia of previous practice; and opinions that guidelines were cumbersome, inconvenient to use, and confusing (26). Physicians also commonly report a perceived loss of autonomy as a concern (14, 27). Lack of awareness is an often-cited reason, with the average clinician lost in reading and evaluating an overwhelming volume of published research (28). There is also a perceived futility to certain treatments when clinical judgment indicates a low chance of functional recovery, a poor overall prognosis, or when response to initial treatment is unconvincing. Levels of evidence used to develop guidelines may also be an influence, and perceived degree of authenticity can influence adoption of guidelines. For example, intracranial pressure monitors are recommended by the Brain Trauma Foundation, although there is lack of convincing evidence regarding their use (29). Gurses et al studied system ambiguity in an ICU setting as a barrier. Their surveys revealed ambiguity and uncertainty surrounding key steps such as tasks to complete for patients and when, patient goals, ICU expectations of compliance with a particular guideline, reminders of compliance rates, applicability of a guideline to a particular patient, and decisions on exceptions to guidelines (30). Additional barriers to adoption of protocols exist at the facility level as well (31). A common example is compliance requiring acquisition of new resources or facilities, such as having a particular service available 24 hours a day and the costs associated with it. However, all centers included in the current study were designated or verified Level I and II trauma centers, suggesting availability of optimal resources.

An important implication of our findings is that there is a need to improve adoption of practice management guidelines at trauma centers. Several strategies have been shown to improve clinical practices. The Cochrane Reviews and the National Guideline Clearinghouse make available thoroughly vetted guidelines. Scanning and alert services such as the American College of Physicians Journal Club, evidence-based journals, and BMJ Evidence Updates are efforts to improve physician awareness of guidelines by allowing customized notifications of new or updated guidelines. However, reliance on passive dissemination of knowledge does not improve protocol adoption (32). Experience in oncology has shown that improved adoption of guidelines is achieved through active dissemination of protocols as well as compliance monitoring and reporting (33, 34). Our findings suggest that increasing use of mid-level providers and daily patient rounds by attending trauma surgeons were associated with improved compliance. This may be consistent with the finding that ICU patients are more likely to receive recommended care, as both mid-level providers and daily patient rounds by attending trauma surgeons are common practice.
in this setting. While the reasons are not clear, it has been hypothesized that protocol-driven care, use of order sets, and close monitoring of trainees and patients by trained intensivists all contribute (30). On the other hand, use of physician extenders and daily attending rounds may simply reflect institutional commitment to providing high-quality care. It is also possible that protocols were put in place to enable institutions to use physician extenders. The findings indicate that, in addition to developing and disseminating management protocols, a system of monitoring compliance is needed at trauma centers. So far, the emphasis of the trauma center designation process has been on ensuring availability of “optimal resources.” Perhaps it is time to expand it to focus on adoption of “optimal practices.” A reporting system that monitors compliance with management protocols may also enhance their adoption.

This study has a few limitations that must be acknowledged. As with all surveys, the findings were self-reported. Additionally, roughly three-quarters of centers surveyed did not respond. However, centers that did not participate in the survey were similar to responders in several characteristics, except that they were more likely to be Level II centers. Low response rates may be partly due to the use of a web-based survey instrument instead of paper (35, 36). Additionally, we did not review the details of centers’ protocols to determine if they were consistent with recommended guidelines. Finally, there is little consensus on the processes of care most crucial to improving trauma outcomes. In the absence of high-quality data, it is possible that adoption of existing guidelines may not improve patient outcomes. Identifying best practices will allow the creation of guidelines that enable clinicians to focus limited resources on implementation of practices that are most likely to improve patient outcomes.

Acknowledgment

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8. The Joint Commission. Surgical Care Improvement Project. Available at http://www.jointcommission.org/surgical_care_improvement_project/.


Effectiveness and safety of Gamma Knife radiosurgery for glossopharyngeal neuralgia

John K. O’Connor, MD, and Shaad Bidiwala, MEng, MD

Glossopharyngeal neuralgia (GPN) is a rare disorder of the ninth cranial nerve characterized by severe, paroxysmal pain affecting the ear, tongue, and throat. GPN can be associated with life-threatening issues such as cardiac arrhythmias, syncope, or malnutrition and weight loss from odynophagia. Though traditional treatment for GPN involves medical management at first and surgery for refractory cases, these therapies are often poorly tolerated in the elderly population. We describe the case of a 99-year-old woman, the oldest reported patient with GPN treated successfully with Gamma Knife radiosurgery. We conclude that Gamma Knife radiosurgery for GPN can be both effective and very well tolerated in the elderly and deserves further study and careful consideration as a treatment option in this population.

CASE REPORT

A 99-year-old woman presented with an 18-month history of searing electric shock–like left facial, tongue, deep pharyngeal, and ear pain occurring at least 10 times a day and lasting 15 to 60 seconds per episode. The episodes of pain were triggered by talking, eating, drinking, and especially swallowing and interfered with her quality of life, leading to a weight loss of 20 pounds over the 18 months prior to presentation. She was diagnosed with GPN and failed trials of gabapentin, pregabalin, carbamazepine, and oxcarbazepine due primarily to medication intolerance. She tolerated low doses of levetiracetam, but did not receive significant relief of her pain and experienced debilitating generalized weakness and syncopal episodes with dose escalation. She received two sphenopalatine blocks; the first provided pain relief for 6 weeks and the second for 4 days.

The patient was evaluated at Baylor University Medical Center at Dallas (BUMC) after she had been hospitalized for pain exacerbations and symptoms related to the dose escalation of levetiracetam. A detailed examination of her cranial nerves disclosed no abnormalities; magnetic resonance imaging (MRI) of the brain showed age-related ischemic white matter changes, but no evidence of extrinsic compression of the brainstem or cranial nerves. We recommended Gamma Knife radiosurgery for her GPN.

The treatment was performed on a Gamma Knife model 4C (Elekta Instruments) in the Baylor Radiosurgery Center at BUMC. The patient underwent stereotactic headframe placement under topical and injected local anesthetic. She underwent a T1 MRI with and without contrast with 1 mm slice thickness and zero interspace gap. A high-resolution computed tomography (CT) scan of the skull base was also obtained. The MRI and CT scan were imported into the treatment planning system (Leksell Gamma Plan, Elekta AB, Stockholm, Sweden) and fused. A three-dimensional stereotactic radiosurgery plan was created targeting the glossopharyngeal nerve at the glossopharyngeal meatus of the jugular foramen with a single shot with the 4 mm collimator (Figure). No plugging pattern was used. Targeting was confirmed on axial, sagittal, and coronal images. A dose of 40 Gy was given to the 50% isodose line, with a maximum dose of 80 Gy. The 50% isodose volume was 0.0895 cm³.
The patient tolerated the treatment well, and there were no acute complications.

The patient experienced substantial pain relief 1 month following her Gamma Knife procedure. At 16 months posttreatment, she remained pain-free and off all medications for pain. She had no difficulty swallowing, speaking, eating, or drinking. Given her ability to eat without pain, she reported a marked improvement in her quality of life. She experienced no acute or long-term adverse toxicity from Gamma Knife radiosurgery.

**DISCUSSION**

Compared with TN, GPN is a relatively uncommon craniofacial pain disorder. The incidence of TN is 28.9 cases per 100,000 person-years compared with only 0.4 cases per 100,000 person-years for GPN (14). While the characteristics of the pain are similar for both TN and GPN, with sudden severe stabbing pains usually lasting seconds to minutes with triggering events, the location is different. While TN affects the face in the V1, V2, and/or V3 distributions of the fifth cranial nerve, the pain from GPN is typically localized to the posterior tongue, throat/pharynx, and ear on the affected side. Additionally, while the diagnosis of both GPN and TN is clinical, GPN is more likely than TN to be associated with an underlying cause such as tumor or infection (15).

Destructive surgical interventions for GPN, including intracranial sectioning of the glossopharyngeal nerve, are associated with dysphasia. Microvascular decompression is a non-destructive surgical technique for GPN, with rates of complete pain relief in the range of 76% to 97% and a lower cranial nerve complication rate of 3% to 19% (5, 9, 11).

Stereotactic radiosurgery is a well-accepted treatment for patients with TN, with high rates of pain relief and low morbidity (16). Extrapolating from the favorable experience using radiosurgery for TN, a few centers have performed radiosurgery on patients with medically refractory GPN (Table). Worldwide, including the current study, only 15 patients have been reported in the literature.

**Table.** Reported cases and outcome of patients with glossopharyngeal neuralgia treated with stereotactic radiosurgery

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Age, gender</th>
<th>NVC</th>
<th>Target</th>
<th>Dose (Gy)</th>
<th>Outcome</th>
<th>Pain recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stieber et al, 2005</td>
<td>–, F</td>
<td>+</td>
<td>Cistern</td>
<td>80</td>
<td>Pain free, off medications</td>
<td>+ (FU 6 mos)</td>
</tr>
<tr>
<td>Lévéque et al, 2011</td>
<td>83, F</td>
<td>+</td>
<td>GPM</td>
<td>60</td>
<td>Pain free, off medication</td>
<td>+ (FU 7 mos)</td>
</tr>
<tr>
<td>Case 1</td>
<td>62, M</td>
<td>0</td>
<td>Cistern</td>
<td>70</td>
<td>Pain reduced 50%–90%</td>
<td>+ (FU 24 mos)</td>
</tr>
<tr>
<td>Case 2</td>
<td>66, M</td>
<td>+</td>
<td>GPM</td>
<td>70</td>
<td>Pain reduced 50%–90%</td>
<td>+ (FU 24 mos)</td>
</tr>
<tr>
<td>Case 4</td>
<td>49, M</td>
<td>0</td>
<td>GPM</td>
<td>75</td>
<td>Pain free, off medication</td>
<td>0 (FU 32 mos)</td>
</tr>
<tr>
<td>Case 5</td>
<td>71, M</td>
<td>+</td>
<td>GPM</td>
<td>80</td>
<td>Pain free, off medication</td>
<td>Pain free, with meds (FU 13 mos)</td>
</tr>
<tr>
<td>Case 6</td>
<td>36, F</td>
<td>0</td>
<td>GPM</td>
<td>80</td>
<td>Pain free, off medication</td>
<td>0 (FU 10 mos)</td>
</tr>
<tr>
<td>Case 7</td>
<td>65, M</td>
<td>+</td>
<td>GPM</td>
<td>80</td>
<td>Pain free, off medication</td>
<td>Pain free, with meds (FU 8 mos)</td>
</tr>
<tr>
<td>Pollock &amp; Boes, 2011</td>
<td>3M, 2F; Median age 61</td>
<td>–</td>
<td>GPM</td>
<td>80</td>
<td>Pain free, off medications</td>
<td>0 (FU 19 mos)</td>
</tr>
<tr>
<td>Case 2</td>
<td>–</td>
<td>GPM</td>
<td>80</td>
<td>Pain free, off medications</td>
<td>0 (FU 16 mos)</td>
<td></td>
</tr>
<tr>
<td>Case 3</td>
<td>3M, 2F; Median age 61</td>
<td>–</td>
<td>GPM</td>
<td>80</td>
<td>Pain free, off medications</td>
<td>0 (FU 13 mos)</td>
</tr>
<tr>
<td>Case 4</td>
<td>–</td>
<td>GPM</td>
<td>80</td>
<td>Pain unchanged</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Case 5</td>
<td>–</td>
<td>GPM</td>
<td>80</td>
<td>Pain unchanged</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Williams et al, 2010</td>
<td>47, F</td>
<td>0</td>
<td>GPM</td>
<td>80</td>
<td>Pain free, off medications</td>
<td>0 (FU 11 mos)</td>
</tr>
<tr>
<td>Current report</td>
<td>99, F</td>
<td>0</td>
<td>GPM</td>
<td>80</td>
<td>Pain free, off medications</td>
<td>0 (FU 16 mos)</td>
</tr>
</tbody>
</table>

F indicates female; M, male; Cistern, cisternal segment of glossopharyngeal nerve; GPM, glossopharyngeal meatus; FU, follow up; NVC, neurovascular compression; mos, months; Gy, gray; –, no information available; +, yes; 0, no.
to receive radiosurgery for GPN. All patients were treated with the Gamma Knife.

The first report of GPN treated with radiosurgery was by Stieber et al for a patient with uncontrolled pain despite maximal medical management (17). The patient refused microvascular decompression and was offered Gamma Knife radiosurgery. The glossopharyngeal nerve root at its entry into the osseous canal of the jugular foramen was targeted. A maximum dose of 80 Gy was delivered with a single shot using the 4-mm collimator helmet. The patient had complete pain relief at 3 months without medication. However, at 6 months the pain recurred, less severe than before, and required no further intervention. The authors postulated that suboptimal coverage of the glossopharyngeal nerve at the entry into the jugular foramen may have contributed to pain recurrence.

A group from Marseilles reported seven patients with medically intractable GPN treated with radiosurgery (18, 19). Patients were treated with a range of doses (60, 70, 75, and 80 Gy). They observed a more durable response at radiosurgery doses ≥75 Gy and when targeting the glossopharyngeal meatus. The authors favored using the glossopharyngeal meatus as the target for GPN radiosurgery for three reasons: first, the opening of the jugular foramen is a good landmark well visualized on CT images; second, at this location the glossopharyngeal nerve is separated from the vagus and accessory nerves; and third, the distance from the brainstem allows higher radiosurgery doses (18). Pollock and Boes reported the results of five patients with medically resistant GPN who underwent Gamma Knife radiosurgery (13). Three patients were pain free and off medications at last follow up. Williams et al reported a case of a 47-year-old woman with medically refractory GPN who refused microvascular decompression and was successfully treated with Gamma Knife radiosurgery (20).

To date, 13 of 15 (87%) of reported patients treated with radiosurgery for GPN have achieved significant pain relief. Thus far, no adverse effects from stereotactic radiosurgery for GPN have been reported. The results tend to favor the glossopharyngeal meatus as the radiosurgery target for GPN. We chose the glossopharyngeal meatus as our target and found the CT useful for this purpose. As with any early and limited clinical experience, further study is warranted into areas of optimal radiosurgery targeting and dose for GPN. Similar dosing as that used for TN (~80 Gy) seems appropriate with a reasonable efficacy and side effect profile in reported cases (17, 18, 20).

Gamma Knife radiosurgery deserves particular consideration in the treatment of elderly patients with GPN. Our 99-year-old patient tried multiple medications and was hospitalized for life-threatening adverse effects linked to these medications. Sphenopalatine injections were only transiently effective, and she was deemed a poor candidate for surgery given her age.

Gamma Knife radiosurgery not only proved to be the only treatment option that she could tolerate, but also provided her with medication-free pain relief, which has continued for 16 months after treatment.

Herpes simplex virus meningitis complicated by ascending paralysis

Mina M. Benjamin, MD, Kyle L. Gummelt, DO, MPH, Rabeea Zaki, MD, Aasim Afzal, MD, Louis Sloan, MD, and Sadat Shamim, MD

A case of herpes simplex virus (HSV) meningitis complicated by ascending paralysis with almost complete recovery following antiviral treatment is reported. We present this case to illustrate the importance of including HSV-induced neuropathy in the differential diagnosis of acute neurologic symptoms following the viral illness.

Both types of herpes simplex virus (HSV) have been known to cause various neurologic syndromes, including meningitis (1–3). HSV-1 remains the most common cause of sporadic encephalitis, while HSV-2 infections of the central nervous system (CNS) mostly are restricted to aseptic meningitis. We report a case of HSV meningitis complicated by ascending paralysis caused by HSV to illustrate another neurological complication that can be treated with antiviral medication.

CASE DESCRIPTION

A 30-year-old African American woman presented to the emergency department (ED) with severe headache, fever (100.8°F oral), chills, photophobia, and tinnitus for 3 days preceded by several days of sore throat and nasal congestion. She was exposed to lead as a child and tested positive but never developed symptoms. She was cognitively intact. Her neck was markedly rigid. She had no skin or genital lesions. Her cranial nerves were intact. She ambulated to her car independently and without difficulty en route to the ED. She was admitted to the hospital and started on broad-spectrum antimicrobial coverage for suspected meningitis. Her initial workup at the ED and after admission is summarized in the Table. The cerebrospinal fluid (CSF) was positive for HSV by polymerase chain reaction with 540 viral copies/mL. A diagnosis of HSV meningitis was made, and antimicrobial coverage was narrowed to acyclovir.

Two days after admission, she developed bilateral lower-extremity weakness. She could barely break gravity on the left lower limb and could fight resistance briefly on the right side; she was weaker distally compared to proximally on both sides. Her bilateral deltoids were slightly weak, with full distal strength in the upper extremities. Her reflexes were brisk, including ankle jerks, and her toes were downgoing bilaterally. She had sensory loss to cold in her lower limbs to the knee with intact vibratory sensation. Within 2 weeks, the patient had significant improvement of weakness in the right lower extremity with complete return of sensation on that side. The left lower extremity, the more severely affected side, had only slight improvement in strength and had continued sensory deficits requiring inpatient rehabilitation.

A nerve conduction study (NCS) and electromyogram (EMG) 11 days after the onset of lower limb symptoms showed bilateral severe peroneal nerve axonal neuropathy, more marked distally and greater on the left than the right side. The remainder of the motor nerves tested (left median, left tibial, right tibial, and left ulnar) had velocities and amplitudes within the normal range. The F-waves were normally present in the left median and right tibial locations. EMG showed diffusely reduced recruitment in all muscles tested (left anterior tibialis, left gastrocnemius, left vastus lateralis, right anterior tibialis, and right gastrocnemius). A repeat NCS and EMG in the rehabilitation facility 35 days after symptom onset showed an overall improvement in amplitudes. She had a repeat CSF analysis for recurrent headache about 5 months after initial symptom onset, which was completely normal. One year after her initial presentation, she was fully ambulatory with rare sensation of tingling in her left leg. She was fatigued with prolonged exertion but did not require any assistive devices and had returned to work.

COMMENTS

Herpetic diseases were probably first described by Hippocrates (4). HSV-1 most commonly causes oral mucosal and facial skin lesions. HSV-2 is known for causing genital mucosal ulceration and is one of the most prevalent sexually transmitted infections worldwide. Persons with HSV-2 infection do not necessarily develop clinical disease, but most intermittently shed virus from the genital tract (5). The clinical manifestations of HSV infections are known to be diverse depending on the
Cerebrospinal fluid

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein (mg/dL)</td>
<td>237</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>52</td>
</tr>
<tr>
<td>White blood cells (per μL)</td>
<td>975 (62% lymphocytes)</td>
</tr>
<tr>
<td>Gram stain</td>
<td>Negative</td>
</tr>
<tr>
<td>HSV PCR (copies/mL)</td>
<td>540</td>
</tr>
<tr>
<td>West Nile virus Ab</td>
<td>Negative</td>
</tr>
<tr>
<td>VDRL</td>
<td>Negative</td>
</tr>
<tr>
<td>Other labs</td>
<td>Negative for adenovirus, Epstein-Barr virus, varicella-zoster virus, coxsackie Ab, cytomegalovirus, cryptococcal antigen</td>
</tr>
</tbody>
</table>

Blood

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cells (per μL)</td>
<td>14,800</td>
</tr>
<tr>
<td>Blood culture</td>
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</tr>
<tr>
<td>HIV</td>
<td>Negative</td>
</tr>
<tr>
<td>Rapid plasma reagin</td>
<td>Negative</td>
</tr>
<tr>
<td>HHV6 PCR</td>
<td>Negative</td>
</tr>
<tr>
<td>Mycoplasma IgM</td>
<td>Negative</td>
</tr>
<tr>
<td>Lyme Ab</td>
<td>Negative</td>
</tr>
<tr>
<td>Monospot</td>
<td>Negative</td>
</tr>
<tr>
<td>TSH/Folate/B12</td>
<td>Within normal limits</td>
</tr>
<tr>
<td>Urine protein electrophoresis</td>
<td>Negative</td>
</tr>
<tr>
<td>Serum protein electrophoresis</td>
<td>Negative</td>
</tr>
<tr>
<td>Heavy metal screen</td>
<td>Negative</td>
</tr>
<tr>
<td>24-hr urine lead</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Imaging

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT scan head</td>
<td>Normal with possible maxillary sinuses</td>
</tr>
<tr>
<td>MRI brain/spine with contrast</td>
<td>No acute abnormalities</td>
</tr>
</tbody>
</table>

Table. The patient’s test results upon initial workup

Ab indicates antibody; CT, computed tomography; HHV6, human herpesvirus 6; HSV, herpes simplex virus; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; TSH, thyroid-stimulating hormone; VDRL, Venereal Disease Research Laboratory test.

organ system afflicted. HSV establishes latency in sensory ganglia following initial acquisition, causing an infection that persists for life (6, 7). Both HSV-1 and HSV-2 have been associated with various neurologic syndromes, including meningitis (1–3). The CSF profile typically includes a lymphocytic pleocytosis, a normal CSF glucose concentration, and elevated protein. HSV DNA detection by polymerase chain reaction in the serum and/or CSF is the most sensitive and specific method for detecting HSV meningitis (8).

Patients with HSV meningitis can develop peripheral nerve involvement. HSV-1 has been implicated in at least one case of atypical lumbosacral pain, weakness in ankle dorsiflexion, and scattered hyperesthesia in L4 to S1 dermatomes unilaterally (2). Paresis of the bladder and anus, paresthesia of the buttocks and lower limbs, and symmetrical weakness in the lower limbs lasting 1 to 9 days (9) have been described with HSV-2. One year after HSV-2 infection, some patients developed paresis of the bladder and rectum as well as lower-extremity weakness even after clinical signs of meningitis had resolved. Given the array of neurological morbidities associated with HSV CNS infections, during the acute episode and following resolution, causes of acute neuropathies from HSV should be considered along with other more common entities, such as Guillain-Barré syndrome (GBS) (2, 4, 9–11).

Mononeuritis multiplex (MNM) is used to group multiple disorders with varying mechanisms of injury that cause damage to two or more separate peripheral nerves. MNM typically presents asymmetrically initially. It can become symmetrical with progression of the disease and can include damage to sensory, motor, and autonomic nerves (12). Causes of MNM include vasculitis, diabetes mellitus, amyloidosis, paraneoplastic syndromes, rheumatoid arthritis, and systemic lupus erythematosus.

Another consideration in our patient was GBS given the apparent ascending nature of the weakness. GBS can be protean in its presentation. Due to its multiple variants, GBS can simulate symptoms of other pathological conditions, making it difficult to reach a definitive diagnosis. The most common and classic description is the ascending paralysis seen in acute inflammatory demyelinating polyradiculoneuropathy. The disease is characterized by symmetrical weakness starting in the lower limbs, with or without sensory symptoms, progressing over hours or days to the upper body. Lower cranial nerves might be affected, leading to oropharyngeal dysphagia and respiratory failure. Sensory symptoms often include deep aching pain in weakened muscles, loss of proprioception, and areflexia (13). Acute motor and/or sensory axonal neuropathy are subtypes manifesting with motor and sensory symptoms with severe respiratory and bulbar involvement. Rarer subtypes include the Miller-Fisher variant, which presents with ophthalmoplegia, sensory ataxia, and areflexia. The pharyngeal-cervical-brachial variant presents with proximal descending weakness. In milder forms of the disease, only the cranial nerves might be affected (14). Acute pandysautonomia is another variant of GBS, which manifests with sympathetic and parasympathetic failure (13–15). GBS is often treated based on history and clinical examination. Spinal fluid and electrophysiological findings are corroborative, but often nondiagnostic. These tests may be limited because of the disease stage and presence of preexisting neuropathies.


Congenital adrenal hyperplasia refers to a spectrum of autosomal recessive inherited disorders of steroidogenesis most commonly identified on newborn screenings. We describe a young woman who presented with abdominal pain and on subsequent imaging was found to have features of congenital adrenal hyperplasia. Imaging findings, treatment, and potential complications are discussed.

CASE DESCRIPTION

A 35-year-old African American woman with known hypertension presented to the Baylor University Medical Center at Dallas emergency department with abdominal pain. Computed tomography (CT) of the abdomen and pelvis revealed sigmoid diverticulitis with contained perforation and marked bilateral adrenal gland enlargement (Figure 1, arrows). The patient underwent partial colectomy with Hartmann pouch reconstruction and did well postoperatively. The marked adrenomegaly seen on CT was initially thought to represent an infiltrative neoplasm such as lymphoma or possibly marked adrenal hypoplasia. From her medical records we discovered that she had 11β-hydroxylase deficiency as the likely explanation for her marked bilateral adrenomegaly. Subsequently the colostomy was taken down and 1 week later she developed sepsis with acute renal and hepatic failure. Repeat CT of the abdomen and pelvis revealed a large retroperitoneal hematoma in the location of the patient’s previously seen markedly enlarged right adrenal gland (Figure 2, arrows). She eventually recovered hepatic and renal function and was discharged home.

DISCUSSION

Congenital adrenal hyperplasia (CAH) is caused by deficiency in various enzymes responsible for steroidogenesis. 21-hydroxylase deficiency is seen in most CAH patients, while 11β-hydroxylase deficiency is seen in only 5% of CAH patients. Patients with 11-hydroxylase CAH have glucocorticoid deficiency requiring lifelong supplementation, 11β-deoxycorticosterone excess resulting in hypertension, and potential virilization in women.

Imaging in children with CAH has mainly entailed ultrasound evaluation, with the presence of markedly enlarged adrenal glands often associated with the diagnosis of CAH. Scott et al described correlation of adrenal size with gestational age, with subsequent authors demonstrating adrenal gland size in CAH infants above the 95th percentile (8, 10). Esser and Chaoui (2) described the evaluation of fetal adrenal gland size on prenatal ultrasound in the late first or second trimesters with findings of bilateral adrenal enlargement in two cases of infants subsequently shown to have CAH. Additional findings supporting a diagnosis of CAH on ultrasound evaluation include ambiguous genitalia and a cerebriform pattern of gyri and sulci within the gland cortex, described by both Chambrier and colleagues (8) and Avni et al (9), and also seen on histopathologic analysis in CAH. Harinarayana et al (1) evaluated six children with untreated CAH using CT: three had diffuse bilateral enlargement with preservation of adreniform shape; two had nodular/tumorous transformation of a unilateral adrenal gland with loss of adreniform shape and histopathologic analysis compatible with hyperplasia; and the final patient showed equivocal enlargement.

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Figure 1. Severe adrenomegaly (arrows) is seen on noncontrast CT. L indicates liver; P, pancreas; S, stomach; A, aorta; I, inferior vena cava; PV, portal vein.
Adrenal hemorrhage is an uncommon complication seen in a variety of conditions: trauma, stress, hemorrhagic diathesis or coagulopathy, underlying adrenal tumors, and idiopathic disease (5–7). The clinical danger entailed in bilateral adrenal hemorrhage is acute adrenal insufficiency in the setting of severe illness, which can lead to rapid cardiovascular collapse and death (6). The incidence of hemorrhage in the setting of CAH is unknown.

It has been established that accurate clinical history results in more accurate CT interpretation (11). This case nicely illustrates the need for accurate clinical information and comparison of relevant prior examinations to guide appropriate patient management. Without such integration in this case, the patient may have undergone an unnecessary costly biopsy and its associated risks to exclude the possibility of lymphoma, as initially questioned on CT scan.

Figure 2. Large right retroperitoneal hematoma (arrow) which measured up to 15.9 x 12.3 cm is present in the area of the previously seen enlarged right adrenal gland. There is no evidence of contralateral hemorrhage (arrowhead).

A 55-year-old man was hospitalized for a neurologic and infectious workup after having hallucinations and productive cough for 2 days. During hospitalization, he experienced dark stools with an acute drop in hemoglobin. Upper endoscopy and colonoscopy were negative for an identifiable source of bleed. Capsule endoscopy was later done and subsequently an anteroposterior abdominal radiograph confirmed the presence of a retained capsule near the junction of the descending and distal transverse colon, likely contained within a colonic diverticulum. In the interim, the patient developed acute right-sided lumbar radiculopathy prompting emergent lumbar spine magnetic resonance imaging (MRI). During the scanning process, the retained capsule was seen and the test was immediately terminated without harm to the patient. Device retention is a complication unique to capsule endoscopy, occurring at a rate of 1% to 1.7%; retained devices are considered a danger and contraindication to MRI.

Capsule endoscopy device retention and magnetic resonance imaging

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Case Description

A 55-year-old man with primary progressive multiple sclerosis and prior pulmonary embolism on chronic anticoagulation was hospitalized for a neurologic and infectious workup after presenting with a 2-day history of hallucinations and productive cough. Following 6 days of hospitalization, the patient noted dark feces accompanied by an acute drop in hemoglobin (from 9.0 to 7.4 g/dL) and positive HemoQuant (>15.6 g Hb/g; normal ≤2 g Hb/g). One unit of packed red blood cells was transfused, and an upper endoscopy was performed without finding an identifiable source of bleed. A colonoscopy visualized no bleeding source up to 15 cm from the ileocecal valve. Computed tomography (CT) enterography noted three subcentimeter enhancing distal ileal lesions radiographically suspicious for carcinoid. To further characterize these lesions, a capsule endoscopy was pursued. Three days after the procedure, the patient had not reported capsule passage despite several bowel movements. An anteroposterior abdominal radiograph disclosed a retained capsule adjacent to the proximal descending and distal transverse colon, likely contained within a colonic diverticulum (Figure 1).

The following day, the patient developed acute right-sided lumbar radiculopathy associated with severe pain. Emergent MRI of the lumbar spine was ordered. During performance of the MRI localizing sequence, a focal susceptibility effect was noted in the region of the pelvis (Figure 2). Prompt investigation by the radiology staff correlated this finding to the prior radiographic report demonstrating the retained capsule. The procedure was immediately terminated without harm to the patient. The large hemoglobin drop was attributed to a large gluteal hematoma identified on a subsequent CT scan. Two days later, the capsule was passed; upon review of the capsule study, no significant pathology was demonstrated to further characterize the suspicious lesions previously noted on CT imaging.
DISCUSSION

Device retention is a complication unique to capsule endoscopy. Recent studies have reported the rate of retention to be between 1.0% and 1.7% of patients undergoing the diagnostic procedure (1, 2). Common factors that predispose individuals to device retention include Crohn’s disease, neoplastic lesions, non-steroidal antiinflammatory drug–induced enteropathy, stenosis, and adhesions (1). The appearance of retained capsules on MRI has been previously documented (3). The feared possible complication of MRI with capsule retention is migration of the capsule and the potential for bowel injury or perforation. We were unable to identify a prior case report that described patient injury in the setting of retained capsules during MRI, but retained devices are considered a danger and contraindication to MRI (4). While this case represents a near-miss of such an event, it highlights the need for enhanced provider awareness as well as institutional safeguards against ordering MRI studies prior to the confirmed passage of an endoscopic capsule. Confirmation of device passage is quickly achieved through abdominal radiographic imaging and should be employed in circumstances where suspicion remains for retention.

We describe transthoracic echocardiograms in three patients with combined quadricuspid aortic valve and prolapsing mitral valve. None had symptoms of cardiac dysfunction. Two patients had precordial murmurs. A third patient was referred for evaluation of infective endocarditis. The fact that a quadricuspid aortic valve is clearly a congenital anomaly supports the view that mitral valve prolapse is a congenital anomaly that may be more strongly associated with quadricuspid aortic valves than once thought.

The quadricuspid aortic valve (QAV), although uncommon, is clearly recognized as a congenital defect. Mitral valve prolapse (MVP), in contrast, is not often thought of as a congenital anomaly. The occurrence of both in a series of patients supports the view that MVP and QAV may be associated congenital anomalies. A description of findings in these three patients and a summary of previously reported such cases are the purposes of this report.

DESCRIPTION OF PATIENTS

Pertinent clinical features in each of the three patients are summarized in Table 1. Echocardiograms were performed in cases 1 and 2 to evaluate asymptomatic precordial murmurs, and in case 3, to evaluate infective endocarditis. These studies disclosed a QAV with mild aortic regurgitation (Figures 1a, 1b). All patients had normal left ventricular systolic function and normal chamber sizes. The three patients also had MVP but with varying degrees of mitral regurgitation (MR) (Figure 1c, 1d, 2d). There was no evidence of vegetation on any of the valves. No patient required surgery for their dysfunctional valves. None had aortic stenosis, coronary anomalies (Figure 2c), or a family history of congenital heart or connective tissue diseases.

DISCUSSION

Each of these asymptomatic patients had both a QAV and MVP. The occurrence of both these valvular anomalies in the same patient supports the observation that they are of congenital origin and may be associated. Five other cases of patients with QAV and MVP have been reported (1–5). To our knowledge, such a strong association between QAV and MVP in a case series has not been described.

Table 1. Features of three patients with quadricuspid aortic valve and mitral valve prolapse

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>41</td>
<td>18</td>
<td>54</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Type of QAV</td>
<td>4E</td>
<td>4E</td>
<td>3E1U</td>
</tr>
<tr>
<td>Type of murmur</td>
<td>MR</td>
<td>AR</td>
<td>None</td>
</tr>
<tr>
<td>Aortic regurgitation (0–4+)</td>
<td>1+</td>
<td>1+</td>
<td>1+</td>
</tr>
<tr>
<td>Mitral regurgitation (0–4+)</td>
<td>4+</td>
<td>1+</td>
<td>1+</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>120/80</td>
<td>140/80</td>
<td>185/90</td>
</tr>
<tr>
<td>Heart rate (beats/minute)</td>
<td>60</td>
<td>70</td>
<td>90</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>21</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>Left ventricular end-systolic diameter (cm)</td>
<td>3.9</td>
<td>3.0</td>
<td>3.7</td>
</tr>
</tbody>
</table>

*Valvular dysfunction scale: 0, none; 1–2+, trace/mild; 3+, moderate; 4+, severe. 4E indicates four equally sized cusps; 3E1U, three larger equal cusps and one smaller cusp; MR, mitral regurgitation; AR, aortic regurgitation.

Table 2 summarizes the clinical findings in five previously reported cases. This review reveals a slight male predominance. The two most common types of QAV were Hurwitz and Roberts type A (four equally sized cusps) and type B (three larger equal cusps and one smaller cusp) (6). Advanced age did not correlate with worsened aortic regurgitation (AR) but did correlate with worsened MR. Only one patient had aortic stenosis and severe AR requiring surgery. Two cases had severe MR requiring surgery.

The occurrence of MVP in patients with the more common congenital aortic valvular anomaly, the bicuspid valve, has been described previously. In a recent study by Roberts...
Table 2. Summary of reported cases of combined quadricuspid aortic valve and mitral valve prolapse

<table>
<thead>
<tr>
<th>Reported cases</th>
<th>Year of publication</th>
<th>Age of diagnosis (yrs)</th>
<th>Gender</th>
<th>QAV type</th>
<th>AR*</th>
<th>AS*</th>
<th>MR*</th>
<th>Method of diagnosis</th>
<th>Valve replaced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yildirim et al (1)</td>
<td>2008</td>
<td>10</td>
<td>M</td>
<td>3E1U</td>
<td>4+</td>
<td>4+</td>
<td>0</td>
<td>OR</td>
<td>AV</td>
</tr>
<tr>
<td>Di Pino et al (2)</td>
<td>2008</td>
<td>11</td>
<td>F</td>
<td>3E1U</td>
<td>0</td>
<td>0</td>
<td>1+</td>
<td>TTE</td>
<td>None</td>
</tr>
<tr>
<td>Ozlü et al (3)</td>
<td>2008</td>
<td>72</td>
<td>M</td>
<td>4E</td>
<td>3+</td>
<td>0</td>
<td>4+</td>
<td>TTE</td>
<td>MV</td>
</tr>
<tr>
<td>Cooke et al (4)</td>
<td>2000</td>
<td>75</td>
<td>M</td>
<td>4E</td>
<td>1+</td>
<td>0</td>
<td>4+</td>
<td>TEE</td>
<td>MV</td>
</tr>
<tr>
<td>Jagannath et al (5)</td>
<td>2011</td>
<td>75</td>
<td>F</td>
<td>2E2e</td>
<td>3+</td>
<td>0</td>
<td>3+</td>
<td>TTE</td>
<td>None</td>
</tr>
</tbody>
</table>

*Valvular dysfunction scale: 0, none; 1–2+, trace/mild; 3+, moderate; 4+, severe.
2E2e indicates two equal larger cusps and two equal smaller cusps; 3E1U, three larger equal cusps and one smaller cusp; 4E, four equally sized cusps; AR, aortic regurgitation; AS, aortic stenosis; AV, aortic valve; MR, mitral regurgitation; MV, mitral valve; OR, operating room/at surgery; TEE, transesophageal echocardiogram; TTE, transthoracic echocardiogram.

et al (7), four patients who had a congenitally bicuspid aortic valve and MVP required replacement of both valves. Our review, however, demonstrated that no patients with a combined QAV and MVP required surgery of both valves.

In patients with QAV, the attention is usually focused on that valve in particular, and so the association with MVP may not have been as strongly linked. Due to the rarity of both anomalies, it is difficult to judge the exact level of association, but it may be stronger than previously noted.

Supplementary material


Figure 1. Case 1 transesophageal echocardiogram. Short-axis view of the type A quadricuspid aortic valve (a) closed and (b) open. (c and d) Midesophageal view of the mitral valve prolapse (arrow).
Figure 2. Case 2. (a, b, c) Cardiac computed tomography scan: (a) short-axis view of the type A quadricuspid aortic valve; (b) view of the quadricuspid aortic valve with symmetrical cusps (RCC, right coronary cusp; LCC, left coronary cusp) and coronary ostia (arrows); (c) view of the coronary arteries revealing no coronary anomalies. (d) Transesophageal echocardiogram of the mitral valve prolapse at the midesophageal level.

A 64-year-old woman with systemic arterial hypertension, dyslipidemia, cigarette smoking, and a history of stent placement in the proximal left anterior descending coronary artery for an 80% diameter stenosis returned to the hospital a year later because of pain similar to the pain she had before stent placement. She also described one episode of dizziness and a feeling of faintness while walking.

An electrocardiogram recorded during this admission showed group beating with four sinus-initiated complexes separated by a pause from three sinus-initiated complexes; pauses also began and ended the tracing (Figure). All seven sinus-initiated impulses had P-R intervals of 0.15 seconds. The intervals separating the first four P waves were 1.04, 1.02, and 0.99 seconds, respectively, and the P-P intervals of the group of three complexes were 1.03 and 0.99, respectively. The P-P interval of the middle pause was 1.87 seconds and, thus, was shorter than 2 times any single P-P interval. These are the findings of typical second-degree sinoatrial (SA) block, type I, with 5:4 and 4:3 Wenckebach periods. The SA conduction times increased in progressively smaller increments so that the P-P intervals became progressively shorter, and the P-P interval containing the nonconducted impulse was shorter than 2 times any single P-P interval.

Unlike typical second-degree atrioventricular (AV) block, type I, where the lengthening of the P-R intervals in progressively smaller increments can be measured, because sinus node depolarization does not register on the standard electrocardiogram, SA conduction times cannot be measured. SA block, type I, is diagnosed by finding progressive shortening of the P-P intervals.

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intervals before the pause with no P wave. This is analogous to the progressive shortening of the R-R intervals before the nonconducted P wave in typical second-degree AV block, type I. Also, analogous to the situation in type II AV block, with type II SA block, SA conduction time does not increase before the nonconducted impulse; the P-P intervals do not decrease; and the pauses are exact multiples of the basic P-P interval (1).

The patient’s electrocardiogram also showed several published voltage criteria for left ventricular hypertrophy when $1 \text{mV} = 10 \text{mm}$: $RI > 13 \text{mm}$, $SaVR > 14 \text{mm}$, $SV_1 + RV_5$ or $V_6 > 35 \text{mm}$, $R + S$ in any limb lead $> 19 \text{mm}$, and in a woman $\geq 40$ years old $RaVL + SV_3 > 12 \text{mm}$ when $TV_1 \geq 2 \text{mm}$ (2–4). Widespread slight nonspecific ST-segment sagging also was present. Her echocardiogram was normal.

The patient underwent repeat coronary arteriography, which revealed a patent left anterior descending stent and nonobstructive coronary arterial disease, and further invasive interventions were considered unnecessary. She continued to have near-syncopep episodes. A review of her electrocardiograms over the past 18 months revealed another episode of SA block and a number of other findings suggesting sick sinus syndrome: sinus bradycardia as slow as 32 beats per minute, at times with a junctional escape rhythm; slow ectopic atrial bradycardia; and sinus pauses of up to 2 seconds that did not fulfill criteria for SA block. Most of this time she was on a beta-blocking drug, at first atenolol 25 mg per day and subsequently carvedilol 6.25 mg once or twice per day, that may well have accentuated her bradyarrhythmias.

Her primary physicians thought the beta-blockers a necessary part of her drug regimen for coronary arterial disease, and the bradyarrhythmias were managed with an AV sequential electronic pacemaker (5).

An abnormal electrocardiographic stress test is typically characterized by ST segment depression. In rare cases, ST segment elevation is observed, which, in the absence of diagnostic Q waves, has anatomic specificity for localized myocardial ischemia. Most instances of ST elevation occurring during cardiac stress testing have been observed with exercise, with only six cases reported with pharmacologic stress. Despite different physiologic mechanisms for inducing myocardial ischemia, development of ST segment elevation during pharmacologic stress, as illustrated by the present case, may also be indicative of critical coronary stenoses, warranting urgent coronary arteriography.

CASE PRESENTATION

An 87-year-old man presented with a 1-month history of worsening intermittent “burning” epigastric pain that radiated to his substernal area. The pain was associated with nausea, eructations, and a bad taste in his mouth, but he denied accompanying dyspnea or diaphoresis. The patient had received a drug-eluting stent approximately 12 years earlier. Subsequent cardiac catheterization 2 years prior to the present episode revealed a patent stent and no new coronary narrowing. His initial troponin I level was <0.05 g/dL, and his electrocardiogram revealed symmetric T wave inversions across the precordium (Figure 1). Given the atypical nature of his symptoms, the
patient underwent a pharmacologic nuclear stress test using regadenoson, a vasodilator similar to adenosine. Following the intravenous administration of 0.4 mg (5 mL) of regadenoson, the patient began complaining of “not feeling well,” and he was given 100 mg (4 mL, 25 mg/mL) of intravenous theophylline. Initial imaging demonstrated a large area of moderately reduced perfusion involving the ventricular septum, left ventricular distal anterior and inferior walls, and apex. Approximately 8 minutes into recovery, sudden severe substernal pain appeared. Electrocardiogram revealed ST segment elevation and hyperacute T waves in leads V2 to V4 (Figure 2). The procedure was terminated immediately and the patient was taken to the cardiac catheterization laboratory. Serum drawn at that time revealed that the troponin I had risen to 0.3 ng/mL. Coronary arteriography revealed a long ulcerated lesion in a large left anterior descending coronary artery just beyond the takeoff of the first diagonal. A drug-eluting stent was placed across the stenotic area without incident, and the patient had an uneventful recovery with complete resolution of his symptoms. He was asymptomatic when seen in follow-up a month after the procedure.

DISCUSSION

Exercise stress testing is frequently limited by the inability of individuals to elevate their heart rate to levels likely to induce myocardial ischemia. Accordingly, pharmacologic stress tests, most often using vasodilators, are employed as a substitute for the traditional exercise stress test. Exercise increases myocardial oxygen demand by increasing heart rate and blood pressure and produces ischemia in areas distal to coronary artery stenosis. In contrast, vasodilator pharmacologic stress tests cause myocardial ischemia by an entirely different mechanism. The pharmacologic agents (dipyridamole, adenosine, or regadenoson) promote coronary vasodilatation through activation of A2A (primarily) and A2B adenosine receptors. Perfusion is increased to healthy well-perfused areas and, conversely, “stolen” away from the stenotic areas, which are already maximally vasodilated.

ST segment depression is the most common electrocardiographic abnormality encountered with stress testing, whether exercise or pharmacologic, and is thought to be indicative of subendocardial ischemia. Conversely, exercise-induced ST segment elevation is rare, occurring in 1.3% of patients (1), and may denote transmural ischemia. Exercise-induced ST segment elevation may also occur in the absence of ischemia in areas of previous myocardial infarction (with diagnostic Q waves and accompanying wall motion abnormalities) (2–4). In contrast to stress-induced ST segment depression, which tends to occur in the inferolateral electrocardiographic leads regardless of the site of coronary artery obstruction, exercise-induced ST segment elevation is usually localized to the area of ischemia (5, 6). Vasodilator stress-induced ST segment elevation appears to be especially rare; review of the medical literature produced only two cases using dipyridamole (2, 7), three cases using adenosine (8–10), and one recently reported case using regadenoson (11). In all but one of these studies, coronary arteriography confirmed ≥75% stenoses in at least one major coronary artery. It has been hypothesized that the lone case without significant coronary artery disease may have been due to overexpression of A1 and A3 adenosine receptors (in comparison to A2 receptors), which...
have been shown to play an inhibitory role in the regulation of coronary blood flow (12, 13). Our case is consistent with the limited experience in the literature and suggests that ST segment elevation in response to vasodilator stress may indicate a critical lesion requiring emergent coronary intervention. Our experience also emphasizes the need for continued close monitoring of these individuals until definitive measures can be taken.

Chylopericardium following orthotopic lung transplantation

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Chylopericardium is an uncommon condition, reported to occur following routine cardiac surgery, orthotopic heart transplantation, cardiac trauma, intrathoracic tumors, or infection. It has not, to date, been reported following uncomplicated orthotopic lung transplantation. This article describes chylopericardium following bilateral orthotopic lung transplantation.

Chylopericardium was first described by Hasebrock in 1888 (1). In 1954, the term “primary chylopericardium” was offered by Groves and Effler for idiopathic cases without an apparent cause (2). Chylopericardium has been reported also as a consequence of various diseases and as a complication of surgical procedures (3). It has been reported rarely following cardiac transplantation (4), but has never been reported as a complication of lung transplantation. This report is the first to describe chylopericardium following lung transplantation.

CASE REPORT

A 54-year-old woman, who had asthma as a child and smoked cigarettes as an adult, suffered from chronic obstructive pulmonary disease complicated by pneumothorax requiring tube thoracostomy in the right hemithorax at age 39 (1997). She did not have alpha-1-antitrypsin deficiency or lymphangioleiomyomatosis, and her chronic obstructive pulmonary disease was treated with inhaled beta-agonist bronchodilators, steroids, and acetylcholine receptor antagonists. She had blood type A. She weighed 142 pounds and was 64 inches tall. She had impaired bronchospirometry with a forced expiratory volume in 1 second of 20% predicted, diffusion of carbon monoxide of 14% predicted, and BODE score (body mass index, airflow obstruction, dyspnea, and exercise capacity) of 9. Her right lung perfusion was 54% and left lung perfusion, 46%. Right heart catheterization demonstrated normal pulmonary arterial pressures.

In May 2012, she underwent an uncomplicated bilateral sequential lung transplantation through a thoracosternotomy based off of the fourth intercostal space. Cardiopulmonary bypass was not required. Her immediate postoperative intensive care unit course was uneventful. Immunosuppression induction therapy and postoperative immunosuppression maintenance were accomplished with corticosteroids, azathioprine, and tacrolimus. She was discharged 2 weeks later.

Her early posttransplant course was complicated by atrial fibrillation treated with flecainide and with hyponatremia thought to be secondary to a syndrome of inappropriate antidiuretic hormone, which responded to free water restriction. She also experienced anemia (hemoglobin 6.5 g/100 mL) with a high serum ferritin level indicative of an iron reutilization defect. Her lung function following transplantation was excellent, with a peak postoperative forced vital capacity of 3.26 L.

Beginning 4 months following her transplant, routine imaging studies demonstrated an asymptomatic increase in the size of her pericardial silhouette (Figure 1). Transthoracic echocardiogram demonstrated a large effusion with mild right atrial compression. In October 2012, she underwent a subxyphoid pericardial exploration and drainage, with evacuation of 650 mL of opaque, lactescent sanguinous fluid (Figure 2) with a triglyceride level of 2139 mg/dL and leukocyte count of 619/μL, with a differential count of 80% lymphocytes. Viral, mycobacterial, and fungal cultures, as well as Gram stain and acid-fast stains, were negative.

Postoperatively she was maintained on a nonfat diet and then transitioned to a low-fat diet. Three days after operation, her chest tube output remained low and serous in nature, despite escalation of her dietary fat intake. She was discharged without recurrence of her effusion and is convalescing well on an unrestricted diet with no evidence of recurrent chylopericardium on evaluation with a chest radiograph and echocardiogram 1 month later.

DISCUSSION

Chylous effusions in the pericardial space can arise spontaneously, following penetrating or blunt chest trauma, or following surgical procedures (2, 3). Known specific causes include...
congenital mediastinal lymphangiectasia (cystic hygroma) (5), gastric carcinoma (6, 7), lymphangiomatosis of the chest/Gorham syndrome (8, 9), primary mediastinal neoplasms such as lymphoma and germ cell tumor (6, 10), mediastinal hamartoma (8), infection with tuberculosis (11), deep vein thrombosis with superior vena cava syndrome (12), pancreatitis (13), allergic alveolitis (14), and Behçet’s disease (15). A review in 1935 identified only three cases of chylopericardium (12), and a more comprehensive review in 2006 identified 33 reported cases, the most common etiology being idiopathic (3). Postoperative causes of chylopericardium reported in the literature include mitral valve replacement (4, 16, 17), coronary artery bypass grafting with left internal thoracic artery harvesting (18), congenital heart surgery (19), and orthotopic heart transplant (4, 20).

Although chylothorax is a commonly reported complication of orthotopic lung transplantation (21) and a rare complication of combined heart/lung transplantation (22), a review utilizing Ovid, MEDLINE, PubMed, and the Cochrane Library databases failed to isolate a single report of chylopericardium following isolated orthotopic lung transplantation. Accordingly, the current case report represents the first of a direct individual pulmonary vein anastomosis. This area of posterior parietal pericardial dissection around the paired pulmonary veins could allow a path of ingress of posterior mediastinal, peribronchial lymph to the pericardial space; absorbed oral fat in the form of chylomicrons could then enter into the pericardial space in this fashion.

The treatment of chylopericardium should be disease specific, with the goals of decreasing chyle production, relieving or treating tamponade (16, 23, 24), or preventing secondary constrictive pericarditis (10, 25); treatment is also tailored to mitigate against the deleterious consequences of lymph depletion in regards to nutritional status, fluid and electrolyte depletion, and immunologic side effects of chronic lymphocyte reduction (25). For idiopathic chylopericardium, successful treatment has most often been reported with simple drainage, either by pericardiocentesis or surgical transmediastinal drainage (19). Dietary modifications to a nonfat or medium-chain triglyceride diet have been reported as useful; refractory cases have required total parenteral nutrition and occasionally the addition of octreotide to suppress chylomicron production. Idiopathic chylopericardium refractory to drainage and dietary modifications and postsurgical or posttraumatic chylopericardium most often require either pericardial drainage or creation of a pleuropericardial window, with or without thoracic duct ligation. Malignancy-related chylopericardium, reported after signet-cell gastric cancer (7), may require the addition of chemotherapy and radiation. Surgical pericardial drainage can be transmediastinal (through the subxyphoid space of Larrey, as occurred in this case) or transthoracic via thoracostomy or video-assisted thoracoscopic surgery, especially if creation of a pleuropertical window is necessary (3, 4, 16, 18, 19, 24). Creation of a pleuropertical window following lung transplantation, in the absence of thoracic duct ligation, may not represent an optimal approach, as there remains the possibility that the chylopericardium will only be replaced with a refractory chylothorax.
Abnormal origin of the left internal thoracic artery detected only by computed tomography

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The origins of the branches of the subclavian artery are known to be variable. We present the case of a 55-year-old man whose coronary artery bypass surgery necessitated the use of the internal thoracic artery as he lacked other suitable venous conduits. The left internal thoracic artery appeared to be absent on subselective subclavian angiography. Computed tomographic angiography revealed a previously undescribed anomaly: origin of the internal thoracic artery from a thyrocervical trunk arising directly from the aortic arch.

CASE REPORT

A 55-year-old steel company supervisor with multiple coronary risk factors had previously undergone multivessel coronary stenting following an abnormal stress test. One year later, a repeat stress test was again abnormal, and a new drug-eluting stent was placed in a de novo lesion. Dual antiplatelet therapy was continued. Several days later the patient reported a progressively severe headache, and computed tomography (CT) scanning revealed an acute right temporoparietal hemorrhagic infarct. All antiplatelets were discontinued. Seven months later, he developed angina pectoris, and repeat coronary angiography showed multiple stenoses necessitating coronary artery bypass grafting (CABG).

During angiography, the operator was unable to visualize the left internal thoracic artery (ITA) even on subselective injections of the subclavian artery (SCA). As the patient had previously undergone bilateral lower-extremity vein stripping, knowledge of the presence and suitability of the ITA was deemed essential given the paucity of potential graft conduits. CT angiogram revealed the presence of the left ITA arising from the thyrocervical trunk (TCT), which arose directly from the aortic arch (Figure). Flow in the ITA was not impeded.

During the operation the left ITA was successfully harvested and had visibly normal flow. It was then sewn in a side-to-side fashion to the large diagonal ramus, and then it was coursed over and was sewn end-to-side to the intramyocardial portion of the left anterior descending coronary artery. The patient’s postoperative recovery was smooth, and 6 months later he was active and symptom free.

DISCUSSION

The ITA, TCT, vertebral artery, and costocervical trunk make up the four major branches of the first part of the SCA. The ITA normally arises from the anteroinferior aspect of the first part of the SCA at about the same level as the TCT, which has its origin on the anterosuperior aspect of the SCA. The TCT has three main branches: 1) the inferior thyroid artery, 2) the transverse cervical artery, and 3) the suprascapular artery (1). Variances in the origin of both the ITA and TCT have been reported. The ITA has been reported to arise anomalously from the TCT as well as from each of its branches (2–4). In addition, the ITA has been reported to arise anomalously from the third intercostal artery (5), from the lateral junction of the SCA and the aorta (6), from the distal part of the SCA (2), and from the axillary artery (2) and to be unilaterally as well as bilaterally absent (7). TCT origin variances include...
origin on the vertebral artery (8), as a common trunk with the vertebral artery or the ITA (3, 9), as well as the absence of the TCT with its branches directly originating from the SCA (2). Additionally, there has been one previously reported case of a common trunk of the left ITA and TCT arising from the ipsilateral vertebral artery (8).

Our patient is the first reported example of an origin of the left ITA from the TCT arising directly from the aortic arch. The clinical implication of our finding is that if the ITA appears to be “absent” on conventional invasive angiograms, there is a great likelihood that it is present but arises from an anomalous location. Unilateral as well as bilateral ITA absences have been reported (7), reinforcing the importance of confirming ITA anatomy in circumstances such as that seen in our patient. A CT angiogram is a useful method of surveying arterial course and suitability as a bypass conduit.

It has been suggested that a common origin of the ITA and TCT would complicate surgical grafting procedures, as the curved direction of the common trunk makes the implant vulnerable to kinking from traction in harvesting (10). This was not observed in our patient.

As in the case of our patient, there are several instances in which it would be necessary to obtain angiographic evidence of proper flow to the ITA prior to CABG. Subclavian stenosis occurring proximal to the ITA may jeopardize flow and produce myocardial ischemia when the ITA is used in CABG (11). Osborn et al found significant subclavian artery stenosis in 6.8% of patients who underwent SCA angiography prior to CABG (12). Patients with coarctation of the aorta, both repaired and unrepaired, may have severely calcified ITAs unusable for CABG (13, 14). Perhaps most importantly are cases of collateralization of the ITA to a lower limb in response to aortic or iliac artery stenosis or occlusion, as well as with coarctation (15). In these cases, the ITA is a critical conduit and its reimplantation may result in lower limb ischemia. Finally, patients who are being evaluated for repeat CABG may have had damage to the ITA during their previous procedure. Feit et al noted two instances in their study in which the ITA had been cut off or snared in the wire sutures from a previous bypass procedure, rendering it unusable as a graft (16).

Feit et al recommend making ITA angiography a routine part of a diagnostic coronary angiography once the patient has been deemed a surgical candidate, as significant findings occurred in 15% of cases (16). A similar study by Bauer et al revealed surgically significant findings in 30% of patients, 4% to 5% of which required modification of surgical strategy (17).

Avoidance of lower-limb amputation by surgical implantation of autologous stem cells

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A 69-year-old Caucasian man was referred to Baylor University Medical Center at Dallas with resting lower-extremity pain and a nonhealing sore above his right ankle (Rutherford chronic ischemia stage 5 of 6) after having failed multiple attempts at revascularization. He was enrolled in a clinical research trial using adult autologous stem cells for treatment of critical limb ischemia. Autologous stem cells from the patient’s pelvic bone marrow were harvested, concentrated in the operating room, and reinjected into the lower leg along the vasculature below the level of complete occlusion of the popliteal artery and around the ulcer. After 3 months, the patient had significant improvement in his ankle brachial index, which increased from 0.10 to 0.40 (normal 0.9–1.01), and early healing of the ulcer. After 12 months, the ulcer was fully healed. Healing of the sore has persisted for 3 years.

In approximately 30% of cases of critical limb ischemia (CLI), revascularization will fail and amputation will be required (1). To avoid amputation, a patient was enrolled in a novel study in which the use of autologous bone marrow–derived stem cells facilitated the healing of his ischemic leg wound and led to resolution of his ischemic rest pain.

CASE PRESENTATION

A 69-year-old Caucasian man with long-standing peripheral arterial disease (PAD) was referred for evaluation of lower-extremity revascularization for limb salvage or possible amputation. He smoked 40 cigarettes daily for 56 years until 2009. He also had a history of hyperlipidemia, hypertension, chronic obstructive pulmonary disease, and heavy ethanol intake until 2008.

The patient’s first procedure for PAD occurred in 2002, when he underwent traditional bilateral femoral-popliteal bypass surgery using saphenous vein grafts. The right femoral to popliteal graft failed in 2008, 6 years after its construction, and a second graft surgery was performed using cadaveric vein from his external iliac to his popliteal artery. This graft occluded acutely but was successfully reopened with thrombectomy and placement of a patch graft to the distal anastomosis during the same hospitalization.

By January 2009, the second graft had also completely occluded and a third right graft surgery was performed using cadaveric vein, this time from the external iliac to the posterior tibial artery at the ankle. Unfortunately, this graft became infected and had to be removed a month later. A saphenous vein harvested from the left leg was then placed to the right ankle but could not prevent the wound dehiscence that occurred above the right ankle. Four months after wound debridement, the patient continued to have rest pain and the wound. Angiography showed complete occlusion of the right superficial femoral artery, right popliteal artery, and all right leg grafts.

Because of his history of acute graft thrombosis requiring surgical thrombectomy, he was treated with warfarin therapy for over a year to keep his grafts open. This had to be discontinued, however, after an episode of gastrointestinal bleeding. During this 7-year period the patient underwent eight additional procedures, including five angiography procedures with four angioplasties and three procedures for PAD on the contralateral leg. He thus had had over 11 hospitalizations and procedures for PAD in the 7 years before stem cell treatment.

At the time of his referral, amputation had been recommended to him, as he had had claudication for 7 years, resting foot pain for 6 months, and a nonhealing ulcer above his ankle for 4 months. When it was determined that the patient had no additional revascularization options for limb salvage, he was enrolled in Harvest Technologies’ “Feasibility Study of the Safety and Activity of Autologous Bone Marrow Aspirate Concentration (BMAC) for the Treatment of Critical Limb Ischemia Due to Peripheral Arterial Occlusive Disease” (2). His right ankle brachial index at the time of referral was 0.1, with a toe brachial index of 0. His PAD was consistent with Rutherford chronic ischemia stage 5 (rest pain with ulceration).

The patient was taken to the operating room where he was randomized into the study by two nonblinded research staff. All other research staff, operating room staff, and the vascular surgery team were excluded from the operating room during this procedure.

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time to maintain the blind. For subjects randomized to receive placebo, a mixture of peripheral blood and saline was made that appeared identical to the prepared stem cell concentrate. In addition, small amounts of bone marrow were collected from each hip so all patients remained blinded to their treatment. Because this patient was randomized to receive stem cells, the hematologist harvested, under anesthesia, 240 mL of bone marrow from both iliac crests.

After preparation of the stem cell mixture, blinded staff returned to the operating room and treated the patient with 40 one-mL injections into his right leg below the knee. Sonographic guidance was used to inject the concentrate along blood vessels beyond the level of the complete vascular occlusion, which in this case was the right popliteal artery, as well as around the edges of the wound.

After 3 months, the patient had significant improvement in his ankle brachial index, which increased from 0.10 to 0.40 (normal 0.9–1.01) (Figure 1). By 12 months, the wound had completely healed and has remained healed through 3 years of follow up (Figure 2). The patient continues to have claudication with significant exertion, but this does not interfere with his usual daily activities, which include baling hay and other rigorous activities in the management of his farm. Since the stem cell implantation procedure, he has had no hospitalizations or operative procedures.

DISCUSSION

Common manifestations of severe CLI are rest pain and tissue loss in the affected extremity (1, 3). Current therapies for improving extremity blood flow include endovascular and surgical revascularization. To generate wound healing in an ischemic limb, blood flow must be restored to the matrix of the wound via blood vessel formation (4–6). Unfortunately, this cannot occur in adults with critical blockages in arteries, and patients with CLI often develop secondary wounds (6). The goal of treatment for CLI-originated wounds is to induce “therapeutic angiogenesis” (6).

This patient developed a wound that could not be healed in the absence of adequate blood flow. He was enrolled in a pilot trial using bone marrow–derived stem cells, which were collected, processed, and immediately returned to the patient in the same procedure (2, 7). In this procedure, a nonspecific mononuclear cell mix was implanted with minimal time spent outside the patient’s body. Because the goal was to encourage growth of collateral vascular circulation, the cells were injected along the blood vessels below the critical vascular obstruction, which in this patient occurred at the knee. While it should take some time for any repair process to be effective, this patient had clear evidence of improvement by days 32 and 53 postprocedure. The sore completely healed by 12 months postprocedure and has remained healed for 3 years after stem cell treatment.

Stem cells are believed to work via a number of mechanisms. The original belief was that adult autologous stem cells can turn into, and replace, any damaged adult cells (8). More recent literature, however, suggests that stem cells may function as repair “traffic cops,” directing both circulating and local cells to areas of tissue damage and stimulating their repair functions (9). Because using body resources to repair tissues is a costly process, activated stem cells appear to have a built-in time-limited function, encouraging local repair between 3 and 12 months. This was demonstrated by the fact that improvement in the ankle brachial index made no further gains after 3 months. At that time, the stem cells may have either evolved into adult quiescent cells or undergone apoptosis and autodestructed.

This clinical research trial demonstrated a statistically significant 50% reduction in the need for amputation in patients with CLI and tissue loss (7). This patient continues to have some exercise-induced claudication, but he is able to perform the functions required of his daily life. Other stem cell clinical research trials for PAD have shown similar increases in ankle brachial indices and an overall decrease in rest pain (3). The first of these trials was the TACT study, which was published in 2002 in Japan (10). This was the same year this patient’s disease was first diagnosed and treated.

These early clinical research trials using stem cells to treat advanced tissue disease only enroll patients with end-stage disease for whom no other therapies are available. This is inappropriate because this is the only patient population for whom the risk-to-benefit ratio is favorably balanced, given our early state of understanding. Interestingly, most stem cell clinical research studies have had excellent early safety profiles, as adult autologous stem cells are well tolerated. Potential risks are due predominantly to manipulation of the cells and the therapeutic procedure performed to deliver the cells to the tissues.

The full potential for the use of stem cells for replacement or healing of damaged tissue has yet to be realized. Due to the time-limited activity of stem cells, patients treated with bone marrow–derived stem cells might benefit further from a repeat treatment. While the routine use of stem

![Figure 1. Ankle brachial index (ABI) measurements over time.](image-url)
cell therapies has not arrived, this one patient experienced relief of pain, wound healing, and prevention of amputation.

Acknowledgments

We would like to acknowledge the invaluable contributions of the superb nurses, technicians, and physicians who labor so that research may benefit the world with each discovery proven to benefit mankind: Jing Wang, RN; Sheila Beasley, ST; Kevin Benoit, Harvest Technologies; Jennifer Maninang, BSN, RN, CNOR; and Laura Linker, BSN, RN, CNOR. We also acknowledge the grant support of Harvest Technologies, Inc.


Figure 2. The patient’s wound at (a) baseline, (b) week 8, (c) week 26, and (d) week 52.
A 70-year-old woman being treated with folinic acid, fluorouracil, and oxaliplatin (FOLFOX) therapy for relapsed colon cancer metastatic to the lung presented to the hospital with a 1-week history of abdominal pain, anorexia, a 1-day history of diarrhea, and a fever of 101°F. Neutropenia and a peripheral eosinophilia were present, and computed tomogram of the abdomen showed thickening of the wall of a segment of small bowel with luminal stenosis. Colonoscopy and double-balloon small bowel enteroscopy found a stenosis in the ileum that upon biopsy revealed small bowel eosinophilic enteritis. She improved rapidly with the administration of dexamethasone. A Medline search for reports of small bowel eosinophilic enteritis in response to any of the components of FOLFOX was unrevealing.

Small bowel eosinophilic enteritis is a rare and poorly described cause of diarrhea and abdominal pain. Here we describe a case of small bowel eosinophilic enteritis in a patient with relapsed metastatic colon cancer following chemotherapy.

CASE DESCRIPTION

A 70-year-old woman presented to the emergency department with a 1-week history of abdominal pain, anorexia, fatigue, a fever of 101°F, and severe diarrhea. She had recently completed her second round of folinic acid, fluorouracil, and oxaliplatin (FOLFOX) therapy for metastatic colon cancer and was neutropenic. The colon cancer was diagnosed when she was 66 years old and was in complete remission after chemotherapy and operative resection until biopsy-proven colon cancer metastases to the lung were discovered at age 69. She had been diagnosed with asthma at age 67. She took nebulized budesonide and albuterol for her asthma in addition to ondansetron as needed for nausea and diphenoxylate/atropine as needed for diarrhea. She was allergic only to sulfa drugs.

On admission her temperature was 101°F; heart rate, 110 beats per minute; blood pressure, 166/69 mm Hg; and respiratory rate, 16 breaths per minute. She appeared ill with abdominal distention and tenderness to palpation with rebound tenderness. Her bowel sounds were normal. Initial white count was 1.9 K/uL with an absolute neutrophil count of 400/uL. Hemoglobin was 8.5 g/dL and platelet count, 80 K/uL. Eosinophils were 200/uL and rose to 500/uL over the next 5 days.

She was admitted with a diagnosis of neutropenic fever and given supportive care with broad-spectrum antibiotics (meropenem and vancomycin), intravenous fluid administration, and filgrastim. Her blood, urine, and stool were cultured. Her white blood cell count and fever resolved quickly, but her abdominal pain and diarrhea continued. An abdominal computed tomography (CT) scan showed a long segment of wall thickening in the small bowel without evidence of perforation or intra-abdominal fluid collection (Figure 1). Enteroscopy found normal-appearing colonic mucosa and normal-appearing terminal ileal mucosa distal to the stenosis (Figure 2). Biopsy of the stenotic portion of small bowel showed moderate to severe acute and chronic inflammatory infiltrates, mucosal edema, eosinophilic infiltrates, and epithelial apoptotic degeneration (Figure 3). There were no granulomas, evidence of vasculitis, or atypical lymphoid infiltrates.

Figure 1. Coronal CT of the abdomen showing a stenotic segment of small bowel (arrows).

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Therapy was started with 10 mg of dexamethasone by mouth daily. She showed a rapid improvement in diarrheal symptoms and pain with radiographic resolution of the inflamed portion of bowel. Peripheral eosinophilia up to 500 cells/μL was noted during her hospital stay and had been trending down to 100 cells/μL prior to corticosteroid administration and resolved upon dexamethasone administration. She was discharged shortly thereafter.

COMMENTS

A PubMed search for small bowel eosinophilic enteritis in response to the components of FOLFOX chemotherapy found multiple reports for small bowel eosinophilic enteritis associated with a drug reaction (1–3) but none specifically for any of the components of FOLFOX. Case reports exist for idiopathic small bowel eosinophilic enteritis (3) and small bowel eosinophilic enteritis due to other conditions such as systemic lupus erythematosus (4, 5) or food allergy (3, 6). Eosinophilic enteritis may also mimic a partial small bowel obstruction (7), as in this case, or even an acute abdomen (8). The most common findings of small bowel eosinophilic enteritis are diarrhea and abdominal pain with peripheral eosinophilia on laboratory studies (3).

Diarrhea and abdominal pain are side effects of traditional chemotherapy regimens due to direct cytotoxic effects of the chemotherapeutic agents upon the lining of the gut. In this case the diarrhea presumably was due to an allergic reaction to one of the chemotherapy agents and differed from the typical diarrhea seen in chemotherapy patients in a few important ways. First, the diarrhea and abdominal pain did not improve with usual supportive care over the course of a week, prompting more invasive investigation. Second, the patient had a history of atopic disorder (asthma) and presented with a mild peripheral blood eosinophilia that resolved with treatment. Next, the CT scan of the abdomen showed small bowel transmural inflammation and edema confined to one segment of the ilium. Finally, colonoscopy and retrograde double-balloon small bowel enteroscopy showed normal colonic and terminal ileal mucosa until the scope reached the stenotic portion of the mid ileum without the pattern of ulceration seen in mucosal toxicity of chemotherapy. The histologic findings of cytotoxic chemotherapy–induced enteritis differ as well. Inflammatory cells invade the lamina propria, followed by loss of mucosal structure and denuding of the overlying epithelium, and finally a slower healing process as the mucosa reepithelializes. In contrast, this case had a significant inflammatory infiltrate including eosinophils, a lack of intraepithelial lymphocytosis, and little loss of surface epithelium. It is not completely certain that the small bowel eosinophilic enteritis was secondary to FOLFOX therapy. The most obvious means of proving the connection would be to rechallenge the patient with leucovorin, fluorouracil, and oxaliplatin in sequence until symptoms redeveloped and, without this, coincidence cannot be completely ruled out.

Pulmonary tumor embolism syndrome is a rare phenomenon that can occur in patients who have an occult neoplasm that metastasizes. We describe a case of an elderly woman with an undiagnosed colon cancer who suffered from respiratory distress and compromised pulmonary blood flow from micro-metastasis in the pulmonary arteries.

Cancer is one of the leading causes of death in the elderly. It can present in a variety of ways, some more subtle than others. This case illustrates the value of traditional autopsy in discovering subtle underlying pathologic processes that explain a patient’s clinical outcome, despite extensive diagnostic, supportive, and therapeutic clinical efforts.

CASE DESCRIPTION

A 76-year-old white woman was transferred to our tertiary care center following a short hospital course characterized by bronchitis, dehydration, and failure to thrive. She had cough, fever, poor oral intake, and a general decline in her overall status for several weeks despite antibiotics and intravenous hydration. She was known to have type 2 diabetes mellitus, hypertension, chronic systolic heart failure, and Alzheimer’s dementia. She had lived at home with her husband and was able to perform most activities of daily living without assistance. On presentation to our hospital she was lying in bed moaning but unable to communicate with the medical team or follow commands of any sort. She was found to have multiple laboratory abnormalities (Table 1).

Chest radiograph showed cardiomegaly and vascular congestion. Ultrasound examination of her abdomen showed increased hepatic echogenicity consistent with hepatic steatosis as well as renal cortical thinning consistent with medical renal disease. Computed tomography of the brain revealed senescent changes and an air fluid level in the sphenoid sinuses. Trans-thoracic echocardiogram showed changes consistent with mild pulmonary hypertension and left ventricular hypertrophy. The patient was started on broad-spectrum empiric antibiotics. Electroencephalogram showed periodic epileptiform discharges and moderate to marked generalized slowing. Levetiracetam therapy provided no clinical improvement. Analyses of the cerebrospinal fluid are shown in Table 1, and there was no evidence of acute infection to explain her encephalopathy. Through the remainder of the hospitalization, the patient’s respiratory distress and renal failure worsened, and she died.

Autopsy disclosed a 1.5-cm, well-circumscribed, dark brown subdural nodule overlying the left parietooccipital region of the brain. The heart weighed 520 g, and the right side was dilated. Her coronary arteries were widely patent. She had arteriolar nephrosclerosis and an atherosclerotic aorta. She had focal necrosis of the distal great toes bilaterally. The cecum contained a 4-cm fungating tumor mass (Figure 1), as well as multiple

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<th>Table 1. Laboratory values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serum test</strong></td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
</tr>
<tr>
<td>Platelets (n/μL)</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dL)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
</tr>
<tr>
<td>AST (U/L)</td>
</tr>
<tr>
<td>ALT (U/L)</td>
</tr>
<tr>
<td>GGT (U/L)</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/L)</td>
</tr>
<tr>
<td>D-dimer (mg/L)</td>
</tr>
<tr>
<td>Fibrin split products (μg/mL)</td>
</tr>
</tbody>
</table>

ALT indicates alanine aminotransferase, AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; PCR, polymerase chain reaction.
firm mesenteric lymph nodes, histologically typical of poorly differentiated adenocarcinoma with prominent lymphovascular invasion (Figure 2). Metastases were present in the liver, bone marrow, adrenal glands, thyroid gland, sphenoid sinus, brain, dura, and lungs. All lobes of the lungs contained intravascular collections of poorly differentiated adenocarcinoma. Tumor cells were present within small arteries, arterioles, and septal capillaries (Figure 3). Many tumor emboli were seen associated with intravascular fibrin.

DISCUSSION

Pulmonary tumor embolism syndrome (also known as pulmonary tumor thrombotic microangiopathy) has been reported to be found in 3% to 26% of autopsies conducted on patients with solid tumors (1–4). Numerous case reports have been published (5–13), and in most cases the diagnosis is not made until after death. The incidence is highest in patients with gastric adenocarcinoma, and fewer cases have been reported with adenocarcinoma of the colon (14–16).

Pulmonary tumor embolism syndrome can present in a variety of ways, ranging from acute hypoxia due to large proximal emboli to indolent pulmonary hypertension developing from lymphatic or microvascular invasion (14). Patients can present with a wide range of symptoms including dyspnea, chest pain, and cough. Patients can have electrocardiographic signs of right-sided heart strain and dilated right ventricles. Arterial blood gases can reveal hypoxia with an associated respiratory alkalosis from hyperventilation. Patients who present with signs and symptoms of subclinical cor pulmonale often progress to death within 4 to 12 weeks (17). Chest radiographs or computed tomography are often normal or, in the case of lymphatic invasion, may show signs of interstitial infiltration. Pulmonary arteriography is usually not diagnostic (16, 18). Typical ventilation perfusion mismatches appear as subsegmental defects. These findings are often numerous, peripherally located, symmetric mismatches that are distinct in comparison to the defects caused by venous thromboemboli and have been described as “checkerboard” like—the so-called “checkerboard sign” (19).

Definitive diagnosis can be made premortem. Roberts and associates (1) described obtaining an aspirate from the distal port of a right-sided heart catheter that had been placed in the wedge position. This sample was stained with the Papanicolaou method, and metastatic carcinoma cells were identified. Patients...
with this syndrome usually die quickly. Treatment is usually unhelpful. Thrombolysis has been attempted but usually causes more harm than benefit (20).

Signet ring lymphomas are proliferations of malignant lymphoid cells containing cytoplasmic inclusions or vacuoles that displace the nucleus to the side, imparting a “signet ring” appearance. These signet ring cells, particularly those with cytoplasmic vacuoles, may be mistaken for an adenocarcinoma rather than a lymphoma, if sufficient material is not available to differentiate the case by immunohistochemical stains or flow cytometry. The pathologist must also be aware of this entity so that appropriate studies may be undertaken.

**CASE 1**

A 62-year-old man who had a history of prostatic carcinoma developed inguinal lymphadenopathy. A needle core biopsy was performed on an inguinal node. The microscopic slides revealed cells with eccentric nuclei and eosinophilic cytoplasm (Figure 1a). A CD45 (leukocyte common antigen) stain was positive, indicating a hematopoietic neoplasm rather than a carcinoma. Sufficient material was available to do additional stains, and a CD20 stain (a B cell marker) and CD10 stain (a germinal center marker) were positive, favoring a B-cell lymphoma of possible follicular origin. Contrast Figure 1a with an adenocarcinoma of the stomach with eosinophilic cytoplasm (Figure 1b).

**CASE 2**

A 41-year-old woman had a history of a gastric carcinoma 2 years earlier. The patient developed abdominal pain, and a peripancreatic mass was discovered by a computed tomography (CT) scan. A CT ultrasound–guided fine needle aspiration yielded tissue composed of “signet ring” cells (Figure 2a). The initial impression was recurrent adenocarcinoma. However, cytokeratin and mucicarmine stains were negative on the cell block, which would be expected to be positive in adenocarcinoma. Since the cell block specimen was limited, CD45, CD20, and CD3 (T-cell marker) immunohistochemical stains were done, and CD45 and CD20 were positive, indicating a B-cell lymphoproliferative process. No further tissue was obtained, and the patient was placed on a regimen including rituximab (Rituxan), which resulted in a regression of the peripancreatic mass. Contrast Figure 2a with a pancreatic adenocarcinoma (Figure 2b).

**CASE 3**

A 36-year-old man was found to have a large mesenteric mass. An ultrasound-guided fine needle aspirate yielded only a small sample containing atypical signet ring cells, which were...
not diagnostic but suspicious for malignancy. An open excisional biopsy was then done, which revealed a signet ring variant of a follicular lymphoma (Figure 3).

DISCUSSION

The first cases of signet-ring lymphoma were reported by Kim et al in 1978 (1). They described seven cases of non-Hodgkin’s lymphoma characterized by an abundance of cells containing clear vacuolated cytoplasm. Since this original description by Kim, approximately 50 cases of signet ring lymphoma have been reported in the literature. The majority of cases involved lymph nodes, and bone marrow involvement appears to be uncommon. The majority of cases have been of B-cell lineage, and most have been associated with follicular lymphoma (1–3) with less association with other B-cell lymphoproliferative disorders (4–9). A few cases of signet ring T-cell lymphoma and anaplastic large-cell lymphoma have also been reported (10–12).

Signet ring lymphomas with clear cytoplasm typically express immunoglobulin (Ig) with a predominance of lambda light chains, while those cases with eosinophilic globules in the cytoplasm are periodic-acid-Schiff positive and more commonly express IgM (1, 3). Clinically follicular lymphomas with the signet ring morphology do not differ in behavior from the more typical follicular lymphoma, and prognosis depends more on grade (1 and 2 low grade and 3A and 3B high grade).

The importance of signet ring lymphoma is not to mistake it for adenocarcinoma, particularly when sample size is limited. It is important that sufficient material is present to perform the necessary immunostains and flow cytometry to differentiate lymphoma from carcinoma. Whenever possible, open biopsies should be performed if the lymph node is readily accessible. At times the location of the tumor and status of the patient will dictate that a fine needle aspiration or core biopsy be obtained. This latter situation is more likely to cause a diagnostic problem. The pathologist also needs to be aware of lymphomas containing signet ring cells so as to obtain the necessary diagnostic stains to make the correct diagnosis.

Invasive mucinous carcinoma of the breast

Kelli Y. Ha, MD, Patricia DeLeon, DO, and William DeLeon, MD

Mucinous carcinoma of the breast is one of the rarer forms of intramammary cancer, often presenting as a lobulated, fairly well circumscribed mass on mammography, sonography, and gadolinium-enhanced magnetic resonance imaging. It accounts for 1% to 7% of all breast cancers and generally carries a better prognosis than other types of malignant breast cancers. Metastatic disease occurs at a lower frequency than in other types of invasive carcinoma. We present an atypical case of mucinous carcinoma in a woman who presented with a palpable intramammary lymph node metastasis from an unknown breast primary. Subsequent magnetic resonance imaging and percutaneous biopsy demonstrated histologic findings consistent with a mixed mucinous neoplasm with a micropapillary pattern.

Invasive mucinous carcinoma of the breast is one of the rarer breast neoplasms and is typically associated with a better prognosis than other types of breast cancer. It often presents as a lobulated and/or well-circumscribed mass on mammography, sonography, and magnetic resonance imaging (MRI). We present the case of a patient with a more aggressive type of mucinous carcinoma: a mixed neoplasm with micropapillary features.

CASE REPORT

A 52-year-old woman presented to her primary care physician complaining of a new lump in the upper outer quadrant of her left breast. A mammogram demonstrated a 7 mm ovoid mass at the 2:00 position of the left breast (Figure 1). Targeted sonographic evaluation demonstrated a well-circumscribed, oval-shaped mass of mixed echogenicity at the 2:00 position, approximately 10 cm from the nipple (Figure 2). Ultrasound-guided percutaneous biopsy results were consistent with metastatic involvement of an intramammary lymph node from a mammographically occult breast carcinoma.

Gadolinium-enhanced breast MRI demonstrated a 3.9 × 5.2 × 1.7 cm area of suspicious nonmasslike enhancement within the lower inner and lower outer quadrants of the left breast. A 1.2 cm focus of masslike enhancement was also visualized at the 7:00 position of the left breast (Figure 3). These two foci of abnormal enhancement were subsequently biopsied; both sites were consistent with an infiltrating ductal carcinoma (grade I/II) with mucinous and micropapillary patterns. The areas of tumor were found in association with extensive tumor emboli within dermal lymphatics, suggestive of widespread neoplastic involvement of the left breast. The lesion was estrogen and progesterone receptor positive.

Figure 1. Spot mammographic view of the left breast demonstrates a 7 mm ovoid mass at the palpable area of concern as designated by a radiopaque marker.
(ER/PR) negative and HER-2 positive (3+ staining). Bone scintigraphy and gadolinium-enhanced brain MRI were negative for extramammary spread of disease. The patient is presently exploring various treatment options with her medical oncologist.

**DISCUSSION**

Mucinous (colloid) carcinoma of the breast is one of the rarer breast neoplasms, accounting for 1% to 7% of all invasive breast carcinomas. A prevalence as high as 7% is found in women over the age of 75 years, while a prevalence of 1% is found in those younger than 35. A mucin component >33% to 50% defines this type of tumor (1). From a histologic perspective, mucinous carcinomas may be divided into pure mucinous and mixed mucinous entities, depending upon the percentage of mucin within the neoplasm. Pure mucinous carcinomas (mucin component >90%) are associated with a better prognosis, a longer disease-free interval, and a lower incidence of axillary node metastasis (2, 3). The frequency of mucinous intramammary neoplasms at Baylor University Medical Center at Dallas is summarized in the Table, with a reported incidence over the 3-year period of approximately 2.5%.

When palpable, these cancers often present as soft masses due to their semisolid mucin constituents. Most mucinous carcinomas are readily detected on mammography. They appear as low-density, well-defined or microlobulated oval masses and generally belong to the category of “well-circumscribed” breast carcinomas (4). Microlobulated margins have been associated with higher mucin content, while irregular or spiculated margins correspond to lower percentages of mucin and infiltrating margins histologically. The irregular and infiltrating margins seen on mammography and histology have been attributed to greater degrees of fibrosis associated with the nonmucinous components (5). Albeit rare, calcifications seen in conjunction with mucinous tumors frequently correspond to the invasive ductal component of the cancer in a mixed mucinous tumor (6).

Sonographically, mucinous carcinomas typically present as complex masses of mixed echogenicity with solid and cystic-appearing components. However, up to 20% of these lesions may present as homogenous masses on ultrasound. They are isoechoic or hyperechoic to subcutaneous fat, with posterior acoustic shadowing. A description of mucinous breast neoplasms visible on mammography over a 3-year period at Baylor University Medical Center at Dallas is summarized in the Table, with a reported incidence over the 3-year period of approximately 2.5%.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Breast</th>
<th>Size (cm)</th>
<th>Palpable</th>
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</thead>
<tbody>
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<td>1</td>
<td>61</td>
<td>Left</td>
<td>1.0</td>
<td>0</td>
</tr>
<tr>
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<td>77</td>
<td>Left</td>
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<td>0</td>
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<tr>
<td>3</td>
<td>80</td>
<td>Right</td>
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<td>0</td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>Left</td>
<td>1.8/0.8</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
<td>Left</td>
<td>1.2</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>74</td>
<td>Right</td>
<td>1.3</td>
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<td>Right</td>
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<td>0</td>
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<tr>
<td>14</td>
<td>58</td>
<td>Left</td>
<td>2.5</td>
<td>0</td>
</tr>
</tbody>
</table>

*Data cover the period from April 1, 2008, to March 31, 2011, and exclude the recent patient discussed in the case report. Mucinous carcinomas comprised 14 of 560 breast neoplasms, constituting a 2.5% prevalence rate over the 3-year period. Three of the 14 mucinous neoplasms (21%) were of a mixed mucinous type.

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**Table. Characteristics of mucinous breast neoplasms visible on mammography over a 3-year period at Baylor University Medical Center at Dallas**

*Data cover the period from April 1, 2008, to March 31, 2011, and exclude the recent patient discussed in the case report. Mucinous carcinomas comprised 14 of 560 breast neoplasms, constituting a 2.5% prevalence rate over the 3-year period. Three of the 14 mucinous neoplasms (21%) were of a mixed mucinous type.

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* indicates no information available.
Invasive mucinous carcinoma of the breast

July 2013


Sentinel lymph node biopsy has become the standard of clinical care in staging axillary lymph nodes for breast carcinoma. While deemed safe and effective, methylene blue dye has been associated with infection, fibrosis, and skin and fat necrosis. The variable appearance of surgical dye-related fibrosis and fat necrosis on imaging studies poses a challenge to both radiologists and clinicians. We present a patient in whom a new enhancing lesion was visualized on follow-up magnetic resonance imaging for known breast carcinoma in the setting of neoadjuvant chemotherapy.

Fat necrosis is a relatively common clinical and radiologic entity, often diagnosed on mammography. We present an atypical case of fat necrosis that manifested as an area of suspicious enhancement on magnetic resonance imaging (MRI). The area of enhancement corresponded to a site of previous sentinel lymph node biopsy.

CASE REPORT

A 52-year-old woman previously diagnosed with grade II infiltrating ductal carcinoma presented to Baylor University Medical Center for a follow-up breast MRI examination. The patient had completed a sentinel lymph node biopsy with methylene blue dye injection approximately 5 months before the follow-up MRI. Methylene blue dye was injected into the lateral left breast at the time. An axial image from the initial breast MRI demonstrated a 2.4 cm spiculated mass at the 8:00 position of the medial left breast, approximately 6 cm from the nipple (Figure 1). Follow-up breast MRI performed 6 months later demonstrated an interval decrease in the size of this mass, with residual dimensions measuring 1.7 × 0.5 × 0.4 cm (Figure 2a). A new area of nonmasslike enhancement was also identified at the 3:00 position of the lateral left breast, approximately 4 cm deep to the nipple (Figure 2b). This area of suspicious enhancement measured 3.6 × 2.0 × 1.3 cm and was not definitively visualized on the initial MRI examination. It corresponded to the site of previous methylene blue dye injection. Given its suspicious enhancement characteristics, percutaneous MR-guided biopsy of the lesion was performed. Histology results were consistent with areas of fibrosis and fat necrosis from prior methylene blue sentinel node injection.

DISCUSSION

Fat necrosis of the breast is a relatively benign and common radiologic entity and may result from trauma, previous surgery (i.e., needle or surgical biopsy, lumpectomy, or reduction mammoplasty), and/or radiation therapy. It results from a vascular insult to adipose tissue. When symptomatic, fat necrosis typically manifests as a small, painless mass, with up to 97% of cases presenting as a palpable abnormality. Concomitant or coexistent infection may further aggravate the development of fat necrosis (1, 2).

Fat necrosis exhibits a variety of diverse imaging appearances on mammography, a finding that is largely dependent upon the degree of ensuing fibrosis. It may present as a lipid cyst, focal asymmetry, spiculated mass, or calcific deposits (3). In the setting of minimal fibrosis, fat necrosis appears as a lucent mass or oil cyst, developing progressive areas of calcium. Fat necrosis may manifest as calcium alone. While these deposits are typically smooth, round, or curvilinear, some may take on a more ominous appearance with branching, rodlike, or...
angular morphologies. As fibrosis progresses, the appearance of fat necrosis changes into that of an irregular, asymmetric, or spiculated mammographic density (2).

Although fat necrosis may exhibit a varied appearance on breast MRI, the most common presentation is that of a lipid cyst, which appears as a round or oval mass with a hypointense T1 signal on fat-saturated images. While a thin rim of enhancement is common, the rim may also appear thickened, irregular, or spiculated. Additional features that can be visualized include fat-fluid levels and thin enhancing internal septations. Fat necrosis is characteristically isointense to fat seen elsewhere in the breast. Variable T1 hypointensity may occasionally be seen and presumably relates to hemosiderin deposition and surrounding inflammatory change. Predominantly fibrotic lesions are especially difficult to distinguish from malignant processes, appearing spiculated and solid rather than cystic. Kinetic analysis is often confounding, as fat necrosis exhibits the full continuum of benign to malignant enhancement patterns, including rapid and slow initial phase enhancement and progressive, plateau, and washout delayed kinetics. Enhancement may be focal or diffuse, homogenous or heterogeneous, and may persist for several years after the initial insult. Enhancement longevity depends upon the degree of ongoing inflammation and the quantity of granulation tissue. In cases in which fat necrosis cannot be confidently identified on the basis of imaging, biopsy should be obtained to confirm or deny histologic suspicions (1, 2).

Our case highlights one of the confounding complications of sentinel lymph node biopsy with methylene blue dye. It reiterates the association between surgical dye for axillary lymph node staging and the nonspecific imaging findings that fat necrosis and fibrosis may portend.

Kummell disease

Larry T. Nickell, MD, William G. Schucany, MD, and Michael J. Opatowsky, MD

Kummell disease, or avascular necrosis of a vertebral body, presents as vertebral osteonecrosis typically affecting a thoracic vertebra with compression deformity, intravertebral vacuum cleft, and exaggerated kyphosis weeks to months after a minor traumatic injury. This rare disease is increasing in prevalence secondary to an aging population and the associated rise in osteoporosis. Treatment with vertebroplasty or surgical decompression and fusion is often required. We present a classic case of Kummell disease to illustrate the salient features of the condition, with associated imaging findings on computed tomography and magnetic resonance imaging.

Back pain is a common presenting complaint of patients in the emergency department and outpatient clinics and is a source of frustration for physicians and patients. Judicious imaging can elucidate the etiology and guide appropriate therapy. We present a case of Kummell disease, a rare but increasingly prevalent cause of back pain with classic imaging features.

CASE DESCRIPTION

A 54-year-old man presented to the emergency department with abdominal pain and back pain. The patient described multiple prior minor traumatic events, namely falls from a standing position. He had end-stage renal disease and was on hemodialysis. He also had epilepsy and HIV infection. Computed tomography (CT) imaging of the abdomen showed multiple thoracic compression deformities and compression deformities of the T8 and T9 vertebral bodies with associated intravertebral vacuum clefts (Figure 1). Magnetic resonance imaging (MRI) of the thoracic spine revealed low signal intensity within the T8 and T9 vertebral bodies on all imaging sequences (Figure 2).

DISCUSSION

German surgeon Hermann Kummell described six patients with vertebral body compression deformities after minor trauma in 1895 (1, 2). Kummell hypothesized that “the nutrition of the affected vertebral bodies is injured,” leading to delayed collapse of the vertebral bodies (3). While initially Kummell disease (KD) was thought to be exceedingly rare, its prevalence is increasing with our aging and often osteoporotic population. The exact incidence of KD is unknown, and there is disagreement as to the appropriate eponym for the disease, with the terms Kummel, Kummell, and Kummell-Verneuil disease all being applied (1).

KD, avascular necrosis of a vertebral body, represents a failure of the fracture healing process after a minor traumatic injury (4). KD occurs most commonly in middle-aged to elderly men who complain of acute back pain after a fall. A number of risk factors have been identified, including chronic steroid use, osteoporosis, alcoholism, and radiation therapy (5).

Imaging studies immediately after the inciting event show no evidence of a compression deformity or acute fracture, although initial imaging is often not obtained due to the perceived mild nature of the traumatic event. Delayed compression deformity of the affected vertebral body and exaggerated thoracic

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kyphosis can be demonstrated on plain radiographs, CT, or MRI. Vertebral osteonecrosis with an intravertebral vacuum cleft is best shown on CT. CT shows compression deformities with sclerosis of the endplates and virtually pathognomonic foci of air within the vertebral body. MRI demonstrates a “double line sign,” where a linear region of low intensity represents the vacuum cleft surrounded by elevated T2/FLAIR (fluid-attenuated inversion recovery) signal of the fracture deformity or intravertebral fluid (6, 7).

Neurologic compromise is more common with KD than with osteoporotic compression fractures. Treatment of KD is designed to eliminate motion at the fracture site and to relieve neurologic symptoms. The preferred treatment method rests on three factors: the patient’s subjective pain level, the degree of kyphotic deformity, and specific neurologic deficits (1). Vertebroplasty has shown favorable results and is successful at alleviating back pain, but surgical intervention is often indicated, especially in the presence of neurologic compromise (4, 5). Surgical decompression and fusion can be obtained from anterior, posterior, or combined approaches, with the goal of restoring near-anatomic sagittal alignment and eliminating pathologic motion.

Behavioral health senior program opens at Baylor Garland

Since admitting its first patient on January 1, 2013, the 10-bed Behavioral Health Senior Program, located at Baylor Medical Center at Garland, has been treating patients aged 65 and older who are experiencing various mental health crises. “Baylor is well positioned to take care of this age group when they experience psychiatric episodes,” explained Radha Kamthampati, MD, MPH, medical director of the program. “There are very few facilities that are able to treat psychiatric patients with associated medical problems such as you find in this patient population.”

Patients who are admitted to the unit have a psychiatric diagnosis as their primary disorder. Severe depression is a common diagnosis, but memory problems, panic attacks, anxiety disorders, and psychosis are not uncommon. The center provides these older adults short-term (7–14 days) inpatient services, working in tandem with Baylor Garland hospital services to ensure both mental and physical health needs are addressed simultaneously and cohesively. The program is focused on recovery and encourages individuals to reconnect with their hopes and personal motivations. The advanced psychiatric and medical care offered is based on a combination of individual, group, and family therapy, including occupational therapy and education. The program accepts referrals from the Dallas–Fort Worth area.

BHVH opens Center for Valve Disorders

The Baylor Jack and Jane Hamilton Heart and Vascular Hospital (BHVH) recently opened its Center for Valve Disorders, which provides comprehensive services for patients with any type of structural heart disease or defect. Many patients travel some distance to receive cardiac care, making a one-stop center more efficient for them. The center comprises a highly skilled multidisciplinary team of interventional cardiologists, cardiothoracic surgeons, and imaging specialists on the BHVH and Baylor University Medical Center (BUMC) medical staff. With the help of advanced technology and techniques, the team provides comprehensive treatment for aortic and mitral valve disease, taking a minimally invasive approach to repairing valves and defects within the heart whenever possible. In some instances, valves can even be replaced through a minimally invasive procedure offered at only a handful of medical centers across the country, which eliminates the need for open-heart surgery. In addition, the center can provide access to clinical trials.

Baylor grows to serve Denton area

As part of Baylor Health Care System’s (BHCS) long-term growth strategy into rapidly expanding communities, The Heart Hospital Baylor Plano (THHBP) recently signed an agreement with North Texas Hospital that is its first step in acquiring the Denton-based surgical hospital. The acquisition will enable Plano-based THHBP to begin offering the Denton community and surrounding areas high-quality cardiovascular medicine in phases over the coming months. This is THHBP’s second heart hospital and its first in Denton County.

Expanding cardiovascular services into the Denton community is further evidence of Baylor’s commitment to its Vision 2015—to improve the health of the communities we serve. Last year, Baylor entered into a joint venture with Texas-based Emerus to create eight freestanding emergency hospitals in the North Texas area. In addition to providing communities with more convenient access to emergency services, this initiative will help relieve emergency department overcrowding at area hospitals by offering a full range of inpatient and emergency medical care services.

Baylor Research Institute, Tiko Med collaborate in phase II clinical trial for treatment of chronic pancreatitis

Baylor Research Institute (BRI), the research arm of BHCS, and TikoMed AB announced an agreement to investigate TikoMed’s product IBolvMIR in a phase II clinical trial. The goal is to improve the engraftment of auto islet cell transplantation in patients with severe, chronic pancreatitis. BRI has developed a therapy for treatment of chronic pancreatitis, and TikoMed believes its product can enhance the outcome of the treatment by improving the survival of transplanted cells by inhibiting a destructive immunological reaction and stimulating growth factors.

ACCOLADES

Joel Allison, president and CEO of BHCS, was listed among the recipients of Becker’s 2013 Healthcare Leadership Awards. The awards recognize leaders who demonstrate “valuable traits the healthcare industry needs in times of change and uncertainty.” In their profile of Allison, Becker’s noted, “Throughout his tenure, Mr. Allison has demonstrated a progressive and community-oriented leadership style. Rather than reacting to industry-wide uncertainty, Mr. Allison proactively forged ahead with ‘Vision 2015,’ the strategic plan he launched in 2010. Vision 2015 included plans for Baylor to create an accountable care organization—which was accomplished through the launch of Baylor Quality Alliance—and other strategies for patient-centered care models and new information technology.”

Becker’s Hospital Review has named Donald Kennerly, MD, PhD, vice president and associate chief quality officer for BHCS, as one of the nation’s “50 Experts Leading the Field of Patient Safety.”

Bradley Lembcke, MD, medical director for hospital medicine at BUMC, and Elizabeth Fagan, MD, emergency department medical director at Baylor Medical Center at McKinney, were selected from thousands of clinicians for national recognition by EmCare physician practice management company. Dr. Lembcke was the 2013 Summit Award winner. The Summit Award singles out a sole hospital medicine physician for the honor each year. Dr. Fagan was the 2013 Commitment to Care Award winner. Her award honors one emergen-cy medicine physician each year.

Jeffrey Schussler, MD, medical director of the BHVH intensive care unit, was one of 12 interventional cardiologists selected for an emerging leader mentorship program by the Society for Cardiovascular Angiography and Interventions in partnership with the American College of Cardiology and Cardiovascular Research Foundation.

In May 2013, D CEO Magazine named Fred Savelserbergh outstanding chief financial officer of a nonprofit group. Savelserbergh has worked for BHCS for over 30 years. Since 2007, he has been senior vice president of hospital finance.
Researchers develop Web 2.0 apps to share vaccine study

In a manuscript published in Immunity, scientists at the Baylor Institute for Immunology Research (BIIIR) and the Benaroya Research Institute at Virginia Mason reported the results of a comparative study of the molecular immune responses to influenza and pneumococcal vaccines. In addition, cutting-edge web technology was used to improve dissemination of data in order to accelerate the pace of scientific discovery. The article features interactive figures that allow for dynamic investigation of the primary data from a web portal that was developed as part of this study and could serve as a model for future scientific publishing and data sharing.

The team, led by Damien Chausssabel, PhD, at Benaroya and Jacques Banchereau, PhD, Virginia Pascual, MD, and Karolina Palucka, MD, PhD, at BIIIR, utilized a systems immunology approach and high-throughput profiling techniques to analyze molecular and cellular responses after vaccination. They found that the influenza vaccine led to gene activity induced by interferon, while the pneumococcal vaccine led to an increase of myeloid- and inflammation-related gene activity, suggesting that the two vaccines elicit immune protection via distinct immune response pathways.

Systems biology approaches like the one presented in this publication generate enormous amounts of data with measurements of tens of thousands of parameters. Often, much of the data sees little investigation. To extend the value of data generated in this study, the authors developed web applications. The article links directly to figures in the web portal, which allows dynamic investigation of the presented figures and underlying data. Readers can interact with and customize the article's figures by adding variables or adjusting parameters. They are able to fine-tune their view of the data based on their own research interests and expertise and investigate additional hypotheses with the full dataset.

“Our goal was to make accessing these very complex datasets simple and enjoyable for investigators who have unique knowledge of immunology or medicine, but who may not have a lot of bioinformatics or statistics experience,” explained Dr. Chausssabel. “They will be able to look up their favorite molecules and gain insights that only they, with their unique knowledge about these molecules, could obtain.”

Baylor Dallas named among nation’s “100 great hospitals”

BUMC was included in Becker’s Hospital Review 2013 list, “100 Great Hospitals in America.” This annual list is based on data from reputable sources including U.S. News & World Report, Truven Health Analytics’ 100 Top Hospitals, HealthGrades, Magnet Recognition by the American Nurses
BHVN earns AACN silver-level Beacon Award

The intensive care unit at BHVN recently earned the silver-level Beacon Award for Excellence from the American Association of Critical Care Nurses (AACN). The Beacon Award for Excellence is “a significant milestone on the path to exceptional patient care and a healthy work environment,” according to the AACN. The award recognizes unit caregivers who successfully improve patient outcomes and align practices with AACN’s six standards for a healthy work environment. Units that achieve this 3-year, three-level award with gold, silver, and bronze designations meet national criteria consistent with Magnet Recognition, the Malcolm Baldrige National Quality Award, and the National Quality Healthcare Award.

Baylor Plano earns two certifications from Joint Commission

Baylor Regional Medical Center at Plano earned the Joint Commission’s Gold Seal of Approval for its hip and knee replacement program and was awarded Advanced Certification as a Primary Stroke Center. These distinctions recognize Baylor Plano’s dedication to continuous compliance with the Joint Commission’s state-of-the-art standards. To achieve these distinctions, Baylor Plano underwent two separate rigorous on-site reviews in January 2013.

Employee cancer prevention efforts earn Gold Standard

The CEO Roundtable on Cancer recently accredited BHCS with the CEO Cancer Gold Standard, recognizing BHCS’s efforts to reduce the risk of cancer for its employees and covered family members by promoting healthy lifestyle choices, encouraging early detection and providing access to quality treatment.

In 2012, BHCS became one of the first organizations in North Texas to stop hiring tobacco users. For employees and their spouses who do use tobacco products, Baylor offers a free cessation program. But Baylor’s employee health and cancer prevention initiatives go far beyond tobacco cessation. The Thrive employee wellness program has paid out thousands of dollars in wellness incentives, while helping countless employees and their family members lose weight, get in shape, eat a healthier diet, and better manage stress—all of which contribute to a lower risk for cancer and other diseases.

PHILANTHROPY NOTES

The Hillcrest Foundation supports Baylor’s smallest patients

Baylor’s smallest patients and their mothers have a new reason to hope thanks to generous support from the Hillcrest Foundation. Kevin Magee, MD, medical director of the Fetal Care Center at BUMC, and his team received a significant gift of more than $590,000 from the Hillcrest Foundation to support an innovative new procedure for correcting heart defects in unborn children. The grant will purchase an essential monitor system, which will provide the physicians with the high-tech tools that will enable them to perform delicate, lifesaving procedures before a child is born.

Very few centers offer fetal cardiac interventional procedures in the US, and those that do utilize methods that require a major surgical procedure. This innovative and less invasive procedure has been highly successful in several experiments and is anticipated to lower both the babies’ mortality and the mothers’ risk.

The grant from the Hillcrest Foundation builds on a legacy of generous support from the Crystal Charity Ball and will allow Dr. Magee and his team to reach a significant medical milestone. They will be first in the world to perform this minimally invasive method of lifesaving in utero cardiac surgery on our most vulnerable patients. Images during the surgery can be live broadcast to remote locations and used for teaching purposes.

Baylor Waxahachie breaks ground on new hospital

On April 10, 2013, BHCS broke ground on the new 299,000-square-foot location for Baylor Medical Center at Waxahachie. Many community members and supporters were in attendance at the celebration of this new chapter in Baylor Waxahachie’s history.

The new campus is located on 52 acres at the intersection of I-35E and Highway 287. The first phase of the estimated $175.5 million hospital project, a 75,000-square-foot medical office building housing physicians and health care-related programs, is slated to open in December 2013. The larger campus project is expected to open in November 2014—the 100th anniversary of Baylor Waxahachie’s grand opening in 1914. A comprehensive fundraising initiative has been launched in support of the new facility.

UPCOMING CME PROGRAMS

The A. Webb Roberts Center for Continuing Education of Baylor Health Care System is offering the following program:

40th Annual Williamsburg Conference on Heart Disease, December 8–10, 2013, at the Williamsburg Conference Center, Williamsburg, Virginia

For more information, call 214-820-2317 or visit www.cmebaylor.org.

The Gold Standard is the latest in a long list of awards BHCS has won for employee wellness. For the past 2 years, the Dallas Business Journal has named Baylor “Healthiest Employer in North Texas.” In 2011, Baylor was named the Live Healthy North Texas Health Care System of the Year and received Start! Fit-Friendly Companies Platinum Level recognition from the American Heart Association.
Acknowledgment of contributors

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We also thank our two anonymous donors. The total amount raised this period from individual donors was $13,145. Any additional donations can be sent to the editorial office or the BHCS Foundation office and will be acknowledged in the April 2014 issue.
Throughout history, medical practitioners have been admonished to do nothing in treating their patients that might result in harming them. It was not until the 20th century that such teaching was codified in specific legislation. Spurred on by the perversity of Nazi doctors during the Holocaust, world leaders produced the Nuremberg Code in 1947 and the Declaration of Helsinki in 1964. Revelations about other egregious acts in the guise of legitimate medical research led to other measures to prevent such mistreatment. Regulations to ensure physician competency and responsibility have mushroomed in the succeeding years. While such measures were coming into being, some of the greatest advances in medicine were being achieved, not least among them those in cardiovascular surgery. Ironically, much of this valuable research would likely not have been approved under regulatory measures now firmly in place. Given the nature of medical research, more often than not a certain degree of risk in all patients entering such trials may be unavoidable. There is always a balance to be maintained between risk and potential benefit.

The 20th century was characterized by an incomparable advance of medical knowledge. Importantly, much of this could be directly applied to the quality of patient care provided in our hospitals and clinics. Patients suffering from infectious diseases, cancer, and cardiovascular disease, as well as other maladies, were all beneficiaries of such research. Coincident with such progress was the need to have patients participate in studies in order to evaluate the validity of new treatments. With this came the responsibility to ensure the protection and rights of both the patients and normal volunteers involved.

The Nuremberg Code was adopted in 1947 primarily in reaction to the horrors inflicted upon many innocent victims of the Holocaust. However, other medical scandals involving patients and volunteers were being uncovered, including the study of untreated syphilis in African American men and human radiation experiments. In recognition of this, the scope of the Nuremberg Code and, later, the Declaration of Helsinki (1964) was widened to include all types of patient involvement in medical research. How vigorously, in practice, such guidelines were followed was and still is of major concern. Some insight into this compliance may be gained by examining some procedures developed in one of the major areas of groundbreaking research during this period, cardiovascular surgery (1, 2).

**LIGATION OF A PATENT DUCTUS ARTERIOSUS**

The ductus arteriosus is a connection between the aorta and pulmonary artery that functions normally in utero when the lungs are collapsed. It closes soon after delivery as the lungs expand and the normal postpartum circulation is established. Failure to close results in a shunting of blood from the systemic to the pulmonary circulation, causing cardiac enlargement with symptoms often occurring in early childhood and death occurring at the average age of 24 years as a result of intractable heart failure or infection.

In 1938, Robert E. Gross was the 33-year-old chief surgical resident at the Children’s Hospital in Boston and the Peter Bent Brigham Hospital. In addition to his surgical training, he had completed 3 years of training in pathology. He had become familiar with the pathological anatomy of many congenital cardiac abnormalities and later observed a number of children suffering from patent ductus. These experiences convinced him that he could successfully ligate this abnormally patent communication (3–5). Others were not so convinced that this could be done without unacceptable risk, among them William Ladd, Gross’s chief, who had specifically turned down this request of his resident.

Despite this, Gross waited for Ladd to be away from Boston before scheduling two children for the procedure. Apparently unaware that an attempt at ligation had been unsuccessful elsewhere at this time, Gross moved ahead. On August 26, 1938, he operated successfully upon a 7½-year-old girl and, soon after, the second patient who had been held in reserve. Ladd was on the high seas, en route to Europe at the time. When he returned he fired his resident.

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THE SURGICAL TREATMENT OF MITRAL STENOSIS

An end result of rheumatic fever in some patients involves damage to the heart valves. Most commonly it is the mitral valve that is involved; most commonly it is a narrowing (stenosis) of the valve opening that occurs (mitral stenosis; MS). Early in the 20th century, even in industrialized countries of the West, many patients suffered from this condition with no effective treatment available. Although it now seems obvious that such an obstruction of the mitral valve could be the source of disability, medical authorities of the time held that the main problem was in the heart muscle and any changes in valve morphology were only incidental. Nonetheless, a few physicians believed that such valvular changes **could** account for the patients’ symptoms and that these changes might be paramount (6). In MS they held that surgical relief of the obstruction could provide significant relief.

As early as 1923, Elliott C. Cutler in Boston had operated on an 11-year-old girl who improved postoperatively and survived an additional 4½ years before succumbing to her disease. This initial success was followed by repeated failures. In 1929, Cutler and Claude Beck reviewed the results in 10 cases of MS worldwide with only two showing any improvement. The rest died while in surgery or shortly thereafter. A moratorium on mitral surgery followed until the 1940s. Then, between 1944 and 1948, four different men in four different locations began to succeed in their attack on the stenotic mitral valve. These were Dwight E. Harken in Boston; Charles P. Bailey in Philadelphia; Horace G. Smithy in Charleston, South Carolina; and Russell C. Brock in London. Their approaches were either through the left atrium or the left ventricular apex, but either technique seemed to work.

The personalities of these four surgeons differed as much as their locations. But while Harken, Smithy, and Brock seemed safely ensconced in their respective academic homes, Bailey more often came across as a loner and a maverick. Some even considered him “a loose cannon.” Bailey was born in Neptune, New Jersey, in very modest circumstances and after completing medical school spent 5 years in general practice before even starting his surgical training at Hahnemann (7). Perhaps he felt a greater need than other surgeons with more impressive backgrounds to assert himself.

He was drawn to the problem of MS after having witnessed, as a boy, his father dying from the disease, and once he had set as his goal the conquering of MS he could not be deflected from it. Efforts to do so at Hahnemann fell on deaf ears. Attempts to perform any more of these procedures. Characteristically, Bailey replied that he felt that he was a victim of “the jury being out before the court had been called into session.” He affirmed his belief in the path he was taking and considered it **his** Christian duty to forge ahead.

Bailey was soon denied operating privileges in three of the five hospitals where he had been on staff. Time was running out; he had already lost three patients, and any further failures would be the end of him. Reminiscent of Gross, he scheduled two patients, one in the morning at the Philadelphia General Hospital and one in the afternoon at the Episcopal Hospital. At this point Bailey contracted measles and had to wait a month before putting his plan into action. The first patient died but the second survived and improved. The crisis of confidence had passed and, with other favorable results being reported by his three colleagues, mitral commissurotomy, as the procedure was to be called, became common.

After this period Bailey developed surgical approaches to other cardiac diseases, but none had the impact of the MS work. When he finally gave up his surgical practice he earned a law degree at Fordham University and then joined a firm specializing in physicians’ problems. Later he founded a nonprofit insurance company. But the problem of valvular heart disease found him once again, in a very personal way. He developed aortic stenosis, to which he succumbed in 1993 at the age of 82.

REFUTING INTERNAL MAMMARY ARTERY LIGATION FOR CORONARY HEART DISEASE

As great a problem as valvular heart disease was that of coronary artery disease. In the years before coronary artery bypass grafting became the standard surgical treatment for this, a number of indirect methods of questionable efficacy were attempted. One that, briefly, seemed to hold promise was that of bilateral internal mammary artery ligation, especially for severe angina. The hypothesis in support of this procedure was that, in the presence of coronary artery obstruction, collaterals would develop from the internal mammary arteries to relieve ischemia of the myocardium at risk. It was believed that this process could be enhanced by ligation of the internal mammary arteries with the backup of blood flow redirected to these collaterals to the heart.

In 1955 a group of Italian investigators reported their preliminary findings regarding this technique (8). Before clinical application, they performed postmortem studies in coronary patients using injections of radiopaque material, methylene blue, or india ink in the mammary arteries to demonstrate any collaterals. In addition, studies were performed in dogs to demonstrate the presence of these vessels. Although neither of these studies demonstrated collaterals to the myocardium, the investigators proceeded to perform the operation in 11 patients diagnosed as having severe angina at rest or with minimal exertion. Four of these patients had suffered previous myocardial infarctions.

The initial results were spectacular: all were completely free of chest pain postoperatively. Improved electrocardiogram patterns were seen in five. Follow-up in all but one patient was limited to 1 to 3 months. By 1959 they reported their results in 304 patients followed from 6 months to 4 years (9). Symptomatic improvement (fair to excellent) was found in 90%, with 5% regressing over the period of observation. They recommended this simple and effective procedure as an alternative to other more complicated indirect surgical procedures proposed for the treatment of coronary artery disease.
such results, if valid, might offer relief to thousands upon thousands of coronary patients throughout the world. The question that remained in the minds of some critics was how much of this symptomatic improvement could be related to a placebo effect.

Two groups of American investigators put this question to the test. Leonard Cobb and his colleagues selected 17 patients with angina (10). The patients were told only “that they were performing.” Specific information regarding informed consent was not mentioned by the authors.

On follow-up, Cobb found subjective improvement in only 32% of those undergoing ligations and 43% of those who received sham operations (10). Dimond noted immediate improvement of chest pain in 15 patients, including 5 patients with sham operations (11). Exercise tolerance was not improved among patients with ligations (10). Despite subjective improvement of chest pain, electrocardiographic changes of ischemia on exercise persisted postoperatively (11). The placebo effect was clearly recognized, and the procedure was discarded.

**OPEN-HEART SURGERY**

The success of mitral commissurotomy emphasized the fact that only a small portion of the various congenital and acquired heart diseases potentially amenable to surgical treatment were being addressed. What was obvious was that most of these diseases could only be surgically approached by opening the heart to perform repairs in a blood-free field. What was needed was a machine to receive all the venous blood returning to the heart, oxygenate it, and then return it to the arterial circulation. Lacking this, surgeons attempted other methods to achieve their goals.

At the University of Minnesota, hypothermia was used to close an atrial septal defect by F. John Lewis in 1953, with the technique pursued by others, most notably Henry Swan (12). However, the technique was applicable to only a limited number of abnormalities and required repair in 6 minutes or less to avoid damage to the patient. Also at Minnesota at the time, C. Walton Lillehei and his team adopted their own approach to the problem. Much as they did in the dog laboratory, they decided to use a normal donor, in this case usually a parent with the same blood type as the patient, to serve as the pump-oxygenator. Criticized as the only operation with possibly 200% mortality, Lillehei’s cross-circulation operation was remarkably successful. Their results in a 30-year follow-up were impressive (13). Among 45 patients operated upon between March 1954 and July 1955, there were only 8 hospital deaths and 2 late deaths.

No donors died or were incapacitated except for one who suffered a cerebral air embolism due to an error by an attending anesthesiologist.

The need for this and other less ideal approaches ended in May 1953 when, after many years of effort, John Gibbon performed the first successful repair of an atrial septal defect with the pump-oxygenator he had developed (14). However, he was unable to repeat this success in the next two patients and abandoned the field. A few scattered attempts were made at various institutions with other versions of this apparatus, but the technique could not be firmly accepted unless a series of patients with successful operations could be reported. John Kirklin and his associates at the Mayo Clinic were determined to correct this deficiency. Using a modification of the Gibbon apparatus, they performed open-heart surgery in eight patients (15). The series was small and the mortality, at 50%, high. Was the glass half empty or half full? The medical community decided that the results were promising, and the era of open-heart surgery had begun in earnest.

**CARDIAC TRANSPLANTATION**

The world was enthralled by the report from Groote Schuur Hospital in Cape Town, South Africa, that on December 3, 1967, Christiaan Barnard had performed the first successful human cardiac transplantation (16, 17). The patient, Louis Washkansky, lived 18 days after recovering from surgery. His death was probably due to infection rather than rejection, but it was the latter that was soon on everyone’s mind after dismal experiences with kidney transplantation due to this phenomenon. Barnard’s second patient, Philip Blaiberg, survived 19 months, providing hope that the problem of rejection might not be as severe as had been found with the kidney. Perhaps the heart was less immunogenic than the kidney? Perhaps the antirejection drugs might be more effective in the heart? Perhaps if they just did enough of these procedures surgeons could ascend the learning curve to achieve truly acceptable results?

Over the next year and a half, hundreds of patients were subjected to the procedure with uniform failure following. One discouraged physician associated with a particularly active surgical team likened what they were doing to manslaughter. Finally a general moratorium was put in place until cyclosporine arrived on the scene in the 1970s (18). Despite the success achieved with this drug, only 2000 or so transplantations have been performed annually since it was introduced. There simply are not enough donor hearts available for the thousands upon thousands of patients with end-stage heart failure awaiting relief.

**THE TOTAL ARTIFICIAL HEART**

Despite the great advances in the surgical treatment of heart disease, a major problem continues to persist: finding an effective treatment for intractable heart failure. An ideal solution would be a mechanical heart that could be easily implanted, free of complications, long lasting, and capable of providing the recipient with a good quality of life. Although experimental work on such a
device had begun in earnest as early as the 1950s, the first clinical application of the total artificial heart was performed on April 4, 1969, by Denton Cooley in Houston, Texas (19–21).

Perhaps no innovation in the history of cardiac surgery aroused as much controversy as the artificial heart. Cooley and his associate, Domingo Liotta, used a device similar to that developed by Liotta while working in Michael DeBakey's laboratory. The patient, Haskell Karp, died 37 hours postoperatively from infection believed secondary to immunosuppressant drugs. On the day of surgery, DeBakey was out of town, and he did not learn of the procedure until after it was completed. He had resisted the use of the total artificial heart in humans, commenting, “Up to then no animal in which we had implanted the heart had survived beyond 48 hours” (22). If you could not keep a healthy calf alive with the device, how could you expect good results in a patient with advanced heart failure?

Regardless of the merit of performing such a procedure, Cooley had violated the guidelines of the National Institutes of Health research grants. Any new procedure on humans had to be approved by the head of the research program (DeBakey), the human research committee at Baylor College of Medicine, and the National Institutes of Health. Cooley went ahead without receiving any such approvals. Although many physicians admired Cooley's ability and may have even sympathized with his position, others felt that, whatever his motivation, Cooley had acted illegally. Years later in an in-depth review of the issue, with which Cooley, unlike DeBakey, had declined to participate, Cooley was deemed at fault (23).

Cooley has always maintained that he was acting in his patient's best interest, the primary responsibility of the physician (21; personal communication, June 13, 2013). He has noted that the quality of surgery performed in the animal laboratory was hardly equivalent to what he performed. Postoperative care in the laboratory, especially back in 1969, was not equal to that available today. He denied knowing of DeBakey's whereabouts on the day of surgery and, even if he did, he would have proceeded, within his rights as the director of the Texas Heart Institute.

In July 1981 he performed a second implant, this time with Tetsuo Akutsu, a pioneer in this kind of research, who was at the Texas Heart Institute at the time. The result was similar to that of Karp. In both patients they described these attempts as bridges to cardiac transplantation when donor hearts became available.

In 1984 a total artificial heart was permanently implanted in a patient, Barney Clark, by William DeVries at the University of Utah in Salt Lake City (24). Working closely with him on this effort was Willem S. Kolff, who had been working on this problem for decades, and Robert K. Jarvik, designer of the artificial heart employed. Clark experienced multiple and predominantly thromboembolic sequelae and died 112 days after a difficult postoperative course. Later attempts at this kind of surgery by DeVries and others were all plagued by similar problems. Despite such disheartening results, some surgeons have continued to use the device with some degree of success. Jack Copeland, for example, has demonstrated that using an artificial heart as a bridge to cardiac transplantation can result in significant increases in survival time to transplantation and improved survival after transplantation (25). Kolff, in his remaining years, maintained his enthusiasm for the total artificial heart and felt that its ultimate success only required better design and better medical management. In the meantime, left ventricular assist devices and occasionally right ventricular assist devices are providing some relief to patients with advanced heart failure, and attempts to develop animal models (pigs) that do not provoke immune reaction are undergoing study.

DISCUSSION

Even with this limited review consisting of only a handful of examples, there is much to ponder. What does it tell us about the different ways in which advances in research come about? What does it reveal about the kinds of individuals engaging in such research? What influence did the profession's mores at the time have on the conduct of research? How would current standards of patient-based research have affected such attempts?

The value of some surgical innovations becomes apparent very early in the game. Successful ligation of the persistently patent ductus arteriosus was achieved on the first attempt by Gross and with equal success with his second patient. More often than not, however, in developing a new surgical technique initial attempts fail. Only after multiple additional surgeries, with lessons learned along the way, is success finally achieved. This certainly applied to the case of mitral stenosis when, it seemed, a critical tipping point had to be reached at several centers before the goal was obtained. This phenomenon is not limited to cardiovascular research. Willem Kolff, inventor of the first workable artificial kidney, never tired of telling how only one of the first 15 patients he treated survived, with that single success probably related to factors other than his receiving dialysis.

Assuming that a critical number of procedures must be reached to ensure success can lead researchers astray, as in the case of cardiac transplantation, where hundreds of patients were, in a sense, sacrificed while the problem of rejection continued to plague their doctors. The acceptance of open-heart surgery using the pump-oxygenator depended upon the conviction that even a 50% survival gave reason to hope for better things to come.

What about the surgeons and their medical colleagues who persist in such endeavors? What really motivates them? Money does not seem to have been a goal, although some surgeons have accumulated wealth as a result of the kind of services they provided. What does seem evident among such individuals is a kind of compulsion bordering on the monomaniacal to pursue their goals. How else to account for John Gibbon's working on a heart-lung machine for about two decades, beginning in the 1930s and culminating in his first and only success in 1953? The responses of other surgeons follow a similar pattern. Charles Bailey, never at a loss for words, expressed his own feelings as follows:

Finally, however, you have to face “the moment of truth,” and the poignancy is so great that I can't really express it. You know that almost all the world is against it; you know that you have a great personal stake and might even lose your medical license, or at least your hospital privileges, if you persist. In fact the thought
crosses your mind that maybe you really are crazy. And yet you feel that it has to be done and that it must be right (26).

What some might view as devious—the scheduling of patients by Gross and Cooley—could well have been motivated by such strong beliefs in the rightness of their cause.

The task of monitoring such efforts, as complex and unpredictable as they are, is daunting. What seems to have evolved from a relatively circumscribed set of rules to prevent abuse and guide the use of patients and other research volunteers is a burgeoning body of regulations apparently increasingly based on the presumption of physicians’ lack of responsibility and inclination toward ethical error. In this view, unless closely supervised and observed, physicians might not be relied upon to maintain or improve their skills, keep abreast of new developments, or even relate to their patients in a humane, caring way.

The Nuremberg Code (1947) and the Declaration of Helsinki (1964) were clearly dedicated to patients’ rights. The Belmont Report (1970) codified such issues, including the establishment of institutional review boards. Subsequent legislation and regulations, some of them even initiated by organized medicine, have, in practice, focused more on physician behavior. The Health Insurance Portability and Accountability Act (1996) was a major step in this direction. Added to this over the years has been the growth of specialty certification and recertification, not always with clear intent or determined outcome (27). Physicians who traditionally attended medical meetings of all kinds wholeheartedly are now required to prove it through documented continuing medical education credits for licensure and staff privileges. Work hour restrictions for housestaff have been imposed without any evaluation of benefit or loss due to the various factors involved. The latest wrinkle in the oversight onslaught in some states is proof of “cultural competence,” without which licensure may not be renewed.

Under the present system of supervision, it is unlikely that many of the successful surgical innovations we have witnessed would have been achieved. Would Gross or Cooley have dared their innovations, depending only on an understanding between them and the families involved? Would Bailey and the other pioneers of mitral valve surgery have been allowed to proceed? Would Lillehei have been permitted to use his patients’ parents as “pump-oxygenators”? Would Kirklin and his counterparts elsewhere in the United States have been permitted to continue performing open-heart surgery with such high mortality rates?

Much mention is made of the balance between risk and benefit in research. The problem is that, in practice, neither risk nor benefit can easily be assessed until after the fact. The men and women now empowered to make such judgments face a difficult task in choosing the right path to follow. The enactment of yet another set of regulations is unlikely to steer them along it. We can only hope that a little less hubris and a little more humility will guide them in overseeing the ethical problems that most certainly will continue to engage us.

**Acknowledgment**

Nastasia Moschos provided translation from Italian to English.

During my 30 years at Baylor University Medical Center at Dallas (BUMC), I have had the opportunity to work with many great mentors. I enjoyed the experience immensely and remain grateful to my teachers. I have also enjoyed working with the business evolution and leadership opportunities in gastroenterology. By far my favorite learning experiences have to do with new and emerging gastrointestinal (GI) technologies.

It has been my privilege to participate in the development and introduction of many new GI technologies, which give gastroenterologists the ability to do so much more for patients. My work with innovating GI procedures started during my fellowship and continued throughout my career. I trust you will also enjoy remembering how some procedures and technologies have come and gone, while others have become commonplace.

In the early 1980s, Dr. Reed Hogan II and I began to do a procedure called endoscopic percutaneous gastrostomy, which had begun in 1979. As part of its development, I changed the name to percutaneous endoscopic gastrostomy, and now it is commonly referred to as a PEG. My involvement with the development of this technique, and the tube itself, came out of an unfortunate experience. Dr. J. Kent Hamilton and I had finished placing a PEG that was manufactured by the company when the patient developed stridor. He was blue. I’m sure he had very low oxygen saturation, but we had no pulse oximetry back then. When we examined the patient, we realized that the crossbar had popped off the end of the PEG and was lodged above the vocal cords. We removed the crossbar endoscopically, and the patient did fine. I was angry.

I immediately called the company and told them their PEG was defective and dangerous. Despite my anger at the time, I subsequently developed a longstanding relationship with the company. This resulted in our participating in animal studies using new PEG tubes with only one piece. The engineers would fly in from Boston, and we would spend an afternoon working on animals and placing multiple PEGs, looking for failures. Subsequently, I became a member of the Institutional Animal Care and Use Committee and, for the past 10 years, have been its chairman. This all happened because of a crossbar falling off of a poorly manufactured PEG tube.

Also around this time, Dr. Reed Hogan II and I embarked upon a study comparing two different methods of placing PEGs. We recruited many patients from a local rehabilitation hospital. This led to a publication entitled “Percutaneous Endoscopic Gastrostomy—to Push or to Pull: a Prospective Randomized Trial,” published in Gastrointestinal Endoscopy. This was my first GI publication.

While working in the animal lab, I found an automated TruCut needle that was used for prostate biopsies. We used this on the animals to do some liver biopsies while we were replacing PEG tubes. Subsequently, further developments occurred, and that automated TruCut needle is now commonly used to perform liver biopsies.

The first balloon catheter was invented by Fogarty in 1963. Everybody knows that Dr. Hogan and I were the first GI fellows to use the through-the-scope balloon dilators. What they do not know is that this experience almost resulted in Dr. Hogan losing his fellowship. This is a long story that had to do with our relationship with other institutions and the use of novel devices.

Also, early in my career, gastric bubbles were approved by the Food and Drug Administration. These were bubbles made of plastic that were filled with air and placed into patients’ stomachs for the treatment of obesity. The idea was that gastric bubbles would cause early satiety and decrease food intake. Dr. John Fordtran never allowed us to use gastric bubbles because he said, “At Baylor, we take out bezoars.” In fact, I had the only bubble at Baylor which I kept in my desk drawer. I was dying to put it in somebody! Gastric bubbles did not go very far. In a study he conducted after his fellowship, Dr. Hogan showed that they were ineffective in causing weight reduction.

BUMC’s gastroenterology department was the first to do a study using disposable biopsy forceps. Initially, forceps came from the Division of Gastroenterology, Department of Internal Medicine, Baylor University Medical Center at Dallas.

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that, and it was a bad idea. Besides, sclerotherapy worked. A varices. I told them that I thought they were crazy, that it would about the idea of trying to put a hemorrhoid band on esophageal ing new endoscopic technology, they asked me what I thought sheathed fi ber optic fl exi-sig scopes were accepted on the mar-

video scopes did not persist on the market for long. However, sheathed fi ber optic flexi-sig scopes were accepted on the mar-

ket for a while. We actually had one in the office. Once video endoscopy came out, we looked at disposable video scopes. However, they could not be manufactured at a price that would compete with buying a scope and reprocessing it. Disposable video scopes did not persist on the market for long.

During one of my visits to a company interested in developing new endoscopic technology, they asked me what I thought about the idea of trying to put a hemorrhoid band on esophageal varices. I told them that I thought they were crazy, that it would be impossible as patients would not sit still for something like that, and it was a bad idea. Besides, sclerotherapy worked. A few months later, the Steigman-Goff endoscopic band ligator came out, and I had to eat my words. Sclerotherapy is now no longer taught to GI fellows.

I was the first at BUMC to perform endoscopic band ligation of esophageal varices. The first patient for whom I used band ligation was from Mexico. He did great. Later, he and his doctor had me travel to Mexico to perform band ligation on a large number of cirrhotic patients who had been waiting a long time for the procedure. I cannot recall how many patients we treated, but we learned a lot about potential scope turnaround time when you are motivated. The fellow was in charge of scope reprocessing. It was also an experience trying to do band ligation with suction provided only by a little pump sitting on the floor, not to mention the complete absence of intravenous access or anesthesia assistance. This was a long time ago in a land far away.

The first transjugular intrahepatic portosystemic shunt (TIPS) was performed at BUMC around 20 years ago because we had a lot of problems with portal hypertension at that time. We still do. The story about the TIPS procedure is that it was first done in San Antonio. Then, one of our interventional radiologists said he would like to try it at BUMC. An interesting thing is that this conversation occurred at a party at a vascular surgeon’s home. I told the radiologist that if I had a case, it would a nontransplantable patient. A few months later, we found one. It took the interventional radiologists 2 days to place their first TIPS. Now it takes only several hours.

Early in my career, I was anxious for BUMC to begin doing endoscopic ultrasound. I made several trips to the Medical University of South Carolina and studied under Dr. Rob Hawes, which was the beginning of a long-lasting relationship. He was an excellent teacher, and I felt quite confident in bringing the technology back to BUMC. After performing endoscopic ultrasound for 5 years, it became apparent that the standard of practice would be for endoscopists to do an additional year of fellowship training in advanced endoscopy and endoscopic ultrasound. Given this and the fact that I was reluctant to return to fellowship, I gave up the art of endoscopic ultrasonography, although only after acquiring new associates who had completed a full year of additional training. However, I still enjoy watching an occasional endoscopic ultrasound. I also taught the cardiolo-
gists how to pass the transesophageal echocardiography (TEE) probe. Dr. Charles Gottlich and I were the first at BUMC to do (and have) a TEE. He wanted to go first, but he could not choke down the probe. So I went ahead and did it on myself. He said that we were now brothers and that I could no longer eat pork!

We started to evaluate endoscopic antireflux procedures. The first one was referred to as the EndoCinch procedure or endoluminal gastric plication. This consisted of having a little sewing machine at the end of an endoscope. I traveled to Memphis and learned the technique under Dr. Rich Rothstein. It occurred to me that I might be in the crosshairs of laparoscopic surgeons if I was taking cases from them and doing this procedure instead of laparoscopic Nissen. To accommodate the differing patient needs, we started the Baylor Heartburn Center to provide both endoscopic and laparoscopic solutions for intractable heartburn. We made multiple presentations to the public, with most attendees being people seeking free food and medical advice. I like to think the advice was better than the food. One seminar was scheduled to take place on 17 Roberts on the evening of September 11, 2001. We canceled it for obvious reasons. There were some upset and hungry potential attendees.

The Baylor Heartburn Center proved to be a dramatic success and, over the course of a year, we performed over 70 endoluminal gastric plications and around 30 or 40 laparoscopic Nissens. The endoscopic gastric plication technology, though, proved to be short-lived and was replaced by Enterex, a polymer injection at the lower esophageal sphincter. This was also short-lived as it was associated with multiple complications, but not before we were able to establish our place as a center of excellence for it. However, because of funding, the technology was withdrawn from the market. Subsequently, we adopted a technique called the NDO Plicator. This endoscopic antireflux procedure was quite effective, but also suffered the same fate of not obtaining a procedure code and not getting reimbursed. The company went bankrupt, and The Heartburn Center wound down.

About the same time, small-bowel capsules came into view. The staff and space that was devoted to the Heartburn Center was converted to the Capsule Endoscopy Center. We were the first gastroenterologists in the area to do capsule enteroscopy, and this led to the need to scope the small bowel to treat the pathology found with capsule enteroscopy. Subsequently, double-balloon enteroscopy was developed. I went to Philadelphia to learn how to do this under Dr. Oleh Haluska and really enjoyed the technology and our relationship.
Fortunately, at this time, we also moved the GI lab to the first floor of the Truett-Johnson area. I dreamed about the floor plan every night. Just before completion, one of our nurses pointed out that I, along with the team of hospital architects, had forgotten to include a laundry chute. We squeezed one in at the last minute and it dumped right into vice president Dr. Irving Prengler’s office downstairs. Oh well.

By this time, I was established as the medical director of endoscopy, and Dr. Rick Boland was chief of gastroenterology. He gave me lots of freedom, since he was focused on finding a cure for colon cancer. The double-balloon enteroscopy required a Fujinon endoscopy system, and we had no Fujinon setups when we moved the GI lab down to the first floor. Since we still had two new rooms to finish, we chose to put Fujinon in these two rooms. This made double-balloon enteroscopy possible at BUMC at a time when the technology was gaining wide acceptance.

We also did some single-balloon enteroscopy and, subsequently, spiral enteroscopy became available. With spiral endoscopy, we could “rotate” our way through at least 50% of the small bowel in 20 to 30 minutes. I am still working on new methods in this area and have been able to get the entire small bowel examined in five patients in approximately 25 minutes using a motorized scope. I subsequently became the lead investigator for the development of power spiral enteroscopy, working mostly offshore. This resulted in many international excursions and subsequent cycles of antibiotics for me.

We then started to look at ways to treat Barrett’s esophagus. Radiofrequency ablation for gastroenterology became available and, prior to doing my first case at BUMC, I journeyed to Houston to watch a case done by my friend Dr. Isaac Rajzman. The best part of this was the trip itself because, by that time, I was flying my own plane.

Polyps are hidden behind folds, and a new technology called the Third Eye was developed. This was also known as an auxiliary retrograde viewing device. We were part of the early studies, and this resulted in several publications that gave our fellows a lot to do in their spare time. Despite the fact that we demonstrated that more polyps could be found using the Third Eye, the technology has still not taken off because of reimbursement issues. In an effort to overcome this, I made several trips to the headquarters of the Centers for Medicare and Medicaid Services outside of Washington, DC. It is a huge place with very tight security, although I am not exactly sure what they are protecting.

From a practice standpoint, I was one of the first to establish outreach programs because I had colleagues who had built up internal medicine practices in Ellis County. I started going there on my afternoon off. Subsequently, a full practice developed, and I felt too busy to be in two places at once. I hired another physician to work in Ellis County, but when he did not treat the practice well, Digestive Health Associates of Texas (DHAT) left Ellis County.

The interesting thing about the formation of DHAT, which is one of the nation’s largest GI groups, was that it actually started with a conversation over a six-pack among three of us (Dr. Dan Polter, Dr. Tom Rogoff, and myself) meeting at a gastroenterologist’s house one evening. Dr. Larry Schiller came up with the name for DHAT, focusing on digestive health rather than digestive disease. I sincerely believe the formation of DHAT would not have been possible without Dr. Dan Polter. He was so well respected and trusted around the Dallas area that he was able to single-handedly recruit the practices that now make up DHAT. Once established, DHAT took on a life of its own. Dr. Dan Polter and I are no longer involved with running the practice, but it has been a pleasure to see DHAT evolve into one of the premier GI practices in the US.

Overall, my GI career has been a tremendous experience. I greatly enjoyed teaching all the fellows and participating in the development of this new technology. I thank all of my mentors, and I also thank all of my students.
Clinical utility of positron emission mammography

Shannon B. Glass, MD, and Zeeshan A. Shah, MD

Several imaging modalities have been introduced over recent years to better screen for and stage breast cancer. Positron emission mammography (PEM) has been approved by the US Food and Drug Administration and introduced into clinical use as a diagnostic adjunct to mammography and breast ultrasonography. PEM has higher resolution and a more localized field of view than positron emission tomography–computed tomography and can be performed on patients to stage a newly diagnosed malignancy. Review of mammograms together with magnetic resonance or PEM images improves detection of disease.

Breast cancer remains the most prevalent cancer in women of developed countries with great social and economic impact. The scientific community is therefore focused on improving imaging methods for screening and staging of breast cancer. Conventional screening has traditionally included a combination of breast self-examination, clinical breast examination, and screening mammography (1).

Among the imaging modalities introduced over recent years is breast magnetic resonance imaging (MRI), a promising technique for the detection, diagnosis, and staging of breast carcinoma. Generally accepted indications for MRI include evaluating response in patients treated with chemotherapy, screening high-risk patients, aiding the detection of primary tumors in patients with nodal metastases of unknown character, and staging known breast carcinoma (2). There are, however, contraindications to MRI, including pacemakers, a metallic foreign body in the orbit, some aneurysm clips, claustrophobia, renal disease, and an allergy to gadolinium. Other factors, such as orthopedic spinal hardware, can degrade the image quality and interpretation.

Another imaging modality that has been utilized in breast cancer patients is positron emission tomography–computed tomography (PET-CT), which has allowed the merging of morphological and functional images, thereby providing information about the metabolic activity of neoplastic tissue and tumor biology. This information can be used to differentiate between benign and malignant lesions, identify metastasis for disease staging, evaluate treatment response, and assess tumor aggressiveness. However, due to the limited resolution of PET equipment and the space limitations of the current protocols for CT acquisition, small breast tumors are not visible with this technique (3).

Positron emission mammography (PEM) is a new imaging modality that has higher resolution than PET-CT and can be performed on patients unable to have an MRI scan. PEM uses a pair of dedicated gamma radiation detectors placed above and below the breast and mild breast compression to detect coincident gamma rays after administration of fluorine-18 fluorodeoxyglucose (18F-FDG), the positron-emitting radionuclide used in whole-body PET studies for the detection of metastatic disease (4). There is currently only one commercially available PEM scanner, the PEM Flex Solo II (5, 6) (Figure 1). This article provides an overview of the technology of PEM and describes its advantages and potential disadvantages for future applications in the clinical setting.

Figure 1. Positron emission mammography scanner. Photo courtesy of Naviscan, Inc.
POSITRON EMISSION MAMMOGRAPHY TECHNOLOGY

PEM is a high-resolution tomographic method for molecular imaging of positron-emitting isotopes. The principle behind this technology is that cancer cells demonstrate increased utilization of glucose. Through use of isotope fluorine-18 attached to the delivery compound deoxyglucose to produce the radiopharmaceutical $^{18}$F-FDG, this utilization of glucose can be visualized. $^{18}$F-FDG is taken up into the cancer cell via glucose transporter 1. Once inside the cell, the radiopharmaceutical becomes phosphorylated and cannot be transported back out of the cell, leading to its accumulation. The fluorine-18 nucleus is unstable, and as it decays a positron is emitted. The collision of the positron with an electron results in the production of two 511 keV gamma rays, which are emitted 180 degrees from each other. In PEM, these gamma rays are detected by striking a pair of dedicated gamma radiation detectors placed above and below the breast. Once the gamma rays are detected, they are amplified by photon-sensitive photomultipliers and translated into an electrical signal that becomes digitized and is stored as computer memory (7) (Figure 2).

The technology of PEM and PET are similar in that they both provide functional imaging employing $^{18}$F-FDG. However, PEM is optimized for small body parts and utilizes gentle immobilization of the breast (Figure 3) to attain higher spatial resolution (1–2 mm for PEM vs 4–6 mm for PET), as well as minimize the radiation dose by reducing breast thickness (8). The crystal detectors in PEM are constructed to provide this improved spatial resolution (1.5 mm in-plane, 5 mm between planes) and count rate efficiency (1 M reconstructed counts in 10 minutes).

The result of PEM imaging is a set of 12 slices each in the cranio-caudal and mediolateral oblique positions, analogous to mammography (Figure 4). The three-dimensional tomographic image set provides detailed location of normal and abnormal FDG uptake as well as features or architectural patterns of any abnormal uptake (9). The smaller overall detector size facilitates the use of high-resolution components and allows closer proximity to the source, enhancing annihilation photon sensitivity (10).

![Figure 2.](image1) The signal received by the detectors is stored as computer memory and utilized to determine spatial information about the lesion. Photo courtesy of Naviscan, Inc.

![Figure 3.](image2) PEM utilizes compression paddles placed on both sides of the breast with positioning similar to mammography, as can be seen (a) schematically and (b) in a patient. Photo courtesy of Naviscan, Inc.
Despite the high sensitivities described for both exam types, PEM suffers from the same specificity issues as those seen in breast MRI. The specificity for detecting carcinoma ranges from 85% to 92% for MRI and from 92% to 97% for PEM (14). A number of nonmalignant lesions can accumulate radionuclide, such as fibroadenoma, fibrocystic change, and fat necrosis (Figure 8). To address this issue, commercially available biopsy systems can be used, which allow vacuum-assisted biopsy of PEM-detected lesions prior to altering surgical management. Positive predictive values of these biopsies have been similar to those seen for MRI-guided biopsy and higher than that seen for mammography.

Additionally, a disadvantage of PEM is the radiation exposure. In terms of relative risk to a 40-year-old woman, a single PEM study involving the use of a label-recommended radionuclide dose is associated with a 15-fold higher

ADVANTAGES AND DISADVANTAGES OF POSITRON EMISSION MAMMOGRAPHY

Relative to whole-body PET, PEM’s advantage lies in its ability to detect small hypermetabolic lesions. PEM can detect lesions measuring <2 cm as a result of its higher spatial resolution of up to 2.4 mm (Figure 5). Even in very small tumors measuring <1 cm, the imaging sensitivity of PEM has been reported to be 60% to 70% (2). When PEM has been directly compared with PET and MRI, the reported sensitivity of PEM was 93% for known index lesions and 85% for unsuspected additional lesions. The sensitivity was comparable to that of MRI and significantly higher than that of PET, particularly in small tumors (11). In another study, PEM and MRI were both shown to have index lesion sensitivity of 92.8%. Whole-body PET demonstrated a sensitivity of only 67.9% (12).

As both MRI and PEM have similar sensitivities, PEM’s role in clinical practice mirrors that of MRI. Detection and characterization of primary breast lesions in preoperative surgical planning or prechemotherapy evaluation remain primary indications for the exam. The utility of PEM has been demonstrated in staging both the ipsilateral and contralateral breasts in newly diagnosed patients as an alternative to MRI (Figures 6–7). MRI has been shown to be more sensitive than PEM in the detection of malignancy, although particularly for ipsilateral lesions, PEM is more specific. It can therefore be concluded that in patients in whom MRI may be contraindicated, PEM can still play a valuable role in the detection of additional foci of malignancy (13, 14).
risk of cancer induction than a single screen film or digital mammogram. Overall, there is also a 25-fold higher risk of cancer-related mortality. In mammography, fibroglandular tissue is the only tissue exposed to a substantial level of ionizing radiation. In PEM, however, all body organs are irradiated with radionuclides. Therefore, the risk from mammography is essentially only that of induced breast cancer, while PEM can lead to cancer induction in any number of radiosensitive organs. This is caused primarily by a reliance on both radioactive decay (fluorine-18 positron emissions having a 110-minute half-life) and biologic clearance for the excretion of radionuclides. The highest radiation dose and cancer risk with PEM is to the bladder (4).

FUTURE OF POSITRON EMISSION MAMMOGRAPHY

PEM was approved by the US Food and Drug Administration and has been introduced into clinical use as a diagnostic adjunct to mammography and breast ultrasonography. PEM is currently under clinical investigation in hopes of improving the sensitivity of breast cancer screening (1). Indications for PEM include initial staging evaluation of patients with newly diagnosed cancer (i.e., determining extent of disease, but not including axillary node staging), distinguishing recurrent carcinoma from scar, and monitoring response to neoadjuvant chemotherapy (15). Currently, PEM is used specifically in patients diagnosed with breast cancer who are considering breast conservation surgery to evaluate for multifocal or multicentric disease (9).

Whereas PEM has high imaging sensitivity for breast lesions, its clinical utility requires further investigation. PEM cannot provide the anatomical detail that is provided by MRI. It can, however, be an alternative form of staging for patients who cannot tolerate MRI, have scheduling constraints due to their hormonal status/menstrual cycle, or have no access to breast MRI, as well as for communities struggling to implement a successful breast MRI program (12). Due to the radiation dose received by a patient during a PEM scan, it is likely that PEM will be employed as an alternative for women who are not candidates for MRI. PEM should be considered a strong adjunct to conventional imaging in those patients unable to undergo MRI who qualify for staging of newly diagnosed malignancy.

5. Springer A, Mawlawi OR. Evaluation of the quantitative accuracy of 2
Figure 7. High-grade invasive ductal carcinoma in a 39-year-old woman who presented with a palpable mass in the right breast. The patient had (a) a diagnostic mammogram that demonstrated a 2-cm mass in the right breast that corresponded to the palpable area of concern, seen on both the cranio-caudal and mediolateral oblique views, and persisted on (b) a magnification view. Prominent lymph nodes were also noted in the right axilla on the mediolateral oblique view (a). (c) The lesion was then further evaluated with right breast sonogram, which showed a highly suspicious hypoechoic solid mass in the region of palpable concern. (d) A sonogram of the axilla demonstrated two prominent lymph nodes, which were concerning for metastatic involvement. A sonographic-guided biopsy of the dominant mass was performed and demonstrated high-grade invasive ductal carcinoma. (e) An MRI was then performed to evaluate the local extent of disease, which showed a dominant irregular enhancing mass within the right breast as well as multiple additional satellite nodules (single arrow) within the upper inner quadrant of the right breast and right axillary lymphadenopathy (double arrows). PEM was then performed to aid in further staging the patient’s disease. The (f) cranio-caudal and (g) mediolateral oblique views demonstrated a hypermetabolic round mass within the right breast with two adjacent subcentimeter satellite lesions, as well as increased uptake within two axillary lymph nodes (gray arrows). The axillary lymph nodes were better seen on (h) an axillary view and were felt most compatible with metastatic disease given their intense uptake on PEM. These findings were confirmed during surgery.

Figure 8. A 51-year-old woman who had a previous left lumpectomy for ductal carcinoma in situ was noted to have a changing appearance of lumpectomy bed on mammogram seen on both (a) cranio-caudal and (b) lateral views of the left breast. She subsequently had a PEM scan that showed a region of increased uptake of radiotracer within the lumpectomy bed on both (c) cranio-caudal and (d) mediolateral oblique views. Although this was felt to most likely reflect postsurgical change, the presence of residual malignancy could not be excluded. The patient therefore underwent ultrasound-guided biopsy, which demonstrated fat necrosis, fibrosis, and granulation tissue, without evidence of residual neoplasm. This case highlights the inability of PEM to differentiate between metabolically active lesions of varying etiology.


Despite the use of combination drug therapies, many patients still have uncontrolled hypertension. Resistant hypertension is defined as a blood pressure that remains above goal in spite of compliance on ≥3 antihypertensive medications of different classes, one of which must be a diuretic. Renal denervation therapy attempts to address this difficult-to-treat population by blocking the sympathetic nerve activity to the kidneys.

Treatment of systemic hypertension with sympathectomy was initiated in the 1930s. In 1953, Smithwick and Thompson described 1266 cases of sympathectomies performed for treatment of patients with systemic hypertension. They found that there was a significant mortality benefit in the treated patients, but at a cost of a significant increase in morbidity, mainly due to postural hypotension, gastrointestinal disturbances, and impotence (1). Dr. Thompson went on to have a long and distinguished career. He practiced vascular surgery at Baylor for over 30 years, during which time he was the chairman of the Department of Surgery from 1982 to 1986.

The Symplicity renal denervation system (Figure 1) is a novel treatment utilizing a minimally invasive catheter-based procedure that uses radiofrequency to ablate the sympathetic nerves lying in the renal artery. It is believed that blocking the sympathetic nervous system will lead to a reversal of fluid and salt retention and reduce the inappropriate release of renin that is contributing to uncontrolled hypertension. Blocking the renal sympathetic nerves has also been shown to have beneficial effects on organs damaged by chronic sympathetic overactivity, including the blood vessels, kidneys, and heart (2).

The nonsurgical procedure is performed endovascularly with access through the femoral artery. Prior to denervation, a renal artery arteriogram is performed to rule out any hemodynamically significant renal artery stenosis. The renal nerves are arborized around the renal arteries and lie within the adventitial layer of the vessel (Figure 2). The Symplicity renal denervation system is placed into each renal artery, and radiofrequency ablation (5–8 watts) is performed with four to six 120-second treatments starting distally and moving proximally, with spacing of 5 mm between treatment sites.

The Symplicity HTN-1 Trial was a multicenter nonrandomized open-label proof-of-concept study that enrolled 153 patients with medically resistant hypertension. Patients received catheter-based renal denervation plus baseline antihypertensive medications and were followed for 36 months. At 6 months, the average drop in blood pressure in the patients was 22 mm Hg systolic and 10 mm Hg diastolic. These results at 36-month follow-up showed a 33 mm Hg systolic and 19 mm Hg diastolic blood pressure reduction (Figure 3). There were no reported events of vascular injury or change in renal function (3).
These data led to the Symplicity HTN-2 Trial, which was a multicenter international randomized controlled study comparing renal denervation plus baseline antihypertensive medications versus baseline medications alone. After 6 months, the treatment arm had a mean reduction of 33 mm Hg in the systolic blood pressure and 12 mm Hg in the diastolic blood pressure (Figure 4). The control arm did not have any change in blood pressure. There were no major procedure or device-related events (4).

These two trials are the basis of the Symplicity HTN-3 Trial, which is a single-blinded, randomized controlled trial designed to evaluate the safety and effectiveness of the Symplicity renal denervation system in patients with resistant hypertension. This trial plans to enroll 530 patients who will be randomized to receive either renal denervation plus antihypertensive medications or a sham procedure and antihypertensive medications. The primary endpoints will be change in blood pressure from baseline at 6 months and the incidence of adverse events at 1 month following randomization. There are three inclusion criteria: 1) having an average systolic blood pressure ≥160 mm Hg; 2) being on three antihypertensive medications, one of which is a diuretic; and 3) being 18 to 80 years old. The exclusion criteria include 1) hemodynamically significant renal artery stenosis; 2) glomerular filtration rate <45 mL/min/1.73 m²; 3) type I diabetes mellitus; 4) symptomatic orthostatic hypotension; 5) stenotic valvular heart disease; 6) acute coronary syndrome or cerebrovascular accident in the past 6 months; 7) planned cardiovascular intervention in the next 6 months; 8) primary pulmonary hypertension; 9) coarctation of the aorta, thyroid disorders, or Cushing’s disease; and 9) alcohol or drug abuse. We at Baylor University Medical Center are currently enrolling patients for the Symplicity HTN-3 Trial.

William Leslie Jack Edwards, MD: a conversation with the editor

William Leslie Jack Edwards, MD, and William Clifford Roberts, MD

Jack Edwards (Figure 1) was born on September 21, 1926, in Dallas, Texas, where he grew up and has lived most of his life. After attending public schools in Dallas, he went to Harvard College in Boston, Massachusetts, finishing 3 years in 2 years. He then went to the University of Texas (UT) Southwestern Medical College in Dallas, where he received his medical degree in 1948. He completed two internships: one in pathology at the Peter Bent Brigham Hospital in Boston (July 1948–June 1949) and one in medicine at the Massachusetts Memorial Hospital (July 1949–June 1950). He returned to Dallas and soon thereafter was called to active duty, serving in the Navy. In 1952, discharged from the service, he went to Birmingham, Alabama, and the University of Alabama Hospitals where he was assistant resident and chief resident and then a National Heart Institute trainee in cardiology under Dr. Tinsley Harrison. He then returned to Dallas, settling in private practice and using primarily Baylor University Medical Center at Dallas (BUMC). From 1971 until 1993, he also was clinical professor of medicine at UT Southwestern Medical College. Jack was a past president of the Southwestern Alumni Association and the Dallas Heart Association. He is a longstanding member of the Little Brothers Journal Club. He was a major player in the BUMC community from 1955 until he retired from active practice in 1993. Jack Edwards is a great guy, and it was a pleasure to visit with him for this interview.

William Clifford Roberts, MD (hereafter, Roberts): Jack, could we start by my asking you about some of your early memories?

William Leslie Jack Edwards, MD (hereafter, Edwards): I was born in St. Paul’s Hospital in Dallas, Texas. The first thing I remember was at age 4, sitting on a curb watching kids playing across the street. My momma told me I couldn’t cross the street, and I was very unhappy.

Roberts: What happened from there?

Edwards: I don’t remember anything more. I grew up on Euclid Street in East Dallas, a couple of blocks from Greenville Avenue. On Saturdays I went to the Arcadia Theater to watch a double feature with at least two cartoons and one or two serials. I’d get there about 12:30 pm and stay until I had to get home for dinner. The whole afternoon cost me 25¢. I had a 5¢ Coke and a 10¢ hamburger and paid 10¢ for admission to the movie—a big entertainment day.

Roberts: How old were you when you started going to the Saturday afternoon theater?

Edwards: I was probably 6 years old (Figure 2). By the time I was 9, my parents let me get on the streetcar and go downtown to the Majestic Theater or any one of the downtown theaters. Most are closed now.

Roberts: You didn’t even think about safety at the time?

Edwards: I was not worried about safety and obviously they weren’t either. During summers I had instructions to be home for lunch by noon and dinner by 6:00 pm. I had no problem going wherever I wanted to go. My friend and I got into a storm sewer drain one time near my house, and we walked all the way to downtown. About the time we were going to go past downtown, we stopped because a crowd of folks was coming from the other direction in the sewer so my friend and I turned around and ran.

Roberts: How old were you at that time?

Edwards: Probably 10 or 11.

Roberts: What was your house address? Is it still standing?

Edwards: It was 2014 Euclid, and it is not still standing. It was a 3-bedroom, 2-bath framed carpenter-style house. It had a molded...
wood plank exterior and 1 × 12 boards for insulation and paper hung inside. During the winter when the wind was blowing, the paper would move a little bit and we could almost feel the wind.

Roberts: What did your father do?

Edwards: My father was a general practitioner in Dallas. He worked at all the major hospitals, but mostly at Baylor. His first office was in the Wilson Building downtown, which is where most physicians began their practices those days. The office was then moved to the Medical Arts Building, and that’s the office I remember because he frequently took me with him on Saturdays to make rounds at the hospital. He parked me in the old Baylor drug store. Then he would park me at the Medical Arts Building while he saw office patients. I played in the stairwell a lot because it was one where you could look over the edge and see all the way to the bottom. Before the building was demolished they did put a wire cage around the interior so no one could jump over the railing.

Roberts: When was your father born?

Edwards: He was named William Leslie Edwards. His nickname was Jack. The whole family called him Jack. When I was born, they thought I was William Leslie Jr. but everyone called me Jack. So I thought I was Jack. I got a scholarship to Harvard, and they wanted a birth certificate. The birth certificate stated that my legal name was “Baby Edwards.” I wanted to be “Jack Edwards” and they wanted me to be “William Leslie,” so we just made a bad mistake and used all three names. We changed the name on the birth certificate.

Roberts: What was your mother’s name?

Edwards: My mother didn’t really like her name. Her real name was Effie Jane Caldwell. She came from a family of 10 siblings. My grandfather was a farmer, and he sent all of his kids to college with the help of an uncle and with the eldest kid helping the next kid down the line.

Roberts: Your mother was born in what year?

Edwards: She was born in 1890 and she died in 1983 at age 93.

Roberts: That was a long time after your father. Did she ever marry again?

Edwards: She never dated or remarried.

Roberts: In your family, did you have brothers and sisters?

Edwards: I was an only child. I had an older brother who died at childbirth.

Roberts: In your time, what was it like growing up in East Dallas and attending grammar school, junior high, and high school?
Edwards: I went to Victory Place (now James B. Bonham) on Henderson Avenue. The Dallas school board plans to close the school and sell the property. James Bonham was an Alamo hero.

Roberts: What do you remember about grammar school?
Edwards: I remember Mrs. Catledge because I didn't like her. She was aggressive with students, not kind at all. I loved Ms. Hughes. She was my absolute favorite, a great teacher.

Roberts: What was so memorable about Ms. Hughes?
Edwards: She liked kids. Mrs. Hughes was young, smart, and gave us lots of extra work if we were so inclined. But it was fun work.

Roberts: Where did you go to junior high?
Edwards: J. L. Long Junior High. It is next door to Woodrow Wilson High School.

Roberts: What do you remember about junior high and high school?
Edwards: I remember that the kids were nice to me. I remember a hayride and I had a date with a girl named Patsy Hayes. Woodrow Wilson High School is in the Lakewood area of East Dallas. It's a pretty building architecturally. When I was there it was about the equivalent of Highland Park High School instruction-wise. There were good teachers there. I did a lot of stuff at Woodrow. My last 2 years were during World War II. I was in the Reserve Officers’ Training Corps (ROTC) and all the guys wore their ROTC uniforms to school. I liked directing the marching band through its paces.

Roberts: What did you play?
Edwards: I started out with the clarinet but switched to bass clarinet because it was easier and because it didn't have that third register, which I never mastered. I ran for captain of the band and beat out Tom Shires, later a prominent surgeon in Dallas.

Roberts: In high school did you play sports?
Edwards: No. I played sandlot football and baseball.

Roberts: What were your other activities in high school? Were you on the debate team or any other clubs?
Edwards: I worked on the school newspaper and was in the physics and chemistry clubs. We did not have a debate team. We did have a speech class and our instructor was H. Bush Morgan. He was also in charge of the senior drama plays. I was in our senior-year play. My girlfriend at the time was too. Patsy and I started going together in junior high and dated for 7 years (Figure 3). We got married when we were 20 years old (Figure 4).

Roberts: Did she grow up in the same neighborhood?
Edwards: No. Actually she grew up in East Dallas when she was young, but her family moved to Irving because her dad wanted some acreage to raise fancy chickens and have a garden and a mule. He was the sports editor for the Dallas Times Herald. So Patsy commuted into Dallas. She drove in with her dad and then caught the streetcar from downtown and rode it to Woodrow Wilson. In the afternoon she got back on the streetcar to downtown, got on a bus, and was met in Irving by one of her parents. Her father had a dual schedule. He worked early in the morning to get the afternoon paper out, was off during the middle of the day, and then attended sports events at night.

Roberts: In school, did studies come easy for you, or did you have to work hard to do well?
Edwards: I liked to study, so studies seemed easy.

Roberts: Were there any particular areas you liked better than others?
Edwards: I liked physics, chemistry, and biology. My best teacher was my English 7 and 8 teacher. One day my chemistry teacher asked me to stay after class. He told me about a contest that he had read about and wanted me to enter. I agreed but wanted to know what it was about. It was the Westinghouse Science Talent Search and it had just begun. I entered but didn't win a prize. I did get an honorable mention, however, and during the next week I got scholarship offers to Harvard and

Figure 3. Jack and Patsy at senior prom in 1943.

Figure 4. Their wedding day, 1947.
the University of Chicago. I picked Harvard. Previously, I had planned to go to Southern Methodist University and live at home.

Roberts: You got a full scholarship?
Edwards: No, I got a partial. I waited tables the first semester and about killed myself because I took six subjects instead of four. All four semesters I took six courses and, as a result, I finished 3 years of study in 2 years.

Roberts: When you were growing up, did your family go on vacations? Had you seen much of the country other than Dallas before you went off to college?
Edwards: We went on vacations to visit relatives. We drove to Houston, San Antonio, Arkansas, Chicago, and South Carolina and saw places of interest in between. Our vacations were relatively short—no more than 10 to 14 days and sometimes even shorter. On several occasions we went to Colorado.

Roberts: What did you do when you were in high school during the summertime? Did you have jobs?
Edwards: Yes, I delivered newspapers. I had one job in a drugstore that served wine and beer in Lakewood but I quit after 3 days. I think they were illegally employing me. One summer I took History 7 and History 8 (US History) at Crozier Tech. I rode my bike from our house down Ross Avenue to Crozier Tech.

Roberts: What did your parents think about you going to Harvard?
Edwards: They were pleased.
Roberts: How did you get there?
Edwards: On the train. It took 1½ days. Then, I took a taxi from the South Station in Boston to Cambridge.

Roberts: You had never been to Boston before? Did you know other Harvard students before arriving? How did it work out?
Edwards: I didn't know anyone, but I enjoyed every minute of it. I was elected to my class committee and to the student council.

Roberts: Where did you live?
Edwards: I lived in Adams House, the same house that Franklin D. Roosevelt had lived in. His room is now preserved.

Roberts: What years were you at Harvard?
Edwards: I was there from June 1943 through October 1944. No breaks between semesters.

Roberts: During that period (17 months) you finished 3 years of college? And then you went into the service?
Edwards: No, I came back to Dallas to wait for the draft and learned that Southwestern Medical School had a class starting in January 1945, and I applied. I arrived that first day as a civilian. The dean asked if anyone could pass a Navy physical examination because they had three openings available because three people had dropped out. Billy Gibbons, Bill Huckabee, and I went to the Houston Office of Naval Office Procurement the next day and came home that night in the Navy V-12 (Figure 5).

Roberts: The Navy paid for your medical school?
Edwards: Only for the first 9 months and then the war ended and the V-12 program was disbanded.

Roberts: You had to pay for the rest of your way?
Edwards: Yes, but it was very inexpensive. Harvard cost $600 a semester for room, board, and tuition. Medical school was less.

Roberts: How many were in your class at Harvard College?
Edwards: About 1000.

Roberts: What was your standing when you completed 3 years?
Edwards: I haven't the slightest idea. I made mostly As and Bs. I made one C in organic chemistry because I was in the hospital for 4 days before the final exam and I had put off studying. I had severe otitis media.

Roberts: You started in medical school in January 1945. When did you decide you wanted to go to medical school?

Roberts: Just watching your daddy?
Edwards: I liked the subject matter and I enjoyed watching my dad, although there were a lot of things he did that weren't very much fun to me. He would make rounds in the morning, go to the office, leave the office, go back to the hospital, come home and have dinner, then make two or three house calls after that. He was busy.

Roberts: What time did he get home?
Edwards: About 9:30 pm.

Roberts: What was your mother like?
Edwards: My mother was a homebody. She did enjoy the physician wives auxiliary and the doctor's wives choral club. She taught a Sunday School class for single working women. She regretted not having a daughter. She had one or two of her nieces to our house every summer. She was a very nice mother.

Roberts: Your family atmosphere was very pleasant?
Edwards: Yes, it was.

Roberts: You got plenty of attention being the only child?
Edwards: Sometimes a little too much.

Roberts: You and Patsy met when you were in the ninth grade?
Edwards: Yes.

Roberts: What attracted you to Patsy?
Edwards: She was pretty, vivacious, and smart. We just hit it off. We got married in the spring of 1947. I was near the end of my junior year in medical school. We lived with my parents. They had moved to a house on University Boulevard and had a four-bedroom house which now would sit in the middle of Shannon Lane just west of the Hunt

Figure 5. Wearing his medical school V-12 (Navy) uniform, 1945.
Building of Highland Park Presbyterian Church. The house was demolished after my mother sold it. My parents let my new wife and me have the two front bedrooms and connecting bath. They had one of the back bedrooms, and my maternal grandfather, Richard Baxter Caldwell, lived in the other bedroom.

Roberts: Were there any professors or teachers in medical school who had a particular influence on you?

Edwards: Tinsley R. Harrison. He was an excellent teacher and a lot of fun. His knowledge was very extensive. Dr. Harrison was the first chief medical resident at the Johns Hopkins Hospital. His acquaintances were all professors. The discussions were interesting. His grand rounds with Carl Moyer were very interesting. Carl Moyer in surgery was a great guy. When I got to Boston as an intern at Massachusetts Memorial Hospital, I was very comfortable taking care of patients. Most of the interns who had been to Harvard or Tufts Medical School had a hard time the first 2 or 3 months. They had not had much clinical experience. We had a bouquet of clinical experience in Dallas at UT Southwestern (Figure 6).

Roberts: Tinsley Harrison wasn’t at UT Southwestern but just a couple of years?

Edwards: He came when the school started in 1943 and left in 1949.

Roberts: In medical school, did you have a hard time deciding what specialty to go into?

Edwards: It was a very easy decision. I liked internal medicine.

Roberts: You interned in pathology?

Edwards: I did and thoroughly enjoyed being at Peter Bent Brigham Hospital, going to medical rounds and the clinicopathologic conferences and writing up the case reports. We had to write a case report for each autopsy with a bibliography for the primary disease causing death. There was a lot of research. I enjoyed what was going on there—working with the Kolf artificial kidney, finding the best uses for newly available cortisone, and working out the sizes of stenotic cardiac valves using formulas for ascertaining how big or small the valve orifices were. Nobody does the latter anymore since the advent of echocardiography.

Roberts: You started your internship at the Brigham in July 1948?

Edwards: Yes. Medical school was a hurry-up schedule at the time. The class started on January 2 and continued until the end of summer; the second year started in the fall and continued to the following summer.

Roberts: Why did you decide to intern in pathology?

Edwards: I wanted to try it. I like pathology and I wanted to get back to Boston. I didn’t think I could get an internship at the Brigham in medicine. But I could get one in pathology and it was nearly as good for my purposes. I got to go to all the clinicopathologic conferences and medical grand rounds.

Roberts: Who was head of pathology at the time?

Edwards: Dr. Alan R. Moritz, whose special interest was forensic pathology.

Roberts: Did you enjoy it?

Edwards: Yes. I almost went to Duke but decided I would rather go to Boston.

Roberts: Before beginning your pathology internship, had you already decided that you wanted to do a residency in internal medicine? You got the job at Massachusetts Memorial Hospital while you were at the Brigham?

Edwards: Yes.

Roberts: How did you like that residency?

Edwards: Yes. I liked it. The hospital later folded when Medicare came along because it was a specialty reference hospital, mostly admitting severely ill patients. Dr. Smithwick was a surgeon treating hypertension; Jesse Thompson was a surgical resident there also. Chester Keefer was chief of medicine. That’s how I got my internship. The relationship between Chester Keefer and Tinsley Harrison was a good one. The reason I came back to Parkland Hospital for residency after that was because Dick Burnett, a nephrologist, had become chief of medicine at UT Southwestern. I really liked him. Unfortunately, he stayed only 1 year in Dallas. He got encephalitis while in Dallas, and his wife didn’t like Dallas. He did well as chief of medicine at the University of North Carolina.

Roberts: You were at Massachusetts Memorial Hospital only 1 year? And then you came to Southwestern and did 2 more years of internal medicine?

Edwards: Not at Southwestern. Four months after I arrived in Dallas for a residency in medicine at Parkland, I was called to active duty for the Korean War. The Army let all their Army Specialized Training Program students out of the reserves, but the Navy kept its reserves. My orders read, “You will proceed to the nearest naval medical installation for physical examination. If any physical defect is found which requires waiver, such waiver will be granted. You will then proceed to . . .” They sent me to San Antonio to the Army. I became Army overnight and wound up fortunately not in a battalion aide station. In 1950, I went over with a planeload of Marines and physicians, about half and half. Of the 50 or so physicians on the plane, three of us stayed in Japan: one was a plastic surgeon, one was an obstetrician-gynecologist, and I
had the 1 year of pathology and the 1½ years of medicine. The Army was looking for a lab officer, so I became the lab officer at the Hepatitis Center in Kyoto.

Roberts: That was a pretty nice place.

Edwards: It was a wonderful place to be—beautiful place to visit.

Roberts: You were there how long?

Edwards: I was there about 8 months and then I reverted back to Navy control. I got orders to go to the US Naval Hospital in San Diego and was on a medical ward for about 3 months. I kept waiting to call for my family. By then I had two children. Finally, I checked with the chief of medicine and as far as he knew I was staying there, but he couldn't guarantee that. I asked my family to come there and the day they arrived I got orders to move to the Naval Hospital in Corpus Christi, Texas!

Roberts: How long were you in Corpus Christi?

Edwards: Until I got out of the Navy.

Roberts: What was in Corpus Christi?

Edwards: A US Naval Air Station and a US Naval Hospital. I was a medical officer (internist) for the dependents section. There were also two obstetricians-gynecologists, one pediatrician, and one surgeon. We rotated call at night. I delivered 80 babies that year. I had one case of an internal rotation and one third-stage massive hemorrhage. On both occasions, he refused. He told me to put the long gloves on and reach in there for the senior obstetrician to come in. On both occasions, he called me to report. On both occasions, he had the 1 year of pathology and the 1½ years of medicine. I delivered 80 babies that year. I had one case of an internal rotation and one third-stage massive hemorrhage. On both occasions, he refused. He told me to put the long gloves on and reach in there for the senior obstetrician to come in. On both occasions, he called me to report. On both occasions, he had the 1 year of pathology and the 1½ years of medicine. 

Roberts: Where did you get out of the Navy?

Edwards: In 1952. Then I went to the University of Alabama Birmingham with Dr. Harrison. I was a resident, chief resident, and a National Heart Institute trainee under him.

Roberts: You were there 3 years?

Edwards: Yes.

Roberts: You decided you wanted to come back to Dallas?

Edwards: Oh yes. I always wanted to come back to Dallas.

Roberts: What date did you get married?


Roberts: How many children do you have?

Edwards: We have three children: Patricia Margaret, born January 14, 1949; Elizabeth Dana, born March 30, 1951; and William Leslie "Bill," born July 29, 1951 (Figure 7).

Tricia graduated from Agnes Scott College and married her high school sweetheart, Thomas (Tim) H. Hight, who graduated from Yale and UT Law School.

Dana went to Smith her first year, UT her second, the University of Madrid on the New York University program the third, and graduated from UT. She also has a master’s in architecture from UT. She married Charles E. Nearburg, who has an engineering degree from Dartmouth.

Bill has a bachelor’s degree from UT; an MDiv from Fuller Presbyterian Seminary, a DMin from Garrett, and a PhD in psychology from UT. He is an ordained Presbyterian minister and now works full-time as a psychologist.

Roberts: Do they have kids?

Edwards: Trish and Tim have four boys: Thomas, Jere, Jack, and Robert. Thomas Hight III graduated from UT Dallas and Denver Law and works for a pharmaceutical company. Jere Hight graduated from Baylor University and Baylor Law School and has a practice here in Dallas. Jack Hight graduated from Harvard and has a PhD in history from the University of Chicago. He has four published historical novels. Robert Hight majored in classical studies at Baylor University and has a law degree from UT.

Dana and Charles have two children, Rett and Anna. Rett was diagnosed with Ewing’s sarcoma at the age of 10. He had multiple surgeries and chemotherapies until his death at age 21. He was a gregarious, artistic, and talented young man. Anna majored in art history at Dartmouth. She works in an art gallery in New York City.

Bill and Anna have three kids: William, Maggie, and Trigg. William graduated from Texas A&M and has an MBA from UT Dallas. He works for a personnel company in Washington, DC. He is engaged to be married. Maggie has a BA from Colorado State and a master’s in accounting from UT Dallas. She works for an accounting firm in Dallas while studying for her CPA exam. Trigg graduated from Kansas University. He had a job teaching English in Spain and now is an intern at a public policy company in Austin.

I have five great-grandchildren: Thomas Hight IV, 12; Abigail Hight, 10; Cora Hight, 19 months; Julia Hight, 9 months; and Hope Hight, 2 months. The Hight grandsons have been active.

Roberts: You had a total of nine grandchildren?

Edwards: Yes (Figure 8).

Roberts: You went into practice in Dallas when?


Roberts: When you started practicing in late 1954, what was an internal medicine practice in Dallas like? Did you partner with anyone else?

Edwards: To get on the Baylor staff at the time, one had to be associated with a member of the Baylor staff. It was very tight in those days. I worked with Mike Scurry, a well-trained physician from a fairly prominent Dallas family. He had a couple of...
Brian very well. When I was at the Brigham, my own office separate from the group. I knew John, Don, and enough to let me have enough space in the new building for a year. I decided I would try to work by myself. Mike was nice a year before me.

It was the first building in Dallas on stilts with diograms for a hospital in Sulphur Springs. They would send the electrocardiograms to him; he would read them and send back his interpretation. We started sharing call duty and finally worked into a partnership. I moved down to the other end of the hall in the same building. It was an interesting move on my part. John had a huge practice and I was immediately busy. Back in my day, you scurried around for patients at the start, and it wasn’t easy to become fully occupied all day long. I received a lot of overflow from John. I also blunted the training I had had in cardiology in that I went in with a noncardiologist. He was known as a gastroenterologist who had worked with Milford Rouse and Cecil O. Patterson. (Earlier, I had a summer job with them doing histories. Patterson was one of the first gastroenterologists using the rigid gastroscope.)

Roberts: How did you know him?

Edwards: When I was in medical school, most of our teaching rounds were made by non–full-time faculty who practiced in the city. There were few full-timers at the medical school: Dr. Harrison, Dr. Arthur Grollman, and one fellow, Louis Tobian. Practitioners devoted their time to teaching students and housestaff. When I started my practice, I worked an 80-hour week, but one third of that time was at the medical school for free: making rounds, going to the clinics, teaching physical diagnosis, etc. I had a good time. Our practice was in a building on the corner of Hall Street and Turtle Creek. After 2 years, Howard Coggeshall, a rheumatologist, Al Harris, a cardiologist, and John Bagwell, a gastroenterologist, decided to build their own office building at the corner of Swiss Avenue and Washington. It was the first building in Dallas on stilts with the parking lot underneath the first and only floor. Mike decided to move into that building. Don Brown had started with Mike a year before me. Brian Williams joined the practice the next year. I decided I would try to work by myself. Mike was nice enough to let me have enough space in the new building for my own office separate from the group. I knew John, Don, and Brian very well. When I was at the Brigham, George Race had a surgery internship at Boston City Hospital. His wife, Anne, and Patsy found an apartment that we shared—two bedrooms, one bath—for one year. We remained friends after that year! It was great for the girls because George and I were gone every other night and weekends. Our apartment was the gathering place for the other Dallas expats.

Roberts: How did you like going into practice by yourself?

Edwards: I didn’t like being on call all the time. John Bagwell was at the other end of the building, and he basically did half internal medicine, half gastroenterology. He would come down to my end of the building and ask for my interpretation of an electrocardiogram. He read electrocardiograms for a hospital in Sulphur Springs. They would send the electrocardiograms to him; he would read them and send

lawyer brothers and went to the Country Day School, which was the predecessor of St. Mark’s. He received his internal medicine training in Michigan.

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Roberts: Were you able when you were so busy to go to medical meetings out of town? Which ones did you go to?

Edwards: I did. I still go to the Texas Club of Internists annual meeting. I started out going to the Atlantic City meetings. One time Brownie Thomas, Al Harris, and I flew to Philadelphia and rented a car. The chief of the Veterans Administration Hospital, Ben Friedman, had a coronary while at the meeting. He stayed in his hotel room, refusing to go to the hospital. He stayed in the hotel until it was time to go home. I drove the car back to Philadelphia and to the airport being quite nervous all the way because I didn't want him to die on the highway. I got a speeding ticket.

Roberts: Did you get him home?

Edwards: Yes, and he lived. He never did go to the hospital.

Roberts: What about weekends?

Edwards: Every other weekend I was on call until there were more physicians in the group. Eventually, there were six in the group, and then I was on weekend call only once every 6 weeks. My group eventually included John Bagwell, myself, Wilson Weatherford, Ray Hicks, John Vorhies, and Richard Strickland. Later, when our group was down to four, we shared call with Billy Oliver and David Hightbaugh.

Roberts: You had some office hours on Saturday mornings?

Edwards: Yes. We saw patients for a half-day on Saturday. Then I would make rounds for the group at the hospital if I was on call and probably admit one or two patients each day while on call.

Roberts: On the weekends, did you make morning rounds and evening rounds?

Edwards: Early in practice, yes. Later, it depended on whether the patients were very ill or not. If so, twice a day; if not, once a day.

Roberts: In general, how did practice change from 1954 to 1993?

Edwards: When I started out I was a consultant. I got a lot of cardiac problems sent to me. When I finished I was doing general internal medicine and sent heart problems to the cardiologist.

Roberts: Mainly for procedures?

Edwards: Yes. I never wanted to do catheterizations. When I started out in medicine, the physicians who did catheterizations basically saw patients with congenital heart disease, a disease category that didn't appeal to me. I just didn't like seeing all those sick kids. When Andrew Grunzig developed coronary angioplasty, cardiology practice totally changed. By then I was too far along to change what I was doing. I didn't want to take a year off and go back for more training. And I would have had to start over with another sign-out partner in a new office. It was time to quit, and fortunately I was able to do so financially.

Roberts: When you were practicing, what did you and Patsy do for entertainment?

Edwards: We were active in a nice four-couple gourmet supper club. We met once a month. The guys really had a deal. The wives did the whole meal. Some of the dinners would take 2 or 3 days to prepare. We always were sure we were not on call. We thoroughly enjoyed good food and good company and good wine. George and Ann Race, Ben and Alice McCarley (pediatrician), and John and Margaret Clayton were the other couples. We also played bridge. It was inexpensive. We took the kids to a friend's house or vice versa. When they were little they went to bed fairly early so we could play without interruption. (Young people don't play bridge anymore.) Eating out at least once a week was mandatory.

Roberts: Bridge is a great game. I play the one in the newspaper.

Edwards: I now play every Friday morning at my church, Highland Park Presbyterian Church.

Roberts: Have you always stayed active in the church?

Edwards: My wife was always more active than I was. I always went to church but she did all the extra things (Bible study groups, women's meetings, etc.). I have taught Sunday School and was a deacon. Patsy also enjoyed her lively and often humorous reviews. She kept up with her Woodrow Wilson girlfriends with a monthly luncheon, the monthly Tri Delta lunches, and the annual girls Mortar Board Retreat (held opening weekend of deer season because their husbands were always gone to their leases).

Roberts: Are you pleased with your retirement decision?

Edwards: Yes. The first year was difficult. I had nobody to leave my charts to, so the first year I was copying charts and sending them to patients if they requested them or to other physicians. When I retired I gave my patients a list of good Baylor internists and asked that they pick one. I had 17 filing cabinets full of charts. I kept the charts the required 7 years and then burned them all.

Roberts: What do you do now? What's retirement like?

Edwards: In 1960, I bought 190 acres 6 miles east of Van Alstyne, Texas. For years the land just sat. Now I raise cows...
build and mend fences, cut trees and brush. I do everything possible to keep the cows happy.

**Roberts:** How many do you have?

**Edwards:** About 30.

**Roberts:** What kind?

**Edwards:** Beefmaster.

**Roberts:** You go up there every week?

**Edwards:** I don’t have a house up there; I commute. I go maybe twice a week.

**Roberts:** You stay in good shape working around there?

**Edwards:** I’m still in pretty good shape except for breaking my hip 2 years ago. I still can work on the farm, but my hip lets me know about it.

**Roberts:** How did you break your hip?

**Edwards:** Stupidly. I wasn’t watching where I was going as I was saying goodbye to a lady on her front porch. I missed the first step, lost my balance, and fell like a tree in the forest. When I hit I knew I had done it. I got out my cell phone and called my son and told him to come take my car home. I called my daughter and asked her to go to the hospital with me. Then I called 911.

I’ve enjoyed my retirement. I have taken French lessons for 10 years. I play bridge with three other guys Friday mornings at church. I still read medical journals, including the *BUMC Proceedings*. I don’t go to BUMC rounds because they are in the morning.

**Roberts:** You are a night owl?

**Edwards:** I used to be a night owl. Now, I get up around 7:00 AM and go to bed around 9:00 or 10:00 PM.

**Roberts:** Jack, is there anything that we have not discussed that you would like to mention?

**Edwards:** I have been very fortunate in my life. I liked medicine. I was married to a wonderful wife, Patsy, for 62 years (Figure 11) before she died of breast cancer 4 years ago. I have wonderful kids, grandkids, and great-grandkids. For the past 2 years, I have dated Karen Uhr (widow of Barry Uhr, who was a Baylor ophthalmologist). Life has been very good to me indeed.
STEVEN JOHN PHILLIPS, PHD: a conversation with the editor with an emphasis on hospital and research safety

Steven John Phillips, PhD, and William C. Roberts, MD

Steve Phillips is the biological safety officer at the Baylor Research Institute (BRI) and at Baylor University Medical Center at Dallas (BUMC). He was born on August 5, 1949, in Chicago, Illinois, and grew up in several cities in that state. He graduated from Knox College in Galesburg, Illinois, with a bachelor’s degree in chemistry and biology in 1971 and received a master’s degree in microbiology from the Ohio State University in Columbus, Ohio, in 1974. In 1977, he received a PhD in microbiology from the same university, specializing in microbial genetics. From 1978 until 1980, he was a fellow in the Department of Microbiology at the University of Rochester School of Medicine in Rochester, New York. From there, he worked at the Dow Chemical Company (17 years) in Midland, Michigan, Occidental Chemical Company (5 years) in Dallas, Texas, and Carpet and Rug Institute (2 years) in Dalton, Georgia, before joining BRI and BUMC in 2004. He has spent many years in the laboratory and some in administration. For his efforts, he has received several honors, including the Alumni Achievement Award from Knox College (1996), the President’s Environmental Care Award (1992), and the Ohio State University Excellence in Teaching Award (several times). He has published approximately 20 articles in peer-reviewed scientific journals and has presented papers at numerous seminars. He refereed high school football games for 34 years. He has been married to Peggy Chivington (née Shirk) for 35 years, and they are the proud parents of a daughter, Amanda. I met Dr. Phillips when he was inspecting my laboratory and was in contact with him on several occasions subsequently. BUMC is fortunate to have this very talented scientist who is a very good guy.

William Clifford Roberts, MD (hereafter, Roberts): I am with Dr. Steven John Phillips at my home on March 21, 2013. Dr. Phillips, thank you for this opportunity to speak with you. To start, could you describe your early upbringing and your family, parents, and siblings? What was your early life like?

Steven John Phillips, PhD (hereafter, Phillips): It is a pleasure and privilege to be here. I have read this feature of the BUMC Proceedings many times and enjoyed it. I was born on August 5, 1949, at Michael Reece Hospital, Chicago, Illinois (Figure 1). The delivering physician was Dr. Harry Levin, a family friend for many years. My earliest living place was Maywood, Illinois, with my parents living with my grandparents. We moved to Des Plaines, Illinois, when I was 2 and lived there until I was 6. My brother was born in 1951 on St. Patrick’s Day; hence his name is Patrick Phillips (Figure 2). He died 3 years ago, probably from alcohol, cirrhosis, and smoking.

My parents (Figure 3) were divorced in the mid 1950s. It was a rough time to be the child without a father. My brother and I went from our home in Des Plaines to a boarding school in Wisconsin for a year, then we lived with a family in Westchester, Illinois, for about 6 months, and then we moved in with our mother in an apartment in Elmwood Park, Illinois, where I went to second and third grades. We then moved to a house in Streamwood, Illinois, where I finished grammar school, junior high, and high school. My mom worked hard. We never wanted for...
anything, but it was difficult for her. Divorce was unusual in the 1950s. I remember a teacher saying, “This Saturday we are going to have a father-son outing with sack races and other fun at the school.” I raised my hand and said, “I don’t have a father.” She got a look on her face like I was talking Martian. She suggested that my mother could come. It was just a difficult time.

Roberts: Did you ever visit with your father?

Phillips: I virtually had no interaction with him from the time I was 6 years old.

Roberts: When was your father born?

Phillips: He was born in Jefferson, Iowa, in February 1918. He died in Butte, Montana, in August 1982. His name was Joseph Francis Phillips.

Roberts: What was your mother’s name?

Phillips: Ruth Ann Benson. She was born in Chicago in August 1918 and died in Streamwood, Illinois, in October 2003.

Roberts: How did your mother provide for you and your brother?

Phillips: She was a secretary. She could take shorthand. My wife did too. That’s how we met. My future wife taught me shorthand when I was in graduate school at Ohio State. I took two 10-week courses of shorthand and then asked her out on a date.

Roberts: I took a typing class in high school, one of the better things I ever did.

Phillips: Me too. My mom said that as long as I could type I would never starve.

Roberts: What was your mother like?

Phillips: My mom was very family oriented. She didn’t have a lot of outside interests besides her two boys. Looking back I’m amazed she didn’t put my brother and me in a sack and throw us off a bridge. We were busy little boys (Figure 4). She was very supportive of our school efforts. Every Parent’s Day at school she came. From an early age I knew that she appreciated education and knowledge. She supported me in all of my academic endeavors. She was a Christian Scientist. When in high school and college, I told her that I had an interest in becoming a physician. At first, she was resistant to that but a few days later she said, “Steve, I’ve always told you that you should be what you want to be, and if that’s what you want to be, that’s okay with me.” We always had books in the house. She read to us. My brother
and I looked forward to those readings. She would sit on Pat’s bed one night and the next night on my bed. She read chapters of Black Beauty or the Bobbsey Twins, for example.

We went to junior high and high school in Elgin. I had a great science teacher for all 3 years in junior high, Harold Edwards. When I was in seventh grade, my mom went to a parent-teacher conference and returned in tears because Mr. Edwards had told her that I was not applying myself and probably would not amount to anything in science if I didn’t change. On the wall of my study, I have my high school diploma, bachelor’s degree, master’s degree, and PhD and the note from Mr. Edwards to my mom. Mr. Edwards showed her a set of problems where I had worked half correctly and half incorrectly. He said that was an example. From then on I studied hard. Mr. Edwards and I developed a good relationship.

In high school, David Brown was my biology teacher. He initiated my interest in biology or at least fanned the flames. I was one of 12 students selected for an Easter out-of-state trip with the three biology teachers. The teachers drove from Elgin, Illinois, to Brunswick, Georgia. We spent one night on the way at Vanderbilt University and stayed in the dorms. We got to spend about 5 days on Sapelo Island, Georgia, the marine biology field research station for the University of Georgia. Our teachers divided us into teams and gave us each an ecosystem on the island to study, and each student gave an oral report the last day we were there. We collected fiddler crabs and jellyfish by seining and put them in formalin containers. It was exciting. The patience of those three biology teachers had to be admired. Driving twelve 15-year-old boys around was huge. They rotated the boys between three cars so we could get to know each other better. It was fun.

Roberts: Did that trip really turn you on toward science or biology?

Phillips: I was already interested in it, but I was very sure that I wanted a career in biology after the trip. When it came time to choose a college, my friend Alan Rubnitz and I had decided that we would be roommates report at the last day we were there. We collected fiddler crabs and jellyfish by seining and put them in formalin containers. It was exciting. The patience of those three biology teachers had to be admired. Driving twelve 15-year-old boys around was huge. They rotated the boys between three cars so we could get to know each other better. It was fun.

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Phillips: How many were in Knox College?

Phillips: There were 1200 when I was there. Knox prided itself on a student-to-faculty ratio of 10 to 1. All professors taught entry-level courses. The chairman of all departments taught the entry-level class, a requirement so that the professors stayed in close touch with the students.

Phillips: How did you like Knox?

Phillips: It had its bumps for me academically. In my freshman year, I planned to major in philosophy, but I made a D in it my first quarter. That was the last philosophy course I took. I just didn't have the knack. But I did have a knack for biology and chemistry. I had a great teacher, Dr. Allen Hiebert, my sophomore year. When I would come to him with a question, he would use the Socratic method to ask me questions that I knew the answers to. He would lead me step by step to the answer to the question I originally had. This would help me to see that I had actually known the answer all along. This was helpful as positive reinforcement. It helped me learn how to think through scientific problems in a step-by-step fashion. On the first test in his class I got a 19 out of 100. When I was a senior I talked to him about that first grade. He told me that he had me pegged for one of those students who would come in, goof off, and get a passing C and then he'd never see me again. That grade shocked me and I went to talk to him. I sat down with Allen for an hour and he went through the problems/questions and explained them to me. With that kind of effort I did better and better and ended up majoring in chemistry.

In my junior year I had organic chemistry with Dr. Lee Harris, a crusty old fellow with a cynical dry sense of humor. At first I was intimidated by him. He would make cracks at me and finally I got tired of it. One day while talking to the stockroom lady about ordering copies of the Handbook of Chemistry and Physics, he walked in and made a comment about my being all hot and bothered about the handbooks. I replied, “Well, some of us weren't around when the first one was written so we have to learn it now.” I could tell that my comment took him aback and that he appreciated my standing up for myself. I had found the mechanism for getting along with him. In my senior year there was a set of Tinker Toys for organic chemistry in the waiting room. When I wanted to see Harris, if his door was open, I would lob those carbon atoms through his door and he'd know I was out there. He was a very encouraging teacher and could put things in terms I could understand. Nearly every professor at Knox was a great teacher. Two other great ones were Dr. Gene Perry (microbiology) and Dr. Bob Kooser (physical chemistry).

Phillips: As you were rolling through college, what were your plans?

Phillips: My plan was to go to medical school. I thought that if I applied to Illinois medical schools and had Knox on my transcript, the grade-point average would be overlooked. Because Vietnam was still active, the lottery system was instituted in the fall of my senior year. The numbers 1 through 366 birth dates were placed in a bingo tub, the tumbler turned, and a birthday number pulled out. My birthday was drawn with the 54th turn, meaning that I was the 54th in line to be drafted. Numbers 1 through 20 were being drafted each month. I reckoned that I would be gone by March of my senior year, but seniors were allowed to finish college. (College was still a deferment, but the only graduate deferments were medical and dental schools.) I was very focused on medical school at the time.

Coincidentally, Dr. Harris came to me one afternoon and indicated that a representative from the St. Louis University Department of Biochemistry was visiting him. He was looking to recruit students for his graduate program. Although the visitor understood my draft status, he nevertheless encouraged me to apply and explained why. He indicated that the draft lottery was hurting his department by keeping good candidates away. I applied and was accepted. In the spring I did not get an acceptance letter from any medical schools.

In the spring of my senior year I was told to go to Chicago for my draft physical. This was another life-changing event. I got on a train with 15 others. Coincidentally, the trains to Chicago were running late and we got to the draft center late and consequently were the last group to go through all the stations. I told the physician doing the examinations that I had problems with a shoulder dislocating in junior high and high school and with a knee dislocating in high school. He told me that he had been drafted out of a cardiac surgery residency and was not happy about that. He said, “I can't find anything wrong with your knee, but I'm not an orthopedic surgeon. Go to Desk #42 and ask for Sergeant Bill. Tell him you want a form 123 (request for physical deferment).” I'll send you back to x-ray to see if they can see something wrong with your shoulder. Recurrent dislocation is grounds for disqualification. If you can get a physician to sign a form that he has treated you more than once for your shoulder I think you're out.” I said, “Thank you so much.” I went to my personal family practitioner and he signed the form. I had already gotten an orthopedic surgeon to review it. I made my appeal to the local board at the last possible minute and then went to graduate school at St. Louis University for my master's in biochemistry.

Phillips: When I got to St. Louis University I had hoped to work with Georg Philipps, who was working on transfer RNAs. But, he had left that summer. The projects that were available at the time in biochemistry did not interest me at St. Louis University. In December, I talked with Dr. Jim Copeland, whom I had worked with at the Argonne National Laboratory in Argonne, Illinois, during a semester of my junior year in college. He became a friend. I wrote an undergraduate thesis paper on the regulation of chromosome replication in Bacillus subtilis. Jim told me that he was leaving Argonne and going to The Ohio State University. I volunteered to be his graduate student. He told me to apply and if I got accepted on my own he would take me. I applied and got accepted. Jim went to Ohio State in June, and I moved there in July 1972 (Figure 6).
Roberts: You got both your master’s and PhD in biochemistry?
Phillips: My PhD was in microbiology. I started in biochemistry in St. Louis but Jim Copeland was in the department of microbiology. Dr. Copeland left my last year of graduate school, but the chairman, Dr. Robert Pfi ster, took me under his wing. Basically, I ran the lab as the graduate student and principal investigator. I did my postdoctoral fellowship at the University of Rochester School of Medicine under Dr. Frank E. Young, who later became the Commissioner of the Food and Drug Administration.

Roberts: How did you go to the University of Rochester? How did that come about?
Phillips: Frank’s interest was Bacillus subtilis also. Bacillus subtilis is a Gram-positive organism that is a model for differentiation because it sporulates. It can differentiate in that a vegetative cell becomes another vegetative cell or a vegetative cell becomes a spore—which is a resting state. There are gene activations that drive the cell one direction or another, and it’s a model for differentiation for genetic exchange.

Roberts: You had met Frank Young earlier?
Phillips: Yes, as part of my graduate work. The Bacillus research community was relatively small at that time. He knew Jim Copeland. I had talked with Frank towards the end of my PhD work about possibly getting a fellowship at Rochester. I applied and he accepted me. My eventual plan was to go into teaching and research in a small college like Knox. I got married my first year of my postdoctoral fellowship in June 1978 (Figure 7).

During my final fellowship year I went to the American Society of Microbiology meetings to see what jobs were available. As I walked into the employment center, I saw Dr. Patrick Oriel from the Dow Chemical Company coming out. We recognized each other because Dow was supporting some work at our lab in Rochester. He arranged an interview before I even walked in the door of the employment center. I interviewed at Dow and liked what I saw. It was the best offer out of the three that I had gotten, so I went to Dow and started a genetic engineering lab in 1980. We worked on cloning the enzyme rennin. It is used in making fine cheeses.

Roberts: You mentioned earlier that you had married the lady who had taught you shorthand. What was her name? What were her features that attracted you to her?
Phillips: Peggy Chivington. Her maiden name was Shirk. She had beautiful eyes, a beautiful smile, and a beautiful personality. There was another feature that I always enjoyed when she turned to write on the blackboard. She was born and raised in Marion, Ohio, about 40 miles north of Columbus, Ohio. We started dating in June 1977 and got married in June 1978 in Marion and drove back to Rochester to start our new life.

Roberts: And it’s been good ever since?
Phillips: Yes. It will be 35 years this June (Figure 8). I’m traveling this weekend to Marion to pick up my mother-in-law, Joann Shirk. We want to move her here to Dallas. She’ll live with us for about 6 weeks. We found her an apartment in senior living in Plano. She’s fallen twice and we can’t take care of her from seven states away. She’ll be only 7 miles away now.

Roberts: How did Dow work for you?
Phillips: We moved to Midland, Michigan, the global headquarters for Dow Chemical. Midland had a population of 30,000, a nice tax base, a great educational system, and an arts center. It is an oasis in the middle of a lot of farms. It is 2½ hours north of Detroit, about 1½ hours from East Lansing, and 2 hours from Ann Arbor. My first day at Dow was August 5, 1980, my birthday. Peggy got pregnant and we bought our
first house and moved in on Good Friday 1981. Amanda was born October 10, 1981 (Figure 9). I was supposed to referee two football games that day.

Roberts: How did you get into football refereeing?
Phillips: An Eli Lilly salesman in Rochester, New York, mentioned the possibility to me. One woman that I worked with in the lab asked me a question about a football signal, and I looked it up and told her what I thought it might be. She said she would ask Ted Alferi the next time he came in because he was a referee. I met him and told him of my interest in refereeing. A few months later he called and said their first football referee meeting was that evening at Brighton High School. They taught courses on the basic mechanics of officiating. I bought my starter uniform and worked my first year in Rochester. When we moved to Midland I got in touch with the football officials and refereed there for 17 years, and then when we moved to Texas, I got in touch with the local officials in the Dallas Football Officials Association. I refereed in Rochester, Midland, Dallas, and Georgia for a total of 34 years. It’s a nice way to meet people and to see a lot of little towns. It’s been fun.

Roberts: How long did it take you to get good at it?
Phillips: If you ask any coach, they’ll tell you you’re never any good at it. But it takes at least 5 years, I think, to gain enough experience where you have the right balance of rules-smartness and situation-smartness to apply the rules fairly so that every little grabbing of a jersey isn’t holding. You learn what to let go and how to adjust your officiating to the level of play. That adjustment is probably the hardest thing to learn. You don’t call a Pop Warner game the same way you call a Division I college game.

Roberts: If you had a boy, would you want him to play football?
Phillips: If he wanted to, I would let him. There is a plaque on my wall with a quote from Vince Lombardi: “Football is like life: it requires perseverance, self-denial, hard work, sacrifice, dedication and respect for authority.” That said, football is not for everyone. Injuries are a part of the game. I got hurt playing the game. When you have two young men running at each other full speed and colliding, somebody may get hurt. There have been some tragic accidents. No fatal or paralyzing accidents have happened on any fields that I’ve been on. I have seen a broken femur or two. That is the most severe injury that I have seen.

Roberts: How much do you run during a game?
Phillips: Depends on your position. When you are a sideline official or back judge you may do a lot more running than if you are the umpire who stands with the defensive backs and doesn’t run much at all. The guys who run the most are the deep judges and the head linesman or line judge. As referee, which was my job most of the last several years, you don’t run much. You follow the play but everything is running away from you and your job is to trail the play. As a result, you want to be behind the last guy so that nothing cheap happens to the last guy.

Roberts: How many officials are on the field during a game?
Phillips: In a high school varsity game there are five.

Roberts: How long do you have to be there before the game starts?
Phillips: 1½ hours. We take charge of the game an hour before it starts. We try to get one official on the field by the time the two teams are on the field to keep anything from happening between teams.

Roberts: You travel a good bit?
Phillips: From Dallas, we would go north as far as the Red River, south as far as Avalon, west a long ways, and east a short distance. We usually carpooled from a mutual meeting place.
**Phillips:** You really get to know these other guys pretty well then.

**Phillips:** Yes, especially with as much moving as I’ve done. Having an instant group of friends to interact with and share similar points of view of life is unique. Officials really don’t care who wins the game in spite of what coaches might think.

**Phillips:** When you watch a football game, particularly a pro football game, what do you watch?

**Phillips:** The officials. Watching football is frustrating for me because the TV cameras don’t cover the kinds of things I want to see. For instance, when the player is tackled I’d like the camera to stay on that pile for a few seconds more because how those guys get up tells me if they made a first down, if there is any cheap stuff going on, things like that. On television, once the player is tackled the camera immediately cuts to a coach scratching his nose or walking up and down the sideline or some player snapping his chin strap. All of this is distracting to me.

**Phillips:** Do you get to know the coaches?

**Phillips:** Yes, some of them. The coach on your sideline tries to help you with your officiating. The best coaches generally don’t try to coach us; they coach their boys. When a coach was screaming at me, sometimes I could look out on the field and see that his players were losing and looking to him for direction. He was too busy screaming at me to do his job and coach them.

In my experience, the coaches who did a good job helped their boys. I was doing a six-man game in Avalon one night and the home team was losing by a lot and it looked like the visiting team was going to score on the next possession and win the game. The coach called a time out and said to his boys, “Boys, in life you are going to be in situations like this, where you are backed up and everything is against you and you’ve only got yourself and each other to rely on. That is what is going to happen in this next play. I want you to rely on each other and do the best that you can to make it through this and to have faith that you played a good game.” Then he walked back to the sideline. He didn’t scream at them or call them names but gave them some sage advice. That’s the kind of coach that really “coaches” his team.

**Phillips:** Are you paid to referee public and private high school football games?

**Phillips:** Yes, but I did not do it for the money. If I had computed how much time I spent on and off the field, the pay would have been about $1.00 an hour.

**Roberts:** Why did you retire from it?

**Phillips:** I’ve got arthritis in my right knee and I can’t run like I used to. I’ve had two operations on it and there isn’t any more cartilage left.

**Roberts:** How did the Dow positions work out?

**Phillips:** The Dow opportunity came along at a time when there were no college teaching opportunities available. Dow paid me well and I got to work on projects that interested me. In addition, I got to start a family and live in a small town of 30,000 people. I got home in 10 minutes from work. I got to be with my family a lot more than if I’d been in a big city. Dow wanted to clone in *Bacillus subtilis*, the organism I had worked with since my college days. The idea was to clone the enzyme rennin and to get it expressed and secreted from the *Bacillus*. Rennin is used in making fine cheeses. The only source is in the stomach of milk-fed calves. The availability of rennin is proportional to the availability of the stomachs of milk-fed calves. When the price of beef goes up, the farmers will keep their calves longer and there will be less rennin available. We cloned it, got it expressed, and got some secretion of it. That took about 5 years. Then, we learned that the market estimates had been off by a factor of between 5 and 10. So it was not a $120 million market but a $20 million market, and that changed the economics drastically. The company put that project on hold. I moved to market research for about 5 years thereafter.

**Phillips:** “Market research” means what?

**Phillips:** It’s looking at the product mix that your market competitors are likely to be coming out with. You can get an idea based on their patents, their disclosures, and your knowledge of the science as to where they are going and where they are. Dow had Merrell Dow Pharmaceuticals, and I worked with market research for both companies, considering what the market needed, what the market was likely to provide in the future, what we had in our pipeline, and where those mixes came together.

While I was in market research, one researcher asked me about enzymology. When he learned of my experience in that area, he invited me to work for him in the laboratory developing a lipase assay. We worked on a noncaloric cooking oil to use in fried foods, like potato chips. Thus, I left the administrative side and went back into the laboratory, working for about 3 years in New Ventures Commercialization. Then, once again, we had a downturn in the chemical industry. (The “basic chemical” or “commodity chemical” industry cycles every 5 years.) That project was put on hold and I was then offered a position in Product Stewardship, which is what brought me to the position I have here at Baylor Dallas. Product stewardship involves issues of safety and health, regulations, litigation liability, and public relations or public perception. If those aspects of a product issue are managed appropriately, then the issue is appropriately managed. If you leave one out, there will be potential problems.

I worked in that area for 7 years. I then got a good offer from Occidental Chemical here in Dallas and worked with Occidental Chemical for 5 years. My boss was Dr. Ladd Smith.

**Phillips:** Is that Occidental Petroleum?

**Phillips:** Yes. Occidental Petroleum is the parent company and Occidental Chemical is a subsidiary. The product mix at Occidental Chemical is similar to that at Dow—chlorine, caustic, and some plastics. I was also brought in because the company was getting into some specialty products, which commodity companies try to do occasionally. A basic chemical company will try to become a specialty chemical company to make niche chemicals, niche pharmaceuticals. Generally, it doesn’t end well.

The culture of a basic chemical company and a small chemical company don’t mix well and generally in <10 years they get spun off again.

I had an opportunity to go to Dalton, Georgia (“The Carpet Capital of the World”) and work for the Carpet and Rug Institute for 2 years, working for Werner Braun, president of CRI. He needed someone with a science background and an issues management background. He had been my boss at Dow. I was the director of marketing communications. The carpet industry
was dealing at the time with issues alleging that carpet made the indoor air quality bad. We had evidence to show that carpet actually acted more like a filter than as a contaminant source. It does hold dirt so if you analyze the dirt you would see a lot, but it stays in the carpet. After about 2 years, the institute was scaling staff back, and I had the opportunity to accept the lay-off package, plus my wife was not happy living there. We parted on good terms. We moved to Atlanta for about 6 months and then I got offered this position at Baylor Dallas. We had hoped to move back to the Dallas area, which we did on June 1, 2004.  

**Roberts:** How did Baylor find you?  

**Phillips:** It was coincidental. Baylor had been looking for about a year for a biosafety officer and had not been successful. I had inquired about a lab manager position in Irving and got a phone call from a recruiter indicating that the organization required only a master’s degree, but she passed my resume on to a coworker. The coworker was the one trying to fill the Baylor position. Two days later I had a phone interview with Ron Kasowski and then another phone interview 4 days later with Brenda Russell, vice president of BRI. They invited me for an interview. I talked to 13 people in 8 hours and got the offer. It was simply by chance that I got snagged for this job.  

**Roberts:** What does a biosafety officer do at a major health care facility?  

**Phillips:** My time is split equally between the safety department and BRI. With BRI, Jacques Benchereau was planning to get into high-interest pathogens and toxins (Brucella, for example), and to do that, an onsite biosafety officer, called a “responsible official,” was needed. A point-of-contact person was needed for the Centers for Disease Control and Prevention and for the National Institutes of Health to contact—a person who designs policies and procedures for how employees should work with these special agents, who does inspections, who designs facilities or at least oversees the design of facilities to contain the organisms, and who makes sure that people are following the rules. That was the research part of my job.  

From the health care system point of view, the Baylor safety department wanted someone who knew about chemicals and biologicals. Baylor did a good job with safety relating to ladders, lighting, and carpal tunnel syndrome, but was not as strong in the chemical and biological areas. Right now I’m working with our various clinical laboratories to develop a master chemical list so that if we buy a new hospital, they don’t have to start from scratch but will have available a Baylorized format. At Dow I had staff that wrote material safety data sheets (MSDSs) for me and I helped write MSDSs at Occidental.  

**Roberts:** Does every hospital have a safety officer?  

**Phillips:** The laboratories have safety officers. I think they are called coordinators. These people make sure their paperwork is in order for the various inspections that are held and their training logs are current for various accrediting bodies. There is a designate at each lab who takes ownership.  

**Roberts:** It sounds like every day for you is a bit different. Could you describe a day in your week?  

**Phillips:** I might do a training class for shipping biohazardous substances. I do one of those each month at BRI. I also will be receiving online training certificates from employees who have taken refresher courses, which are required every 2 years. There may be a biohazardous waste issue concerning the handling of it properly in a lab situation. The chemical master list takes about an hour of my time daily. We are developing a training program for response to chemical spills at research that is patterned after a program safety design for chemotherapeutic spills in the clinical areas. We had a chemical spill of mercaptoethanol (which is a stench agent), and that incident revealed some of our opportunities for improvement. We have developed a program to address that issue.  

**Roberts:** We met when you came to inspect the cardiovascular laboratory. Describe what you did at that visit.  

**Phillips:** The initial response was that one of the stored reagents was leaking. It was an old plastic bottle that had aged enough to crack and spill its contents. Your lab fell on the line between research, the hospital, pathology, and the health care system, and nobody knew whose line it fell on. We’ve now agreed that it’s part of my monthly inspection cycle. First, we cleaned up the chemical spill. My colleague, Gino Rubio, was a big help here. Then we went through the chemicals that were not being used anymore. Those were disposed of. We made some recommendations about the containers on the floor and the potential for tripping accidents. We addressed some other housekeeping items, some inspection items that the Joint Commission might notice. We noted stained ceiling tiles and sprinkler head stanchions coming through the ceiling. All those changes have been implemented.  

**Roberts:** Your knowledge has to be broad to respond properly to questions you are asked and the problems you have to solve.  

**Phillips:** You are right. There are things that I had to learn when I came here—for instance, how do you ship stuff on a common carrier, a truck, from Waxahachie? Or how do you ship items internationally? What sort of permits do you need? I have built on the breadth of experience that I had from the chemical companies as well as what I picked up in the health care system. Yes, it is very big waterfront to cover.  

**Roberts:** How have you found hospital activities versus industry activities? What has surprised you about hospital operations?  

**Phillips:** The hospital industry is not as assertive in challenging federal agencies. In the chemical industry, if a federal regulatory agency comes out with a rule and the industry thinks it is unnecessary or stupid, the new rule will be challenged. The hospital industry tends to take what the regulatory bodies say as truth, even if it knows the policy requires a lot of work and will not improve things. It’s a cultural thing. I told a lawyer friend, Mark Wine, in Washington, DC, how surprised I was about this. He thought it might be because I’m dealing with a different type of industry with a different economic model that drives it. It is more of an accommodation culture than a challenge culture.  

There are great people in healthcare (Figure 10). I found that at Baylor everyone is interested in doing a good job. I am very impressed with what I’ve seen as Baylor’s culture. People are accommodating. In many other research areas where I’ve worked, people are much more turf conscious, unwilling to
Dr. Mike Ramsey, as president of BRI, and Elizabeth Cothran, my immediate supervisor, emphasized that we are trying to do a good job, not just for the institute but also for the entire Baylor system. Dr. Ramsey has opened the gate for me so that I can deal more with issues that affect the whole health care system. The same safety precautions need to be applied in both the research and clinical laboratories.

Roberts: What do you do now for fun? What are your present extracurricular activities?

Phillips: I read. I teach two nights a week at Mountain View College. I teach biology for nonmajors on Tuesdays and Wednesdays from 6:00 to 9:00 PM. I enjoy college teaching and I guess I’ve made that dream come true. Also, I’m a doctor in a hospital, although I’m not an MD, so I’ve made that dream come true as well.

Roberts: Are you enjoying getting back with young students?

Phillips: Yes, very much. The students are in their late 20s to early 30s—adult learners.

Roberts: You seem to keep your paws in a lot of activities. What do you do the other nights?

Phillips: This year I’m still getting used to being without football. I leave for work about 6:30 AM and get home about 6:30 PM. Bill, I think you call this “working half days.” By the time I walk the dog, eat dinner, do the dishes, and make my lunch and breakfast for the next day, Peggy and I might watch a TV show, and then it’s usually time for bed. I try to get to bed by 10:30 PM. I get up at 5:00 AM. Weekends have been occupied with housecleaning and/or repairs. Sometimes, I have a Saturday workshop at the college. Because of my mother-in-law’s health, we’ve had challenges and opportunities there also.

Roberts: Sounds like the vacuums have filled up pretty quickly. Steve, is there anything that we haven’t talked about that you would like to discuss?

Phillips: I would like to share a little word of advice that a psychologist friend of mine, Dr. Paul Johnson, once said to me: “Everybody in life needs LAUF: to feel loved, appreciated, understood, and forgiven. If you feel loved, appreciated, understood, and forgiven in your work, in your marriage, in your interactions with people, then you are going to be happy. If you find yourself unhappy, you might go down that checklist and see if one of those parts is missing and how you might be able to satisfy it.” Thanks for the opportunity to talk to you and the readers of the BUMC Proceedings.

Roberts: Thank you.
About 20 years ago I had the good fortune to be invited to a symposium sponsored by the John A. Hartford Foundation which was designed to bring geriatricians and gastroenterologists together to stimulate interest in geriatrics by gastroenterologists. It was clear to the gastroenterologists attending the meeting that we knew very little about geriatrics, the process of aging, and the impacts of aging on gastrointestinal function and illnesses. The geriatricians at the meeting learned something about trends in gastroenterology and how that knowledge might be applied to their elderly patients, but were there largely to encourage us to conduct research on gastroenterology in the elderly. The symposium accomplished its goal, and subsequent years saw an increase in knowledge about the aging gut and how that knowledge could be applied to the care of the elderly.

The organizers of that symposium would be delighted by the new textbook, *Geriatric Gastroenterology*, edited by the eminent gastroenterologist, C. S. Pitchumoni, and the prominent geriatrician, T. S. Dharmarajan. The book is constructed thoughtfully with a unique point of view of the subject matter. Much more than just a series of organ-centered chapters, this handsome volume covers broad disciplines, such as the physiology of aging, epidemiology, pharmacology, nutrition, imaging, pathology, palliative care, and surgery, always emphasizing what is and isn’t known about these subjects in the aged. The second half of the book includes focused reviews of important gastrointestinal and liver diseases written by experts. Each chapter maintains sharp focus on the impact of aging on the presentation, course, and management of these conditions. Chapters contain clear tables, pertinent illustrations, and lists of key points that make it easy to follow the exposition of the topic. The book comes with access to supplemental materials online, including questions keyed to each chapter.

This book will be of use not only to gastroenterologists and geriatricians, but to internists, family practitioners, and trainees. For those of us who treat or study the elderly, the book makes it easy to find—in one place—current information about the aging process in the gut and its impact on aging patients. It belongs in every institutional library and on many physicians’ personal bookshelves. We all are growing older; this book makes us smarter about that process.

The reviewer, Lawrence R. Schiller, MD, is program director of the gastroenterology fellowship at Baylor University Medical Center at Dallas. He can be reached at LRSMD@aol.com.

Cholesterol and Beyond: The Research on Diet and Coronary Heart Disease 1900–2000 by A. Stewart Truswell

Reviewed by Arthur S. Leon, MD

This very readable 254-page book provides a concise overview of the chain of evidence accumulated during the past century supporting the relationship between dietary habits and blood levels of cholesterol and the associated relationship between blood total and low-density lipoprotein (LDL) cholesterol and the etiology of atherosclerosis and risk of coronary heart disease (CHD). The author, Arthur Stewart Truswell, MD, DSc, an emeritus professor at the University of Sydney, is a nutritionist who has made significant contributions to this body of research.

The book describes how CHD became the leading cause of adult mortality in the United States and other economically advantaged Western countries during the first half of the 20th century. Despite a subsequent dramatic decline, beginning in the 1960s, CHD remains the leading cause of age-adjusted adult deaths in these countries and currently worldwide. Environmental, lifestyle, and medical developments contributing to these dramatic swings in CHD rates in specific countries and regions of the world across the 20th century are also reviewed.

The described sequence of methodology supporting the so-called “diet-heart hypothesis” resembles that used in the late 19th and early 20th century to establish the relationship between dietary habits and potentially fatal human vitamin deficiency, i.e., beriberi and pellagra. These methods include the following:

- Anecdotal reports and astute clinical observations
- Experimental research using animal models
Epidemiologic observational studies
- Randomized, controlled interventional trials
- Identification of plausible underlying pathophysiologic mechanisms
- Public health recommendations, interventions, and policies

The book opens with a description of the initial clinical and necropsy recognition during the first two decades of the 20th century of myocardial infarctions due to thrombotic occlusions of coronary arteries. The underlying disease process in involved coronaries was correctly attributed to subendothelial cholesterol deposits and an associated inflammatory process, which results in fibrotic deposition in the lesions. Hence, the term “atherosclerosis” was proposed for this process, with the “athero” part of the term referring to its gruel-like cholesterol content and the “sclerosis” portion to the connective tissue component of these lesions. The presence of cholesterol in these lesions was the basis of the hypothesis that the disease was of dietary origin. This hypothesis was initially tested by a Russian pathologist, Nicolai Anischkow, and his colleagues, who fed large volumes of cholesterol to rabbits. Cholesterol feeding resulted in marked necropsy recognition during the first two decades of the 20th century of myocardial infarctions due to thrombotic occlusions of coronary arteries. The underlying disease process in involved coronaries was correctly attributed to subendothelial cholesterol deposits and an associated inflammatory process, which results in fibrotic deposition in the lesions. Hence, the term “atherosclerosis” was proposed for this process, with the “athero” part of the term referring to its gruel-like cholesterol content and the “sclerosis” portion to the connective tissue component of these lesions. The presence of cholesterol in these lesions was the basis of the hypothesis that the disease was of dietary origin. This hypothesis was initially tested by a Russian pathologist, Nicolai Anischkow, and his colleagues, who fed large volumes of cholesterol to rabbits. Cholesterol feeding resulted in marked hypercholesterolemia and severe aortic atherosclerosis. However, rabbits are a mammalian species uniquely sensitive to dietary cholesterol, because of no prior dietary exposure.

This hypothesis was subsequently challenged by human preliminary feeding studies that suggested that dietary cholesterol is only a minor contributor to blood cholesterol levels in humans. Subsequent controlled isocaloric, cross-over feeding experiments by Ancel Keys and colleagues at the University of Minnesota in the late 1940s and early 1950s confirmed that the fat content of the diet, rather than the cholesterol, was the principal contributor to blood cholesterol levels in humans. Further, these investigators quantitated the effects of different classes of dietary fatty acids found in animal and plant fats on blood cholesterol levels. These studies demonstrated for the first time that saturated fatty acids (SFA) present in animal products and in tropical oils were the major dietary contributors to raising blood cholesterol, with dietary cholesterol only a relatively minor contributor. In contrast, omega-6 polyunsaturated fatty acids from vegetable oils reduced blood cholesterol to half the raising power of the SFA. These findings were summarized in Key’s now famous 2 S-P regression equation. Mark Hegsted’s group at Harvard University independently derived a similar equation from human feeding studies. Dietary monounsaturated oleic acid in both laboratories did not affect blood cholesterol. The increase in blood cholesterol in these equations was subsequently shown to be primarily reflected in levels of low-density lipoprotein (LDL) cholesterol.

The next step in elucidating the relationship between blood cholesterol and CHD described in the book was case-control and ecological observational studies performed in the middle of the 20th century. Case-control studies confirmed earlier reported associations between CHD and blood cholesterol levels. Further, ecological studies by Keys, Paul Dudley White, and others demonstrated a high correlation between population-based blood cholesterol levels and the prevalence of reported CHD cases. These astute observations provided the impetus to conduct long-term, longitudinal, cohort studies on initially healthy people to identify dietary and other risk factor markers for development of future CHD. Thus, multiple well-designed prospective studies were performed worldwide in the 1950s and 1960s. In this book, Truswell focuses attention on the landmark Seven Countries Collaborative Study (7CCS) directed by Keys and the still ongoing Framingham Heart Study, now following the third generation of the original male and female cohort. In the 7CCS, the cohorts consisted of initially healthy, middle-aged men with mean blood cholesterol levels ranging from 160 to 260 mg/dL among the 14 cohorts. Strong consistent positive associations were found between serum cholesterol levels and risk of development of fatal and nonfatal CHD events over a 10-year follow-up period. In addition, chemical analysis on aliquot dietary samples from the cohorts showed a strong consistent relationship between SFA consumption and both serum cholesterol and CHD events. The 7CCS also is credited with directing attention to the apparent cardioprotective effects of traditional Mediterranean diets, despite their relatively high fat intake from monounsaturated fatty acid–rich olive oil.

The next logical step in testing the postulated diet-blood cholesterol-CHD relationship, described in this book, consisted of major randomized controlled dietary intervention trials. Ten such trials of 1 to 12 years’ duration were performed in the 1960s in the United States and Europe. Metaanalysis of the results of these randomized controlled trials (RCT), involving a total of over 10,000 men, revealed a 10% to 20% reduction of blood cholesterol in the intervention groups, which was associated with a significant reduction in CHD mortality, but not in total mortality.

Later RCT using cholesterol-lowering drugs subsequently conclusively proved that reducing blood levels of total and LDL cholesterol reduces risk of major CHD events. These RCTs in the 1970s included the Coronary Drug Project using niacin (150 times the recommended daily allowance of niacin as a vitamin); the Lipid Research Clinic’s Coronary Primary Preventive Trial (LRC CPPT), using cholestyramine, an anion-binding resin; and the Helsinki Heart Study, using the fibrate gemfibrozil. A shortcoming of these studies was that at the 5-year termination mark, none showed a significant reduction in all-cause mortality, as compared to the groups receiving placebo; however, in the CPPT at 15-year follow-up, total mortality was lower in the niacin-receiving group.

Briefly mentioned later in the book is the contribution over the past three decades of RCT using statin drugs, which provided final conclusive evidence that reducing LDL cholesterol significantly reduces the incidence of both initial and recurrent CHD events, as well as all-cause mortality. During the past decade statins also have been demonstrated to have multiple pleiotropic primary and secondary cardiovascular protective effects, even in those with normal or low blood cholesterol levels. Statins are now considered one of the most important medical and public health breakthroughs of the 20th century. Other lipid topics discussed are evidence that high LDL cholesterol...
and triglycerides are independent risk factors for CHD and the effect of trans-fats on blood cholesterol.

In addition to presenting the evidence of the role of dietary and blood lipid levels in CHD, Truswell provides concise descriptions of observational and experimental research findings on obesity and a wide variety of dietary components affecting blood cholesterol and lipoprotein levels. These include sucrose, dietary fiber, fish oils, alcohol, coffee, antioxidants, plant sterols, and soy proteins. Further, there is a brief discussion of homocysteine level as a risk factor for CHD and of the relationship of sodium and potassium to risk of hypertension. The author also briefly mentions the importance of fruits and vegetables as part of dietary patterns proven to promote heart health, including traditional Mediterranean, Japanese, and vegetarian diets and the American Heart Association–promoted DASH (Dietary Approaches to Stop Hypertension) diet.

I strongly recommend this interesting little book to health professionals and journalists dealing with promotion of dietary changes and blood lipid management for CHD prevention. It also is an important resource for anyone interested in the history of medicine, particularly as it relates to cardiovascular health, and to provide to skeptics of the causative relationship between diet-blood lipids and cardiovascular disease. Further, it provides a valuable source of references for those preparing scholarly papers on the wide variety of topics covered in the book.

The reviewer, Arthur S. Leon, MD, MS, FACC, FAHA (e-mail: leonx002@umn.edu), is affiliated with the Laboratory of Physiological Hygiene and Exercise Science, School of Kinesiology, College of Education and Human Development, University of Minnesota, Minneapolis, MN.

Avocations
The Boston Marathon

On April 17, 1978, on Patriot’s Day, I finished the Boston Marathon, my first marathon, when I was almost 40 years old. I planned to attend the conferences of the American Medical Joggers Association and the American College of Physicians.

Shortly after the start of the 26.2-mile race with some physician friends of mine from Atlanta, a young man running beside me asked, “Are you a doctor? It’s my first marathon, and I’m somewhat scared.” I said to him, “I’m scared too, and it’s also my first marathon.” He was Mike Sinsky, a freshman at Boston College, and we decided to run together. A few years later, I ran the Boston Marathon again and the day before, I went by Boston College and had a premarathon dinner with Mike and gave him a reprint of an article I had written on the marathon, “A Race to Remember,” published in Forum on Medicine in 1979. We have corresponded several times since then. Marathoners are part of an unusual bond around those 26.2 miles on their feet. Finishing the race is usually a moment of joy and euphoria, similar to marriage or the birth of a child.

Twenty years afterwards, I completed 50 marathons and ultramarathons, including eight Boston Marathons. It was a unique achievement and a culmination of years of work.

I am now almost 75 years old, and this year’s Boston Marathon on April 15, 2013, resulted in weeks of chaos and horror. The two brothers from Chechnya seemed to have planned the bombs for the masses with 4-hour success and their families, rather than for the elite runners who had already reached the finish line. Some of these slower runners are dehydrated and exhausted from running the marathon. Their legs were beat up and now a few faced amputation. The bombers thus wanted to hurt the most people.

The citizens of Boston and their law enforcers were admirable for their support of this disaster. Boston’s people and its marathon deserve better than to have perverted terrorists on their holy ground.

—S. Robert Lathan, MD
Atlanta, Georgia

Kudos

Dear Dr. Roberts:
I wanted to share with you my experience with Baylor University Medical Center Proceedings, particularly in reference to patient referrals and insurance company reviewers.

Each year I have at least 8 to 10 patients who tell me that they learned of me through articles published in BUMC Proceedings. The important fact is that BUMC Proceedings is online with free access to the articles for health care providers as well as the public. Many of my patients refer to those articles as their source of information about their specific condition and then seek my expertise for their treatment. This makes BUMC Proceedings unique, has helped my practice, and has stimulated my interest in publishing more articles in the BUMC Proceeding.

Another interesting fact is that medical reviewers for authorization of surgical procedures also access these articles. In point, I talked to a reviewer last week who had already investigated the diagnoses of one of my patients, and he found an article written by me in Baylor Proceedings. Based on his review of this published article, he approved the patient’s surgery. The fact that medical reviewers can easily access this information is helpful in working with the medical insurance industry.

Thank you for the excellent work that you do in editing this journal.

—Larry M. Wolford, DMD
Dallas, Texas

Dear Dr. Roberts:
I have been a reader and writer of the Baylor University Medical Center Proceedings for years. The journal is excellent, and I especially enjoy your editorial features and appreciate the efforts of managing editor Cindy Orticio. I am a retired internist for the past 7 years, and the one and only journal I use is the Proceedings, which I read from cover to cover.

—S. Robert Lathan, MD
Atlanta, Georgia

Dear Dr. Roberts:
For not having an “impact factor,” Proceedings sure has an impact on me! This journal is amazing and I believe it gets better every time! Great job!

—Jenny Adams, PhD
Dallas, Texas

Dear Dr. Roberts:
I always read your “Facts and ideas from anywhere” with interest. Of note, the reference to “Jay Robert Oppenheimer” should be “Julius Robert Oppenheimer.” I thought that the section was very interesting, as are all of your entries, and this is a minor comment.

—James Trotter, MD
Dallas, Texas
From the Editor

Facts and ideas from anywhere

SIMPLIFY

In his book *Walden*, Henry David Thoreau made the case against the complexity of modern life as he saw it in the 19th century. “Our life is frittered away by detail. An honest man has hardly need to count more than his 10 fingers, or in extreme cases, he may add his 10 toes, and lump the rest. Simplicity, simplicity, simplicity!” he wrote. “Let your affairs be as two or three and not a hundred or a thousand; instead of a million count half a dozen, and keep your accounts on your thumb-nail. . . . Simplify, simplify.” Alan Siegel and Irene Etzkorn have written a book entitled *Simple: Conquering the Crisis of Complexity* (1). They stress that “complexity is the coward’s way out.” There is nothing simple about simplicity, and achieving it requires following three major principles: empathizing (by perceiving others’ needs and expectations), distilling (by reducing to its essence the substance of one’s offer), and clarifying (by making the offering easier to understand or use). Empathy, they write, is the only way to truly shorten the distance between an organization providing services and the individual receiving them.

The Cleveland Clinic, they indicate, understands that empathizing with patients is critical, so it does not just focus on simplifying medical care but looks at everything the patient experiences: smells, sounds, greetings, hospital gowns, security, and appointment scheduling. It was not until staff members were wheeled through hallways lying in hospital beds that they realized how disconcerting and dizzying that experience can be. Preparing patients for the “thrill” ride is simply a gesture to allay fears. The clinic’s guiding principle—patients first—is used as a mantra by chief executive Delos Cosgrove, who weaves patient experience stories into all of his presentations. Everyone at the hospital, regardless of his or her job, is called a “caretaker.” Through this simple change in vocabulary, the Cleveland Clinic is able to send an important signal to everyone in the organization about what is expected.

What makes the biggest impression during a patient’s stay in a hospital? The Cleveland Clinic staff found that it was the small details: how long it took a nurse to answer the call bell, the availability of food on request, whether staff members follow the “10-4 rule” (“when 10 feet away from a patient smile and make eye contact; when 4 feet away address the patient”). Borrowing from the hospitality industry, the Cleveland Clinic has even paid attention to the scent in the air. No antiseptic aroma; the air smells like a signature fragrance favored by 4-star hotel chains. Everything from the way physicians talk to patients (in plain English and with a willingness to answer questions until there are none left), to the hospital gowns (designed by Diane von Furstenberg to combine ease of access with a touch of dignity), to the clear, concise bills patients receive when checking out reflects a commitment to simplifying the interaction between a human being and a large complex medical establishment. The hospital has achieved simplicity through the elimination of “hassles” and the addition of clearer, more human communication.

One key to achieving empathy is feedback. The hospital gathers lots of it from patients and displays the data in patient experience “dashboards.” For staff members eager to do well and for comparison with their peers, “bedside manner” becomes a measurable attribute, not an intangible quality.

Sometimes simplicity can be a matter of life and death. A decade ago, worried that confusing prescription labels threatened the health of her grandparents, Deborah Adler decided to do something about it. A graphic designer, she took on the challenge for her master’s thesis. Rearranging the small type on the typical prescription label, Ms. Adler put the information in a logical order, giving prominence to the things that most people need to know at the moment they are reaching for their medicine. She divided the label into two parts, separated by a thick black line, and placed the critical information, such as the name and dosage of the medication, at the top, with everything else relegated to the bottom. Ms. Adler next considered the shape of the bottles. The wraparound labels on conventional round bottles were difficult to read, so she designed a flat tube-shaped container that stood upright on its cap with plenty of room for a large flat label that could be read easily at a glance. Also, by color-coding the bottles, she made it possible for family members to distinguish among their individual medications. Her simpler, clearer drug packaging has been adopted by Target Pharmacies nationwide.

William C. Roberts, MD.
Siegell and Erzkorn go on to ask “What do we still need to simplify?” For ordinary personal and commercial transactions, they indicate we need brief online contracts with interactive features explaining key words, concepts, and computations. We need personal health records that can be easily used and updated by all health care providers. We need summaries of our home and automobile insurance that clearly explain how we will be reimbursed when the next storm hits; clear, 1-page hospital bills that will allow us to recognize each element in the care that we receive; and a simplified tax code that will eliminate the need for costly tax return preparation by professionals.

Simplicity may sound like a narrow standard, but it can winnow down unnecessary choices and clarify messages to customers, clients, patients, and citizens.

DEFINING A GOOD LIFE

George E. Vaillant has just published Triumphs of Experience: The Men of the Harvard Grant Study (2). The following comes from his book.

In 1938, Dr. Arlen V. Bock, professor of hygiene and chief of Harvard Student Health Services, launched a study of 268 Harvard male sophomores, selected as the best and the brightest in the classes of 1939 through 1944. (John F. Kennedy was one of those selected.) The study was meant to last for 15 to 20 years and answer the question of what defines the best health possible, something, it was assumed, this highly privileged group would exemplify. Financial support originally came from William T. Grant, owner of a chain of “dime stores” who wanted to find out what makes a good store manager. Later, support came from other sources and eventually from the National Institutes of Health.

Despite the original intention to end the study after 2 decades and despite financial trouble after Grant pulled out in 1947, it continues to this day, still known as the Harvard Grant Study, although officially renamed the Harvard Study of Adult Development. The study’s aim has grown broader to determine which early traits best predict a successful life. Most of the surviving men now are in their 90s. It is thus one of the longest prospective studies of adult development ever conducted and certainly the most exhaustively documented.

Over the course of the men’s lives, a team of investigators collected a vast amount of information about them. They performed physical and psychiatric examinations, IQ tests, and various medical and lab tests and conducted repeated interviews with them as well as their parents and later their wives and children. At least every 2 years, the investigators used lengthy questionnaires to delve into everything from the men’s daydreams to whether they like their subordinates at work. So frequent and intimate was the contact between the investigators and subjects that a bond formed between them, and except through death there were very few dropouts.

In 1954, when it looked as though the study would end for lack of funding, the Tobacco Industry Research Committee stepped in and provided most of the money for about a decade, ostensibly because it wanted to learn about the “positive reasons” people smoke. After that, funding came from several sources, including the National Institute on Alcohol Abuse and Alcoholism, which required the investigators to pay particular attention to alcoholism. The study is now supported by the National Institute on Aging.

During the 75 years of the study, there have been only four directors, and George Vaillant, MD, who served from 1972 to 2004, had the longest term by far. He is now 78 years old, with a string of papers and 3 books about the study to his credit, and the 2012 book is expected to be his final summary of the overall findings.

With no definition of what constitutes a good life and so many possible predictors, it has been difficult to draw unambiguous conclusions, except for a few major ones. During the early years it was thought that success was largely determined by physical constitution, so one of the criteria used to select men for the study in the first place was a muscular body build thought to be characteristic of men destined for success. By the time Vaillant, a psychiatrist, took over the directorship, the emphasis had shifted to the quality of personal relationships, particularly in childhood. Now, with a new director and new technology, there is renewed attention to physical findings—not muscles, but brains—as revealed by imaging studies.

In 2009, Vaillant attempted to define what constitutes a good life in men, aged 60 to 80, by devising what he called a “decathlon of flourishing.” It consists of 10 variables, including being listed in Who’s Who in America, earning income in the study’s top quartile, and being in a good marriage. Using these variables, each man could be given a score ranging from 0 to 10. Vaillant then looked back at the data collected in earlier years to see what factors best correlated with a high score in late life. Vaillant concluded that since the quality of personal relationships (for example, a “warm childhood”) was the strongest predictor of a high score, the “most important influence by far on a flourishing life is love.” The “decathlon” includes few measures of feelings of usefulness to society at large or enjoyment, for example, of solitude.

There is nothing ambiguous about some of the study’s findings. The men in the Harvard Grant Study were extraordinarily long lived; fully 30% of them survived into their 90s, compared with only 3% to 5% of men in the general population of that generation. We have long known that being affluent and well educated is the best possible insurer of good health. But the size of the effect in the study is startling. So strong is the correlation with education that the study men who went to graduate school lived even longer than those who didn’t.

One of Vaillant’s major themes is that adult development continues long after adolescence. In the Harvard Grant Study, the factors associated with flourishing changed with age, and those that were important in youth or middle age were not necessarily important in old age. In fact, many were so inconsistent that one has doubts about how much importance one can attach to them. In general, however, these men seemed more content with their lives as they aged and they reported happier marriages—whether it was a long first marriage or a recent second. Where they landed at about age 70 seemed to matter most.
Another of Vaillant's themes is the devastating effects of alcoholism. According to him, alcoholism was the cause, not the consequence, of unhappiness in these men. Most of the 62 divorces were associated with alcoholism, either in the men or their wives, as were professional setbacks and early death. Vaillant is absolutely certain that alcoholism is the horse, not the cart. The men did not drown their sorrows in alcohol, he believes, but inherited a vulnerability to alcohol which then caused their sorrows. There is no other study of lifetime alcohol abuse as long and as thorough as this one, and he believes that this aspect of the study is perhaps its greatest contribution.

The main strength of the Harvard Grant Study—namely, its long life—is also one of its main weaknesses. These men were dinosaurs in the sense that the world they inhabited for most of their lives is gone forever. Vaillant, for example, found that a warm childhood was a predictor of success, but that almost surely meant something different in the 1920s than it does today. Parents were stricter then than today's doting parents. Also, the household then probably revolved around the husband, not the children as today. Marriages were different too. Although Vaillant does not say, it is likely that nearly all the study men had wives who didn't work outside the home—something unlikely now. Thus, many of the findings are dated, and even when they provide unambiguous conclusions, they are unlikely to apply to people today.

Dr. Marsha Angell, the reviewer of the book in The New York Review (3), asked why the men in the Harvard Grant Study, despite all common sense expectations, seem to grow more content and not less content in old age. After all, by the time they were over 70, they were no doubt experiencing many of the physical limitations of age and they had to know that their time was running out, that any day they could become seriously ill and begin an inexorable decline to decrepitude and death. Why were they happier than they seemingly had any right to be? Maybe one answer, as Dr. Angell suggests, is that they had learned to live in the present, not the future, and in the present, most of them had acquired enough resources to live comfortably, yet didn't have to work anymore or work as hard if they didn't want to. So the tension of competing at work was relaxed; their children were probably married and self-supporting, and they had freedom. These were ambitious men who probably cared a great deal about professional advancement. (A quarter of each class became lawyers or physicians; 15% became teachers, mostly at the college level; 20% became businessmen; and the remaining 40% entered other fields. Four ran for the US Senate, one served in a presidential cabinet, one was a governor, and one was president [John F. Kennedy].)

After they retired, perhaps it was a relief not to be thinking ahead to the next professional goal and also not to experience gaps between career aspirations and achievements. They could find serenity in cultivating their garden—or taking up watercolors or carpentry or otherwise broadening their interests at leisure. And living in the present helps people not to think about the looming existential threats of illness and death.

The fact that marriages were happier after age 70 no doubt added to the contentment. But why were they happier? Was it simply a matter of having found the right partner (about a third of the happiest marriages were not the first) or perhaps having rubbed up against each other so long that the barnacles had worn away? There may be another reason, Dr. Angell questions, one that would have been particularly relevant for marriages that had taken place when men and women had sharply divided roles and men were dominant. As they age, women tend to become psychologically more independent for a variety of reasons, while men become more dependent, particularly when they retire and spend more time at home (the traditional woman's domain). As the men of the Harvard Grant Study and their wives became more equal and probably shared more interests by virtue of being together more, they probably became more companionable. Vaillant refers to "hormonal changes that 'feminize' husbands and 'masculinize' wives." He also believes the "empty nest is often more of a blessing than a burden." Angell speculates that old age takes many men almost by surprise; it sneaks up on them and is all the more disturbing for that. In contrast, women are all too aware of aging, starting with their first gray hair or wrinkle. By the time they are in their 50s they are well accustomed to the loss that comes with age. That may make them better able to help and support their husbands, as the men find that having been a master of the universe is no protection against old age.

But this happy outcome—more contentment and better marriages—depends crucially on having the means to live in comfort. Without that, it is hard to imagine such equanimity in the face of old age. If you don't know whether you can afford to heat your home next winter or pay your medical bills or hire a helper if you become disabled, old age is a particularly harsh time of life. Financial security is no doubt something that distinguished the study men from less privileged men. As the founders of the study intended, these were the most fortunate of men, and it is wrong to assume that others will age in the same gentle way. A golden old age also depends on remaining reasonably healthy, and they did well in this respect, too, although about a quarter of them who reached their 90s had dementia.

Dr. Marsha Angell, now also in her 70s, also finds many offsetting advantages of getting older. One of them is a sharper sense of what is important in life. She indicates that she has a clearer sense of what matters and what doesn't. Her sources of pleasure are different now and more varied. She indicates that, for example, she takes greater pleasure now in beautiful vistas. Ordinary daily activities, like reading the paper and discussing the news with her husband over breakfast, have taken on an added pleasure beyond the activities themselves just because of the ritual. Although she is still active professionally, she is less concerned with maintaining a professional presence. She looks forward to learning Italian, taking a course in astronomy, and finally reading War and Peace.

She has become much more pessimistic about the state of the world: the unsustainable population growth, potentially disastrous climate change, depletion of natural resources, pollution of the oceans, increasing inequality both within and across countries, and violent tribalism of all forms, national and religious.
Nearly everyone over a certain age observes that time seems to pass much more quickly. So extreme is the acceleration, says Angell, that she wonders whether it isn’t a result of some physical law, not just a perception. Maybe it’s akin to Einstein’s discovery that as speed increases, time slows. Perhaps this is the reverse—as our bodies slow, time speeds up. In any case, the rush of her days is in stark contrast to the magically endless days of her childhood. She also finds it hard to remember that she is no longer younger despite the physical signs, since she is still the same person and in many ways has the same feelings. I feel the same way. It’s particularly disquieting to recall that many people and places I knew no longer exist except in my memory. Still, she opines that although she dislikes the fact that her days are going so quickly, that’s the way it is and she has had a good run like the men in the Harvard Grant Study.

ARE YOU WEALTHY?

Scott Burns (4) asked four questions to determine one’s wealth: 1) Do you make payments on your house or car? If yes, one is not wealthy. 2) Does your interest and/or dividend income exceed what you pay in interest? The more income one has from sources that don’t involve working, the closer you are to being wealthy. 3) Can you keep what you have without actually working? If losing your job means the repo guy will be visiting soon, you are not wealthy. 4) When you are asked “What do you do?” do you reply by stating your occupation? If so, you are not wealthy and may be a workaholic. Scott Burns suggested answering that question by saying “In the event of what?”

PHYSICIAN-PATIENT E-MAILING

According to Sumathi Reddy (5), just under one third of physicians reported e-mailing patients in 2012, up from 27% in 2007, according to annual studies of more than 3000 physicians conducted by Manhattan Research, a health care market research firm. Those texting rose from 12% in 2010 to 18% in 2012. Physicians who shun e-mail cite concerns ranging from privacy and security issues to liability, inconvenience, and the risk of miscommunication of important medical information. Also, time spent e-mailing patients is unpaid. Few physicians charge for the service. Those who do e-mail say it is a convenient way to communicate with patients without the hassle of playing phone tag and that it can keep patients from relying on Google searches that can sometimes lead to inaccurate information. Patients tend to love the access. Some physicians give every patient a business card that includes their e-mail address, but others give it only when asked. E-mailing with patients apparently generates good will. One physician indicated it improved his reputation and his online ratings. A physician in Manhattan apparently ends each new patient visit by asking if the patient would like to communicate via e-mail. If so, he asks the patient to sign a form agreeing to communicate electronically about health matters and giving him authority to discuss medical issues over e-mail. The form ensures that he is compliant with the Health Insurance Portability and Accountability Act, commonly referred to as HIPAA, designed to protect the privacy of health information. HIPAA compliance is a major concern raised by physicians who do not e-mail. The law requires that electronic communication related to an individual’s health is protected and secure.

As part of the federal government’s Stimulus Act, physicians are being encouraged through financial incentives to use electronic medical records. One part of that effort includes the use of secure messaging to share health information with patients through, say, an online portal. Opinions on this matter would be welcomed by readers.

DESIGNER DRUGS

These are synthetic drugs that duplicate the experiences of LSD, marijuana, cocaine, ecstasy, and amphetamines (6). Because laboratory-created compounds differ slightly in chemical structure from the illegal drug they mimic, consumers of the drugs can claim that their purchases from websites or head shops are legal. Many national governments have declared some of the new compounds illegal, but they have trouble keeping up. Since 2008, drugs with names like 2NE1, after a Korean girl band, and SS-135, which was NASA’s final space shuttle mission, have been appearing at a rate of one a week, according to the United Nations–affiliated International Narcotics Control Board. In July 2012, the US Congress voted to list 26 new chemicals under the Controlled Substances Act. The drugs, however, are sold over the Internet from countries where it is legal to countries where it is illegal. The profits can be enormous. Synthetic marijuana, often labeled “plant food” to confuse police, can earn retail profits of $90,000 to $136,000 a pound, compared to $1000 to $5000 for the real stuff. In March 2013, the Narcotics Control Board labeled new psychoactive substances the fastest growing category of drugs in the world and identified more than 1000 compounds that have entered the market since 2008. According to the US Drug Abuse Warning Network, some 28,000 emergency room visits in 2011 were caused by known marijuana synthetics—more than double the 2010 number. Legal systems for banning drugs are not set up to handle a market in which a new drug emerges weekly. Chinese manufacturers are the main suppliers of the chemical compounds used in synthetics. Most of the suspect ingredients are legal there. After 4 years of meeting with the Chinese, US officials can point to a single success: pushing China to prohibit mephedrone, a cocaine synthetic that is marketed in the US as “bath salts,” a rapidly increasing problem.

HEROIN IS BACK

Donna Leinwand Leger (7) in the USA Today indicates that heroin is back. In Charlotte, North Carolina, it has become so easy to get that dealers deliver to the suburbs and run specials to attract their young professional, upper-income customers. These lawyers, nurses, policemen, and ministers are showing up in the detox wards at Charlotte hospitals desperate to kick an opiate addiction that often starts with powerful prescription painkillers, such as OxyContin and Vicodin. The Carolinas Medical Center analyzed the patients’ zip codes to see where heroin had taken root and discovered that its heroin patients were coming from the five best neighborhoods in Charlotte. They believe
they are witnessing a growing and more dangerous wave of drug addiction sweeping the country, ensnaring several hundred thousand Americans into the heroin trap and importing crime to America's suburbs. Prescription painkiller addicts are finding their drug of choice in short supply, so heroin becomes their drug of last resort. As adults move from legitimate prescriptions to the black market of pure precisely measured narcotic pain pills to the dirty world of dealers, needles, and kitchen table chemists, health officials and police are noting sharp increases in overdoses, crime, and other public health problems. One expert indicated that "when you switch to heroin, you don't know what is in there from batch to batch."

The number of people who say they regularly abuse painkillers dropped from 5,093,000 in 2010 to 4,471,000 in 2011, according to the National Survey on Drug Use and Health. Young adults who said they regularly abused painkillers dropped from a high of 1.62 million in 2006 to 1.22 million in 2011. The survey estimated that 281,000 people aged 12 and older regularly used heroin in 2011, up from a decade low of 119,000 in 2003. The number of people seeking treatment for heroin found increases in 30 of 39 states reporting data in 2011 to the Substance Abuse and Mental Health Services Administration. In 2011, 238,184 sought treatment for heroin addiction. The 2013 National Drug Control Strategy released on April 24, 2013, confirms that heroin use appears to be increasing particularly among younger people living in suburban and rural areas. To counter the escalating overdose problem, the strategy includes a plan to make Naloxone—a medicine that can reverse heroin or opiate overdose—more accessible.

OxyContin, a narcotic painkiller in the opiate family, came on the market in 1996. By 2001, it became the nation's best-selling brand-name narcotic pain reliever. Although it's a highly effective drug for people suffering from chronic pain from diseases such as cancer, the Drug Enforcement Administration noted high levels of abuse particularly in West Virginia and Kentucky, where it became known as "hillbilly heroin." To stem abuses of pain pills, authorities over the past decade began cracking down on clinics, and drug companies began creating pill formulations that made them harder to crush and snort for a quick high. As bad as OxyContin is, heroin is worse, and the users of heroin are getting younger and younger. Heroin given intravenously is particularly dangerous because addicts may share needles, exposing themselves to bloodborne disease such as HIV and hepatitis, and can easily overdose when injecting heroin directly into their bloodstream.

In Charlotte many of the opiate addicts in the Carolinas Clinic started with powerful painkillers prescribed after surgery or a broken bone. As doctors cut off their prescriptions and the black market supply withered, they turned to cheaper, easier-to-find heroin. The going rate for a tiny balloon filled with a dose of heroin is $9. A heavy user may take up to 10 doses a day. In contrast, prescription pain pills containing OxyContin sell for up to $1/mg—$80 for an 80 mg pill.

Thus, once considered an urban drug, heroin has found an unwelcomed home in small towns and suburbs. With the introduction of street drugs came the crime wave. The addicts will do almost anything for a quick dollar, stealing from parents and committing burglaries.

**LEARNING TERRORIST PREVENTATIVE TACTICS FROM ISRAEL**

Israel is perhaps one of the most targeted nations for terrorists, and per capita it has lost more citizens to terrorist attacks than any other nation (8). As a result, it has spent years developing ways to prevent terrorist plots before they occur. One method is to instill in Israelis a keen awareness of their surroundings. In the 1970s, schoolchildren were taught in the classroom to avoid loaves of bread and cigarette packages on the ground because they could be booby trapped with bombs. People call the police whenever they see an unattended package, especially in airports, bus stations, and train stations, and the sight of a bomb robot is common now in the streets of Tel Aviv and Jerusalem.

In Israel things changed after the 1967 war in which they conquered East Jerusalem and tens of thousands more Arabs became residents of Israel. Jews and Arabs in the new territory mingled in ways they had not before, and Israelis sometimes had difficulty determining friend from foe. Some Jews of Arab or North African descent would wear the six-pointed Star of David as a talisman around their necks to signal that they were no threat. The mingling led to profiling in which Israeli security experts disseminate the characteristics of people who are far likelier threats of terrorist attacks than others. In Israel they won't check an old blond American woman but they will check a dark-skinned young guy who might be of North African descent. They compromise social values to be more efficient.

During the Palestinian uprising called the Second Intifada, suicide bombings killed hundreds of Israelis in cafes and restaurants from 2000 to 2005. In March 2002 alone, 139 Israelis were slain in such attacks. Another way Israel halted such bombings was by stopping them at their source: the Palestinian territory of the West Bank. Israel erected a fence between the West Bank and Israel that has effectively ended most unauthorized travel between the two sides. The state's most important tool for stopping terrorist plots is aggressive surveillance and infiltration of Palestinian society to find and stop the planners. In addition to electronic methods, Israel also employs a network of informants and spies who are recruited with cash. Acts of terrorism, like the bombings at the Boston Marathon in April 2013, may alter the behavior of ordinary US citizens in the future.

**MORE WEIGHT → HIGHER AIRFARES**

Samoa Air, a tiny South Pacific airline, charges passengers based on their weight, namely 42¢ a pound for each flight (9). Samoans are renowned for their weight. According to the World Health Organization, about 55% of the country's population over 20 years of age is considered obese. Only Nauru and Tonga have a higher percentage, namely 71% and 60%, respectively. The US ranks fourth, 32%, followed by Australia and United Kingdom, each 25%. In contrast, China is 6%. These are 2008 figures.
OCEAN ACIDIFICATION

According to Dan Vergano (10), the ocean’s water is shifting toward the acidic side driven by climate change, which has brought increasingly corrosive seawater to the surface along the West Coast of the USA. Normally, plankton in the ocean suck up carbon dioxide via photosynthesis, and the more carbon dioxide they ingest, the less warming of the atmosphere. When those sea plants die, they fall to the depths and some of the consumed carbon ends up dissolved in deep ocean waters. The ocean water in the depths is 3 times more acidic than that near the surface. In addition, the ocean absorbs 23% of all human-made carbon dioxide emitted into the air by burning coal, oil, and other fossil fuels, according to a 2012 *Earth System Science Data* report—more than 8 billion tons of the stuff every year. When conditions are right, strong winds blowing over ocean water along steep coasts, such as along the West Coast of North America, generate “upwelling” of the deep waters.

The more acidic the ocean, the fewer shellfish develop. In recent times, baby oysters grown in some Pacific Coast hatcheries were dying en masse. The entire West Coast oyster business faced collapse without the larvae that seeds the shellfish. The shellfish farmers in 2008 began figuring out that the deep ocean water being more acidic was coming to the surface and was likely dissolving the fragile young oysters. Without industrial emissions of greenhouse gases, however, the upwelling would not be a problem because really corrosive water would not get high enough to reach the surface. It is the extra kick from human-made carbon that is pushing the saturation point higher. Shellfish rely on calcium to build their shells, and more corrosive water makes that harder for them to the point of becoming impossible. Some seawater scientists in 2012 definitively showed that those deep waters do dissolve baby oysters only a few days old, ones which rely on a very soft form of calcium for their initial growth spurt. More carbon in the air means more carbon in the ocean.

Deep water upwelling is not a problem so far on the US’s East Coast, but warmer waters there have shifted crab and fish populations, while acidic mud on the main seafloor has hurt clamming. The acidification taking place in the waters along the US West Coast guarantees the same for the rest of the world’s oceans in the years ahead.

US UNEMPLOYMENT

As John Cassidy emphasized (11), 12 million Americans are out of work, 8 million are working part-time for economic reasons, and 2.5 million say they want a job but have given up looking. At the start of 2008, when the recession began, the civilian population of the US aged 16 and up (and excluding prisoners and members of the armed forces) was 232.6 million, of whom 154.1 million were in the labor force, that is, they were working or looking for work. Over the past 5 years the working-age population has grown steadily. In February 2013, it was 244.8 million, an increase of 12.2 million since 2008. But the labor force has hardly grown at all. In March 2008, it stood at 155.5 million, a rise of just 1.4 million in 5 years. The proportion of the population in the labor force has fallen from 66.2% in January 2008 to 63.5% in February 2013. That fall off may not sound very dramatic. If the participation rate, however, were still at its level of 5 years ago, there would be 162.1 million people in the labor force instead of 155.5 million. Thus, as many as 6.6 million workers have vanished from the economy, robbing it of their efforts, skills, and creativity. The result is more personal hardship, a weaker gross domestic growth, lower spending, and less wealth creation.

MOBILE PHONE AT FORTY

It was 1973 when inventor Martin Cooper made the first call on a mobile phone using a prototype Motorola DynaTac (12). The original DynaTac was 10 inches long and weighed 2.5 pounds. The world now has 6 billion cell phone subscribers, and more and more of them are moving into the realm of smartphones. Most modern smartphones weigh between 4 and 6 ounces. Smartphones have changed the world.

**E = MC²: EINSTEIN’S BIG IDEA**

A 90-minute *Nova* video has traced the development of the theory establishing the connection between energy, matter, and light (13). The “squared” portion of the theory of Albert Einstein (1879–1955) was presaged by Émilie du Châtelet (1706–1749), a brilliant and rebellious daughter of Louis XIV’s secretary. She discovered advanced math at the age of 23, fell in love with Voltaire, and began an institution to rival the Royal Academy. She dared to challenge Isaac Newton’s gravity thesis as “flawed.” An experiment of the Dutch scientist Willem ’s Gravesande convinced du Châtelet that the energy of an object is a function of the square of its speed. In 19th-century London, the very notion of “energy” had not yet crystallized. Energy was thought of in terms of disconnected powers or forces, unique to various materials and activities. Michael Faraday, a blacksmith’s son, became a lab assistant to Sir Humphry Davy, the great physicist of that era. He dumbfounded his mentor by articulating the theory that electrical current “emanated outwards” from wires, rather than flowing through them like water through a pipe. The result was the invention of a primitive electric motor—and new physics.

Einstein grew up in the world of electricity at a time when scientists thought that all forms of energy had been discovered. Far from a model student, he was “obsessed” with the nature of light. The speed of light was computed before the 19th century, but no one knew what light actually was. Einstein, who suffered from poverty and was unable to secure promotion in his job, published five major articles in 1905 establishing the speed of light as a cosmic speed limit and postulating that energy becomes mass at a speed of light. The formula $E = mc^2$ expresses the unity of matter, energy, and light.

Theoretical physicist Max Planck (1858–1947), who originated the quantum theory, encouraged the world’s leading physicists to take Einstein seriously. In short order, $E = mc^2$ became the Holy Grail of scientific research, and Einstein won the Nobel Prize in physics in 1921.

Einstein thought it would take 400 more years of research to develop applications of his theory, but he had not banked
on a young Jewish woman in Hitler's Germany, Lisa Meitner. She and her collaborator, Otto Hahn, studied the atom, about which little was known. As a result of her work, she became the first German woman ever to achieve the title of professor. On the brink of major discoveries she was forced to flee the Nazis, but she continued her collaboration with Hahn by letter. They felt that if they could add neutrons to the 238 in the nucleus of uranium, they could make a heavier element. Hahn's experiments kept producing lighter ones. Eventually, Meitner realized that the uranium atom had become so large it had split. She and her nephew, Otto Frisch, published the first article on nuclear fission, but Hahn was given all the credit and the Nobel Prize.

Einstein's theory not only led to the development of the atomic bomb, but also explained the birth of the universe—pure energy becoming matter in the Big Bang—and the process by which stars burn, giving off energy, eventually leading to the emergence of life.

EDITORS, JOURNALISTS, AND PUBLISHERS

I have been a newspaper junkie for decades. I subscribe to The Dallas Morning News, The Wall Street Journal, USA Today, Barron's, and several magazines. Additionally, I have collected a number of books on famous newspaper editors/publishers/writers, including Joseph Pulitzer, William Randolph Hearst, Eugene Meyer (Washington Post), James A. Wechsler (New York Post), Richard H. Meeker, Vermont Royster (The Wall Street Journal), Eric Sevareid, Ralph McGill (Atlanta Journal Constitution), Hedley Donovan (Time), and James Reston. Studying some of their comments, I believe, has helped me in my own editing endeavors.

One of my favorites through the years has been Al Neuharth (Allen Herald Neuharth), who started USA Today in 1982 (14). He was born on March 22, 1924, in a German-speaking household in South Dakota, growing up in Eureka and Alpena. His father died when Al was 2, and his mother raised him and his brother by washing dishes and taking in laundry. He was a sergeant in the infantry in World War II and then went to college at the University of South Dakota in Vermillion, where he worked on the college newspaper. After graduation he was hired as a reporter for the Associated Press, but he decided to start his own newspaper by launching a weekly called SoDak Sports to cover South Dakota sports in unprecedented detail. In 1954, he moved to Florida to work at the Miami Herald. In 1963, he joined Gannett, becoming president in 1970 and chief executive officer in 1973. In the years that followed, Gannett became the most profitable newspaper company in history. In 1982, he started USA Today, which in actuality reinvented the American newspaper and set the stage for digital storytelling.

He emphasized that a newspaper must reflect all its readers. He had seen his own mother work for less pay than what men got. Gannett, accordingly, put unprecedented numbers of women and minorities in important jobs. Neuharth tried to shatter those barriers not only inside the newsroom but in the pages of the newspaper itself, where diversity in images and content was stressed from the top.

Selling USA Today to Gannett's board of directors was not easy in the shaky economy of the early 1980s. Neuharth chose the name, picked the editors, and approved the newspaper box, designed to look like a television set. Just 2 years after USA Today was launched, it was losing $340,000 a day. To raise USA Today's profile, Neuharth toured 50 states during “BusCapades” in 1987; the next year he visited 32 countries on a “JetCapade” to meet world leaders. In 1989, he retired as Gannett chairman but started a column that appeared every Friday; since 1989, he wrote over 1000 of them. One Friday in April 2013, I searched for Al's column and it was not there. The next day I learned that he had died.

Al Neuharth was a colorful and controversial figure, but his USA Today became the most read newspaper in the country after several years. It surpassed for a time The Wall Street Journal, which has subsequently recouped that position. Nevertheless, the fantastic graphics and color of USA Today forced most newspapers around the country to change the appearances of their papers. He taught me that most medical publications do not need to be as long as they are. The American Journal of Cardiology (AJC) publishes, for example, more articles each year than any other cardiovascular journal in the world, including publishing the most tables and figures. It is the text that is primarily shortened. (I became editor of the AJC the same year that USA Today was launched.) I will miss you, Al.

BROTHERS

My brother and I are quite different and almost from the beginning went our separate ways. It was a bit hard for me to understand how two boys growing up with the same parents and raised by the same mother could be so different. Thus, I was elated to see the recent book entitled Brothers by George Howe Colt, who demonstrated that differences among siblings are not nearly as rare as I had thought. He gives numerous examples of major differences: the Robespierres (Maximilien became the rigid, merciless overlord of the Reign of Terror, known to supporters as the “Incorruptible”; his younger brother, Augustine, became a self-indulgent lover of luxury known to friends as “BonBon”); the Melvilles (Gansevoort became a dutiful, responsible lawyer; his younger brother, Herman, became a world traveler and iconoclastic writer known to the family as “The Runaway Brother”); the Carters (sober and pious Jimmy became president; his younger brother, Billy, played the court jester and drunken buffoon); the Browns (John was the cynical hard-drinking Rhode Island slave trader, and his idealistic abstentious younger brother, Moses, became a leading Quaker abolitionist); the Capones (Al became the most powerful gangster in Prohibition-era Chicago, and his eldest brother, Vincenzo, was town marshal and Boy Scout commissioner in a small town in Nebraska and a prohibition enforcement agent responsible for busting up illegal stills).

Colt asked, “How can siblings, who share so much genetically and environmentally, be so different?” Studies in the past 3 decades of intelligence, personality, interests, attitudes, and psychopathology have concluded that siblings raised in the same family are, in fact, almost as different from each other as
unrelated people raised in separate families. Paradoxically, Colt indicates that the longer they live with each other, the more different siblings become.

Colt shows that biological siblings share, on average, half their genes; if personality traits were entirely genetic, siblings would be 50% similar and 50% different—even before factoring in the effects of being raised in the same family by the same parents. But biological siblings have personality correlations, according to Colt, of about 15%! (Even identical twins have only about a 50% overlap.) Although siblings share about half of each other's genes, not only is the genetic contribution of each parent halved, but the sequence of those shared genes is rearranged through a process called recombination. The behavioral geneticist David Lykken observed that siblings are like people who receive telephone numbers with the same digits arranged in a different sequence. Just as those telephone numbers, when dialed, result in entirely different connections, genes that have been scrambled will express themselves in widely different personalities.

According to Colt, there is a growing amount of research suggesting that siblings may be influenced most strongly by the things they do not share: birth order, age, friends, teachers, and the vagaries of chance. And they do not even really share the things that they appear to have in common—if not identical genes, then seemingly identical parents, homes, and often schools—because each of them perceives these things differently. Psychologists have indicated that the experience of each child within a family is so distinct that each grows up in his own unique "micro-environment"; in effect, each sibling grows up in a different family.

Colt's Brothers is a terrific book—brilliantly conceived, daringly organized, endlessly fascinating. Colt, nearly 60, is second in a line of four brothers. They have no sisters. The book is part family memoir, part celebrity biography, and part recapitulation of research about sibling dynasties. The celebrities include not only Edwin and John Wilkes Booth and John and Will Kellogg, but also Vincent and Theo van Gogh, John and Henry David Thoreau, and the Marks brothers, with brief mentions of the Kennedys (four brothers) and the Eisenhauers (six brothers), among others.

Edwin and John Wilkes Booth. Edwin and John Wilkes Booth, <5 years apart, are described in detail. Their father, Junius Brutus Booth, lived two different lives. On the stage he was the greatest American actor of his day, a man of prodigious talent. He also was a drunkard, was intermittently insane, and tried to kill himself at least twice. His other life was a relatively sane one in a four-room log cabin in rural Maryland 3 miles from his nearest neighbor and 25 miles from the nearest theater. Here Booth created a 150-acre sanctuary with dairy, stables, vineyard, orchard, vegetable garden, and swimming pond, to which he could retreat between professional engagements. Here he was known as "Farmer Booth." Here he was a devoted family man to Maryann and their 10 children, six of whom would survive childhood. Booth, unlike most Marylanders, refused to own slaves. He believed that men's souls were reborn into animals' bodies and thus forbade the eating of meat or fish or the felling of trees or the picking of flowers. The Booth children were not permitted to see doctors. Their illnesses were treated by home remedies. The boy who grew up to commit the most infamous murder in American history was raised as a vegetarian, forbidden to kill even a mouse or to brand a cow for the pain it would cause the animal.

Edwin Booth, the older son, grew up on the road with his father, forced to fend for himself from early on. When his older brother, June, outgrew the task, Edwin was taken from school at the age of 13 to storm the country as his father's dresser and to keep his father sober for the show, sometimes locking him in his hotel room on the day of a performance and after the final curtain tailing him down to waterfront bars and waiting outside before helping his father back to the hotel. When his father was overtaken by madness, Edwin was expected to lure him back to sanity. Edwin listened to the play night after night through the keyhole of the dressing room in which he had been left with his schoolbooks. Edwin made his first professional on-stage appearance at 15. After caring for his father for 5 years on the road, Edwin started his own career and by the time Lincoln had been elected president, Edwin was the nation's most respected and admired actor.

Edwin never had a childhood, unlike John Wilkes, called "Johnny" by his family, who enjoyed a perpetual adolescence right up to his death at the age of 26. While Edwin was babysitting his father in cities and towns across the country, Johnny was being spoiled by his mother on the farm. While Edwin grew up in the company of men traveling by stagecoach on muddy roads, eating and sleeping in flea-ridden beds at theatrical boarding houses, Johnny spent most of his time with his older sister, Asia, who later would devote much of her adult life to writing about her father and brothers in an effort to restore the family name.

If Junius Brutus Booth had been born 150 years later, he would likely have been diagnosed as bipolar. It seemed, according to Colt, as if Edwin and John had inherited a different pole. Edwin was shy, somber, introspective, and frequently depressed. He rarely smiled. His laugh was soundless. John Wilkes (Johnny) reflected his father's manic side. From childhood he was gregarious, headstrong, and unpredictable. He told his sister, "Don't let us be sad. Life is so short and the world is so beautiful. Just to breathe is delicious." While Edwin liked being alone, Johnny preferred a crowd. He made friends easily and at school became the magnetic center of a circle of boys. Edwin Booth had a profound melancholy; Johnny had an "exaggeration of spirit, almost a wildness." But Johnny seemed the sanest of the Booth children. Edwin grew up expecting doom; Johnny grew up expecting glory, believing he was destined for fame.

There was another factor that made it seem as if Edwin and John had been born into different families: John Wilkes was his parent's favorite child. Johnny was easy to love: cheerful, charismatic, exuberant, and handsome to the point of beauty. Johnny most resembled, of all the children, his high-spirited father in looks and manner, a fact that surely contributed to his "favorite" status. As an adolescent, Johnny spent his time playing cards, getting drunk, starting fights, skipping school,
and pulling pranks. (According to Freud a person who has been the indisputable favorite of his mother keeps for life the feeling of a conqueror, that confidence of success that often induces real success.)

John Wilkes Booth was 9 when Edwin Booth first left home to tour with his father. Johnny was 18 when Edwin returned. Although John admired Edwin, Edwin, like almost everyone who met John, couldn’t help liking his younger brother, they hardly knew each other. Edwin began helping John, casting his brother in several Shakespeare plays. At first, John’s acting was crude and lacked confidence; he stuttered and forgot his lines. But Edwin stuck with him and at every opportunity covered up his mistakes, arranging the staging so John was never out of range of the footlights, and gave him more prominent billing than his experience warranted. It was on Edwin’s recommendation that John, after only 3 years, was hired for the first time as a leading man.

Several biographers have explained Lincoln’s assassination as an extreme case of sibling rivalry, suggesting that John was a second-rate thespian who, realizing he would never eclipse his older brother Edwin and inherit the paternal mantel, was driven to seek fame on another stage. A proud man accustomed to getting his way, he may have resented being given direction by Edwin in their early joint appearances. John was realistic about his own acting, apparently, and in awe of Edwin’s. If there was a theatrical sibling rivalry, John had no doubt who was the winner. Although John Wilkes Booth is now remembered only as Lincoln’s assassin, at the time of his death he was one of the most popular actors in the USA, with reviews as glowing as those of any other performer excepting perhaps his brother Edwin. John T. Ford, owner of the theater in which Lincoln was killed, observed, “Doubtless he [John Wilkes] would have been the greatest actor of his time if he had lived.”

John was all raw instinct and undisciplined bravado. If the brothers’ acting style differed, so too did their motivations. Edwin sought excellence; John wanted renown. Edwin was a student of the theater and worked exceedingly hard; John had little patience for hard work and was easily bored. If Edwin was most comfortable alone in his study, John was most at home at the center of a party, telling stories, playing practical jokes, chatting expansively about politics, literature, war, nature, and the theater. He was a familiar sight in Washington’s bars, billiard rooms, 10-pin alleys, shooting galleries, and brothels. John was often described as “the most handsome man in America.” Like Edwin, John had wavy black hair, fair skin, an aquiline nose, and unnaturally long eyelashes, and he was an inch taller than Edwin and far more muscular (he exercised regularly) and sported a thick mustache. John was besieged by adoring female fans at stage doors, received 100 love letters a week from women he had never met, and was propositioned by women of every social station. His first biographer described him as “one of the world’s most successful lovers.” The treasurer at the Ford Theater where Lincoln was shot described John Wilkes as one of the simplest, sweetest-disposition, and most lovable men he ever knew.

Even as John’s theatrical fame grew, he longed for a more tangible form of glory. Edwin’s heroes were the great actors of the past. John Wilkes admired the abolitionist John Brown for his daring. The brothers surprisingly shared a deep fraternal devotion. If John was in awe of Edwin’s discipline and talent, Edwin would have liked to possess some of John’s easy charm.

In the Civil War, the two brothers took different sides. Edwin, who had spent much of his life in the West and Northeast and whose friends were Northerners, naturally sided with the Union. John had grown up in Maryland, where slavery seemed to be the status quo everywhere except on the Booth farm. During his 2 years in military school, he was friends with the sons of some of the South’s most prominent slave-owning families—in a region where, in the 1860 election, only 1 in every 40 votes was cast for Lincoln. John was passionately, virulently for the South. The restrained, circumspect elder brother Edwin was a Northerner, and the impetuous feather-ruffling rebellion-loving younger brother a Southerner. John had a Southern gentlemen’s patrician sense of social order, reinforced by the sense of entitlement he enjoyed as the family favorite.

It is not clear when John Wilkes decided to assassinate Lincoln. His sister, Asia, thinks when Richmond fell on April 3, something in her brother snapped. Ten days later, on the night of April 14, while Edwin was on stage in the Boston theater, John entered Lincoln’s box at Ford’s Theater, held his single-shot Philadelphia derringer pistol 2½ feet from the back of the president’s head, and pulled the trigger.

While on the run through the forest and swamps of Maryland and Northern Virginia after killing Lincoln—cold, wet, hungry, and feverish, with a broken leg—John still believed that his act would win him a place among the pantheon of heroes. He was devastated to learn that his act was reviled throughout the USA. Although many people refused to believe that the charismatic John Wilkes Booth could be the assassin, the moment Edwin Booth heard of the president’s death and read in the newspaper of the brandished dagger, the cry “sic semper tyrannus” and the leap to the stage, he recognized his brother’s histrionic touch. Just as John early in his career had resented being known as Edwin’s brother, now Edwin resented being John’s brother. Seeking fame for himself, John had inadvertently made Edwin even more famous. In 1889, Edwin founded the Players Club, a gathering place for actors on Gramercy Park South, where he lived in two rooms upstairs. Four years later when he suffered a massive stroke and died at the age of 59, there was a portrait of John on his bedside table.

**John and Will Kellogg.** In the Calhoun County Courthouse in Southern Michigan in 1917, the plaintiff and defendant in *Kellogg vs. Kellogg* were brothers. The plaintiff, John Harvey Kellogg, the man everyone called “the Doctor,” was the flamboyant founder and director of the Battle Creek Sanitarium, a combination spa, hospital, Chautauqua where the well-heeled came to see and be seen as they followed a customized regimen of rest, exercise, and diet. A short (62 inches), plump, 65-year-old Banty rooster of a man, the “Doctor” dressed all in white “to allow more of the health-giving rays of the sun to reach his body.” The only person in the courtroom the ebullient doctor didn’t try to charm was the defendant, 57-year-old Will Kellogg, known as “W.K.,” the founder and president of the Toasted...
and topped 350 bushels of Bermuda onions. He was paying for etables for the local market. Th e summer he was 9, he pulled a stock boy at his father's factory after school and on Sundays. But he was a plugger. At the age of 7 he was working as board. Finally, at 20 he got glasses. Will wasn't much to look at "dim-witted" because he couldn't read the words on the black-school he attended through the fi  fth grade assumed he was cautious, deliberate, and taciturn. A teacher at the Adventist spare moments.) an adult he carried a vest-pocket dictionary to peruse in his began borrowing from neighbors. Words fascinated him. (As soon exhausted his parents' meager collection of books and sorting broom corn for $2 a day. John educated himself. He for only 2 years to work 10-hour shifts in his father's factory, wrote poetry, and made up stories where he cast himself as the hero. He considered games a waste of time. He attended school for only 2 years to work 10-hour shifts in his father's factory, sorting broom corn for $2 a day. John educated himself. He soon exhausted his parents' meager collection of books and began borrowing from neighbors. Words fascinated him. (As an adult he carried a vest-pocket dictionary to peruse in his spare moments.)

The twelfth Kellogg child, Will was uncompromising, cautious, deliberate, and taciturn. A teacher at the Adventist school he attended through the fifth grade assumed he was "dim-witted" because he couldn't read the words on the black-board. Finally, at 20 he got glasses. Will wasn't much to look at either. But he was a plugger. At the age of 7 he was working as a stock boy at his father's factory after school and on Sundays. On summer mornings, he uprooted, bunched, and washed vegetables for the local market. The summer he was 9, he pulled and topped 350 bushels of Bermuda onions. He was paying for his own clothing at age 10 and supporting himself at 14. There was little time for fun. Later in life he said "I never learned to play." He felt especially self-conscious and inadequate next to his cocksure older brother who rarely let Will forget the 8 years that lay between them. John made Will shine his shoes. He made Will mind his manners. If Will complained, John gave him a whipping.

The Kelloggs weren't the only ones who considered John promising. The family shared a pew at the Battle Creek Tabernacle with elder James White and his wife, Ellen. Impressed by 12-year-old John Kellogg, the Whites invited him to learn the printer's trade at the Adventist publishing plant, where John advanced rapidly from errand boy to apprentice typesetter to proofreader. At 16, he was editing the Advent Review and Sabbath Herald. As he worked on various Adventist publications, John was intrigued by the church's minimalistic approach to nutrition. He decided to become a vegetarian. John became the Whites' protégé, living with them for months at a time, helping Pastor White with his writing.

In 1866, the Whites opened a small medical boardinghouse where ailing guests convalesced on a regime of rest, exercise, and hydrotherapy along with a diet of fruits, vegetables, graham bread, and water. But the Western Health Reform Institute, as it was called, didn't attract many customers, and the Whites decided they needed a first-rate physician to distinguish it from the other spas and water cure establishments that were springing up across the country. The Whites sent John to Bellevue Hospital Medical College, and he graduated in 1875. The following year they made him physician-in-chief of the faltering institute. John, only 24 years old, changed the name to Battle Creek Sanitarium and added a barrage of new treatments, including massage, calisthenics, electrical stimulation, deep-breathing exercises, and surgery. He led sing-a-longs and played his violin. He wrote pamphlets and magazine articles describing the work. Within 2 years, business at "The San," as people called it, was so good that John tore down the old farmhouse and built a 5-story Victorian building enough for 200 patients—the largest building in Battle Creek.

Will was also singled out by the Whites but for a less exalted position. While John was dissecting cadavers in New York City, 14-year-old Will was driving a horse and cart across Southern Michigan peddling his father's brooms. Though painfully shy, Will was a determined salesman who rarely took no for an an-swer. When Will's father broke his hip, he put Will in charge of the family business. He did so well that 2 years later when the Whites needed someone to manage a struggling Adventist broom factory, they sent Will. Supervising 60 men 1000 miles from home was a challenge for a shy 19-year-old, but Will turned the company around within a year. Back in Battle Creek, he took a course in bookkeeping at the local business college and prepared to marry his long-time girlfriend, a grocer's daughter he called "Puss." In April 1880, John Harvey Kellogg asked his younger brother to come work for him at the San.

By 1900, the Battle Creek Sanitarium was the largest and most popular spa in the country with 400 guestrooms, two indoor swimming pools, a surgical hospital, a 1000-seat chapel, 20 cottages, a lakeside resort, and 400 acres of farmland. Here some 3000 patients a year pursued what John Harvey Kellogg called "biologic living," described in one San brochure as "daily cold water and air baths, swimming, work in the gymnasium, wearing of light and porous clothing and frequent changes of underwear." The Doctor believed that the key to happiness lay in a healthy diet—defined at the San largely by what people couldn't eat: meat ("only proper food for hyenas and turkey buzzards," said the Doctor), tobacco ("destroys the sex glands"), coffee ("cripples the liver"), ice cream ("unnatural"), vinegar ("a poison, not a food"), oysters ("swarming with bacteria"), bouillon, tea, sugar, cheese, chocolate, alcohol, and spices, to name a few. San cuisine consisted largely of nuts and grains. The San offered 26 basic tithes, but each guest had his or her own customized plan. Ever since the Doctor had visited a colony of orangutans in Algeria and noticed that our primate cousins defecate almost continuously, he had maintained that frequent
bowl movements were the key to what he called “getting the stomach right.” Not all patients had the fortitude for the recommended five enemas a day, a regimen made possible with the help of a high-speed machine capable, according to the proud Doctor, of forcing 15 gallons of water through the intestines in a matter of minutes. Between meals—and enemas—patients submitted to massages, exercises, hydrotherapies, electric light baths, salt scrubs, etc. At the end of each day, patients gathered on the roof where the Doctor led them in a series of elaborate baths, salt scrubs, etc. At the end of each day, patients gathered on the roof where the Doctor led them in a series of elaborate marching patterns and the official San song, “The Battle Creek Sanitarium March.” Although the “biologic living” sounded a bit joyless, there were gym classes, cooking classes, folk dancing classes, greenhouse tours, Indian club demonstrations, picnics, bird walks, sledding and sleigh rides, and nonsectarian weekly church services.

The Doctor was the wizard behind the vegetarian Oz. His goal was to change the way Americans ate, breathed, dressed, exercised, and defecated. To that end, he churned out nearly 50 books, more than 200 medical papers, and so many pamphlets for the lay reader that even the publicity-conscious Doctor couldn’t keep count. He founded a nursing school, a school of hygiene, a liberal arts college, and a medical school, which provided the San with a steady stream of low-paid employees. He helped establish more than 30 San franchises across the country. He gave more than 5000 lectures. He made frequent trips abroad to examine the latest exercise equipment or to study advanced surgical techniques or to learn about new bowel cleaning methods. He invented a heated operating table, a vibrating chair that increased blood circulation, an electric belt cleaning methods. He invented a heated operating table, a vibrating chair that increased blood circulation, an electric belt...

set up to sell his health foods, surgical devices, and exercise machines. He answered the San mail—some 60 to 100 letters a day. He was the unofficial credit manager, a member of the labor committee, a volunteer security guard, and, on occasion, a hospital orderly. Each afternoon he was besieged by wealthy patients requesting extra services; disgruntled employees airing complaints; financially strapped patients seeking discounts on their bills. The Doctor had strict admission standards: no one contagious, no one on a stretcher, no one who looked sick. His ideal patients were overweight or neurasthenic women and overworked and dyspeptic men.

Will might not have minded serving his brother had his contributions been acknowledged. The Doctor never named him business manager, never gave him a title or a job description during his 25 years at the San. It rankled him that he worked there 10 years before his brother allowed him an office, and he worked for 14 years before his brother paid him enough to enable him to get out of debt. It rankled him that, like the 1000 other employees, he was expected to call his brother “Dr. Kellogg.” Dr. Kellogg didn’t seem to notice that he was humiliating Will. Will worked for 7 years before the Doctor allowed him a vacation. But, the Doctor treated most people that way. The Doctor found it nearly impossible to apologize, admit a mistake, or delegate. He was a czar and a law unto himself, ignoring his associates and subordinates, recalled Will. John was envious of Will for being 5 inches taller; Will envied John for being a doctor. Family members said that Will dreamed of becoming a physician himself but was so busy supporting his family on the meager salary his brother paid him that he never had the opportunity.

The brothers’ antipathy was intensified by their differences: the Doctor in fancy white and Will in drab, baggy, inexpensive suits; the Doctor escorted by a convoy of nurses and Will working behind the scenes, a quiet, almost furtive presence; the Doctor expressing himself in hyperbolic verbal torrents and Will speaking slowly and carefully when he spoke at all. The brothers who lived only a few blocks from each other rarely socialized. The Doctor, something of an intellectual snob, spent his spare time hobnobbing with the celebrities who frequented the San. Will, embarrassed at never having gotten beyond sixth grade, spent his with Puss and their children. The Doctor treated his wife, Ella Eaton, more like a business associate than a wife. They spent their honeymoon revising the Doctor’s new books. The Doctor believed that sex bred disease and bragged that he and Ella never consummated their marriage and never intended to. Fearful of germs, he tended to shy away from physical contact of any kind. Over the years, however, the Doctor and his wife took in 42 abandoned or needy children, at least nine of whom they formally adopted. Convinced that a healthy diet and proper upbringing could trump any hereditary deficits, the Doctor treated his “waifs,” as he called them, more like research subjects than loved sons and daughters. Housed in dormitories on the far side of “The Residence,” the Doctor’s 20-room Queen Ann mansion, they were raised and homeschooled by Ella and a cadre of San staffers on a modified biologic living schedule of vegetarian meals, chores, and calisthenics. (In the late 1880s,
Ella, who served as San dietician in addition to overseeing the Doctor's adoptees, had a nervous breakdown and lived as a semi-invalid until her death in 1920.)

Whenever the Doctor patronized him or overturned one of his orders to the staff, Will fumed. Will, however, had grown accustomed to living in the shadow of his genius brother. In 1883, a few years after Will came to work for his brother, the Doctor established an experimental kitchen in the basement of the San, where the brothers tried to create palatable recipes from the nuts and grains that dominated the San diet. Over the next 20 years, more than 80 different culinary confections would emerge from the kitchen. The brothers followed their customary modus operandi: the Doctor jotted down his ideas and passed them along to Will, who, after his 15-hour workday, experimented into the night. At one point, Will developed yet another nut and grain concoction and took it to his brother for approval. In 1897, the Sanitarium Food Company, with Will as manager, offered 42 different kinds of biscuits, breads, crackers, and ersatz coffee, available by mail order for those who wished to practice biologic living at home.

In 1895, the brothers began manufacturing Granose Flakes in a barn behind the San. That first year, despite minimal promotion (the Doctor permitted Will to advertise only in San publications), they sold almost 57 tons. Will knew they could sell much more. The Doctor refused to let Will advertise nationally. In 1900, while the Doctor was away, Will visited several members of the San board of directors and told them that, given the opportunity, the San food business would someday be so large that the sanitarium itself would be a mere “side show.” The board members agreed to let him build a small factory behind the sanitarium bakery to house the granose operation. When the Doctor returned from his trip and heard that the factory cost $50,000, he was furious. Saying he had not authorized the project, he insisted that his brother pay for it. Will, who had to beg friends and relatives for the money, eventually paid off the debt. But he never forgave his brother. And when a few months later the Doctor pressed ahead on moving the San business office, Will exploded. During the argument that followed, he quit. After 21 years at the San, Will would not find it easy to cut ties to his brother.

On February 18, 1902, 6 months after he left, the San burned to the ground. Having spent more than half of his life there, Will felt a responsibility to help rebuild the place in which he had invested so much. He offered to work without pay for “as long as my services were needed.” The Doctor put him in charge of financing the new building. Fifteen months after the fire, during which Will had worked 18-24-hour days, a new San rose: a 6-story, 560-foot-long, 1220-bed Italian Renaissance edifice with mosaic marble floors, a solarium, a roof garden, a gymnasium, and a glass-domed courtyard filled with orchids, orange trees, and 20-foot banana palms.

Will might never have broken permanently with his brother had it not been for C.W. Post, a 36-year-old inventor, real estate broker, and blanket manufacturer from Fort Worth, who had arrived at the San in 1891 with a 10-gallon Stetson, an emaciated frame, and an empty bank account. Though he stayed at the San for 9 months and gained almost 50 pounds, Post pronounced his treatment a failure. In 1892, he opened a scaled-down cut-rate meat-serving version of the San across town. A few years later, Post—who had spent much of his time at the San sniffing around its experimental kitchen and peppering the staff with technical questions—began to market Postum, a bran and molasses coffee substitute that bore more than a passing resemblance to the Doctor’s caramel cereal. By 1898, Postum sales totaled $840,000, and by 1903, they had risen to $10 million. Will was envious. Post was doing exactly what Will had urged the Doctor to do: pouring money into advertising and promotion. It galled Will to slave 16 hours a day for meager pay while others made fortunes pirating the San work. He begged his brother to let him take on the competition. The Doctor refused. Not only was he parsimonious by nature, he worried that associating his name with commercial advertising would jeopardize his reputation in the medical community. Will grew frustrated with his brother. At times they quarreled fiercely; at times they stopped speaking to each other.

Hoping at least to distinguish the San cereals from their imitators, Will suggested that they use his name on the packaging, making it clear that Will, not the Doctor, was endorsing the product and thereby protecting the Doctor from accusations of venality. The Doctor gave in. In 1903, these red-inked words began appearing on a few San products: “Beware of imitations—none genuine without the signature—W.K. Kellogg.” It was the first step not only in differentiating San products from those of its competitors but in differentiating Will (or W.K. as he would soon be known to the world) from his brother.

In 1898, the Kellogg brothers had produced a flaked corn cereal, but it lacked flavor. In 1902, they added malt to their flakes, which gave them a richer, nuttier taste. The Doctor, however, discouraged promotion, insisting that their mail order sales were perfectly respectful. Fed up with his brother, galvanized by Post, Will forged ahead without the Doctor’s permission. He sent salesmen door to door with free samples. He advertised in newspapers, put up street car signs, and sponsored store window displays. Reasoning that there were more well people in the world than sick, he marketed cornflakes as something tasty rather than something healthy. In 1905, while the Doctor was on a trip to Europe, Will did the unthinkable—he coated the flakes with sugar. When the Doctor returned, he had a fit but sales soared and the sugar stayed.

The end came when insurance executives came from St. Louis and offered to help finance a company devoted solely to cornflakes. Will presented the idea to his brother but the Doctor wasn’t interested. Will offered to buy the cornflake rights from his brother; they haggled for 6 months before the Doctor, still in debt from the fire, settled for $35,000 cash and more than half the new company’s stock. In February 1906, Will opened the Black Creek Toasted Corn Flake Company. Although Will was president and chief executive, the Doctor, as majority stockholder, retained the controlling interest. Not believing his brother’s company would amount to much, the frugal Doctor distributed chunks of his stock to San physicians in lieu of salary increases before traveling to Russia to observe the work of
a physiologist named Ivan Pavlov. He returned several months later to find that while he had been watching dogs salivate, his younger brother had been tracking down and buying up the stock that the Doctor had so cavalierly given away. Will now had the controlling interest in his own company. On the eve of his 46th birthday, he was no longer his brother's lackey.

Will Kellogg liked to say he was "an old man" when he finally went into business for himself, but he quickly made up for lost time. In his first year, he handed out 4 million free samples, convinced that once people tried his cornflakes, they would continue to buy them. He spent $30,000—one third of the company's initial working capital—on a single full-page ad in Ladies Home Journal. By the end of 1906, Will was indeed selling cornflakes by the carload. Although his plant burned down the following year, Will had a Chicago architect on site within 12 hours and a new fireproof plant in full production within 6 months. In 1907, while the Doctor was abroad, Will changed the name of his product to Kellogg's Toasted Corn Flakes. The Doctor was infuriated by his brother's success. With his brother, "For 22½ years I had absolutely lost all my individuality to you. I tried to see things with your eyes and do things as you would do them. You know in your heart whether or not I am a rascal. You also know whether or not I would defraud anyone, under any circumstances."

The war began in 1908 when the Doctor, claiming he had never liked the name, changed the Sanitas Nut Food Company to Kellogg Food Company. Will was outraged. The Doctor had never shown the slightest interest in using the Kellogg name on his products—indeed, he had insisted on not using it—until his brother began printing it on his cornflake boxes. This suit was settled the following year with an out-of-court compromise in which the Doctor agreed not to use the word Kellogg on any flake cereal food or display it conspicuously on any packaging. The truce lasted, however, only a few months. Their suits continued for a number of years. Even as they battled in court, the Kelloggs goaded each other to greater achievements. The San prospered in that magnificent new building Will's work had made possible. Its 1390 beds filled with movers and shakers, including Upton Sinclair, Henry Ford, Amelia Earhart, Johnny Weissmuller, Charles Edgar Welch, President William Howard Taft, and William Jennings Bryan.

The brothers later tried to rival each other in philanthropy. Each tried to give away more money than the other. The Doctor gave away his money as soon as it came in. Will let his money grow and then gave it away. The W.K. Kellogg Foundation became one of the largest charitable organizations in the US. The man who had never learned to play was determined that others might have the opportunity: he built schools, libraries, parks, playgrounds, swimming pools, gymnasiums, auditoriums, Boy Scout camps, hospitals, bird sanctuaries, and farms. Kellogg's was one of the first companies to institute 8-hour shifts and 5-day weeks and provide insurance, a health plan, and day care.

In all nonfraternal matters, Will preferred anonymity. Though he was now at least as famous as his brother, Will shunned publicity. He declined honorary degrees, refused to be listed in Who's Who, and rarely appeared at public gatherings, especially those designed to honor him. If he couldn't avoid being present, he sat in the back row. He often traveled under a pseudonym to avoid being recognized. Asked to prepare a short autobiography, Will came up with a mere 16 sentences, dismissing his quarter century at the San in a single phrase: "Took a job in April 1880, continued same for 25 years."

Despite Will's success, he was an insomniac. Like the Doctor, Will rarely handed out compliments and didn't tolerate failure. He was a strict moralist who always interfered in his children's personal lives. Although he went out of his way to help his employees enjoy themselves, he didn't know how to do so himself. He replaced his modest stucco home with a 30-room Tudor mansion, complete with a seven-car garage, tennis court, croquet pitch, greenhouse, and 800-acre Arabian horse ranch in Southern California, a home in Palm Springs, an Italian style villa on the Gulf Coast of Florida, and an apartment building across the street from the San, from which he could keep an eye on his brother's operation. He began traveling and feasted on his forbidden favorites—lobster, chocolate, and oysters—despite suffering from gout. Despite his wealth, Will was no less shy than he had been as a boy. He appeared to always feel inadequate next to his charismatic brother. Will was always formal and self-conscious with his children, hugging them only when he knew no one was watching. He did not approve of strong feelings of any kind unless pets were concerned. He was considered by his friends to be a lonely, isolated individual.

For all his ebullience, the Doctor too was lonely. He had thousands of acquaintances around the world, many of them famous, but few close friends. After his wife died, he never remarried. He remained proudly and publicly celibate. He seemed hardly able to keep track of his adopted children.

As the brothers aged and their lawsuits faded into the past, their relationship seemed at times almost guardedly cordial. Pride, however, kept both brothers from reaching out far enough to forgive each other. Although rivalry usually mellows with age, this was not so with the Kellogg brothers. On October 3, 1942, Will called on his brother. At 90, the Doctor had difficulty hearing and, even with an eyepiece, could barely recognize himself in the photos he autographed for San guests. Eighty-two-year-old Will had been diagnosed with glaucoma 5 years earlier and was completely blind. He got around with the help of a white cane and a German shepherd. The conversation, which lasted more than 5 hours, did not go well. Will tried to convince his brother that he was too old to control the San. If he wasn't willing to relinquish control, then he should at least let an old Adventist colleague help him. The Doctor rejected his brother's advice. After 66 years running the place, he wasn't about to give up the San. The Doctor died at 91, and 3 years later at 85 years old, Will Kellogg resigned from the Kellogg board of directors, although he continued to keep track of each new advertisement, salary increase, and sales report. Although his children and grandchildren would have liked to visit more often, they were afraid to show up at his house without an invitation, and Will wasn't the inviting kind. He spent several Christmases alone with his household staff. He was, perhaps, closest to his nurse, who read aloud to him and listened to him talk about the
vicissitudes of his life. Will expressed regrets several times that he and John Harvey never reconciled. At 91, on October 6, 1951, Will Kellogg died. Although he had outlived his brother by 8 years, he was 3 months younger than the Doctor when he had died. Will was buried next to his brother. In happier times, Will and the Doctor had put up matching twin monuments on their plots. At some point during their estrangement, however, Will had ordered his monument torn down and replaced by another: a bronzed sundial on which a robin tugged a worm out of the earth. Will, it seemed to say, was the proverbial early bird who got the worm—or at least before his brother got it.

In contrast to the Kellogg brothers, some famous brothers worked together beautifully: the Wright brothers (“Whatever it was they would do it together”); the Mayo brothers (Will and Charlie always remained as close as they had been in childhood, sharing a bank account and for a long time living next door to each other); and the White brothers (Sam, a physician, and Byron, a Supreme Court justice—Byron was asked once who he admired most: “My brother Sam” was his response) (16).

William Clifford Roberts, MD
6 May 2013

7. Leinwand Leger D. Heroin is back: your neighborhood could be next. USA Today, April 25, 2013.
8. Dorell O. In Israel, keeping your eyes open has become a way of life. USA Today, April 17, 2013.
for nab-paclitaxel versus docetaxel was observed in patients with a short DFI (43 vs. 33%; \( P = 0.019 \)). Safety results were similar to previous reports of the ITT populations. nab-Paclitaxel demonstrated similar efficacy in patients with poor prognostic factors as in the ITT populations of these two trials. In each trial, ORR was significantly higher for nab-paclitaxel versus the comparator taxane among patients with visceral dominant metastases.

**BRITISH JOURNAL OF DERMATOLOGY**

Tumour necrosis factor-\( \alpha \) inhibitor use in psoriasis patients with organ transplantation

Mansouri B, Patel M, Menter A


The use of biologic agents has revolutionized psoriasis treatment. However, little is known about biologic agent use in conjunction with antirejection therapies in organ transplant recipients. Our review of the literature yielded nine manuscripts which reported a total of 24 patients who received anti-tumour necrosis factor-\( \alpha \) (TNF-\( \alpha \)) therapy for either inflammatory bowel disease or severe, recalcitrant psoriasis. Only three of the 24 reported cases were of patients with severe, recalcitrant psoriasis and prior organ transplantation. Overall, anti-TNF-\( \alpha \) therapy improved the underlying condition (inflammatory bowel disease or severe psoriasis), showed few adverse effects, and there were no reports of allograft dysfunction in any of the 24 patients.

**CLINICAL LYMPHOMA MYELOMA AND LEUKEMIA**

Role of plasmapheresis in Waldenström’s macroglobulinemia

Stone MJ, Bogen SA


Despite the absence of randomized trials, plasmapheresis has consistently demonstrated efficacy in treatment of Waldenström’s macroglobulinemia (WM) patients with hyperviscosity syndrome (HVS). This procedure can promptly reverse most clinical manifestations of serum HVS. Early diagnosis is crucial and usually can be made from the funduscopic exam. Serial viscosity measurements can be monitored by the Ostwald tube method which is simple, reproducible, and for which there is substantial clinical correlation. The concept of a symptomatic threshold, whereby each WM patient has a distinct viscosity threshold for the development of HVS, seems valid. Maintaining serum viscosity below each patient’s symptomatic threshold effectively prevents recurrent HVS. Plasmapheresis is sometimes necessary as an emergency procedure and is useful maintenance therapy in selected patients. Prophylactic plasmapheresis should be considered in patients at risk for HVS after rituximab therapy. Vigorous plasmapheresis in WM patients with syndromes because of autoreactive immunoglobulin M antibodies requires further study.

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**BEST PRACTICE AND RESEARCH IN CLINICAL GASTROENTEROLOGY**

Definitions, pathophysiology, and evaluation of chronic diarrhoea

Schiller LR


Definitions for ‘chronic diarrhoea’ are arbitrary and are not evidence-based. The duration of illness that would differentiate acute from chronic diarrhoea is often taken as four weeks and serves best to exclude most infectious causes of diarrhoea which run their courses within that time interval. Patients tend to identify loose stool consistency rather than increased frequency of bowel movements when they say that they have diarrhoea. Some patients complaining of diarrhoea have frequent passage of formed stools and some have fecal incontinence. It is incumbent on the treating physician to inquire exactly what is meant by diarrhoea by a given patient. The pathophysiology of diarrhoea is complex, but generally comes down to explaining why there is excess water in stools. This can result from impaired absorption, excess secretion or retention of intraluminal fluid due to osmotic forces generated by poorly absorbed substances. The evaluation of diarrhoea is challenging. An algorithmic approach is feasible.

**BREAST CANCER RESEARCH AND TREATMENT**

nab-Paclitaxel for first-line treatment of patients with metastatic breast cancer and poor prognostic factors: a retrospective analysis

O’Shaughnessy J, Gradishar WJ, Bhar P, Iglesias J


Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) has demonstrated clinical benefit in metastatic breast cancer (MBC) in a randomized phase III trial versus paclitaxel (CA012; N = 454) and in a randomized phase II trial versus docetaxel (CA024; N = 300). This retrospective analysis examines whether patients with poor prognostic factors demonstrate similar outcomes to the intent-to-treat (ITT) populations in these trials. This retrospective analysis evaluated the efficacy and safety of previously untreated patients with MBC with the following poor prognostic factors: visceral dominant metastases and short disease-free interval (DFI; ≤2 years). In CA012 (n = 186 first-line patients), nab-paclitaxel demonstrated a significantly higher overall response rate (ORR) versus paclitaxel in patients with visceral dominant metastases (42 vs. 23%; \( P = 0.022 \)), whereas the higher ORR for nab-paclitaxel in patients with a short DFI (43 vs. 33%; \( P = NS \)) was not statistically significant. In CA024, a significantly higher ORR for nab-paclitaxel 150 mg/m\(^2\) versus docetaxel was observed in patients with visceral dominant metastases (76 vs. 37%; \( P < 0.001 \)). No significant differences in ORR were observed in patients with a short DFI. Although progression-free survival (PFS) and overall survival showed trends similar to ORR, statistical significance was only achieved for comparisons of PFS in patients with visceral dominant metastases in CA024 (13.1 months for nab-paclitaxel 150 mg/m\(^2\) vs. 7.8 months for docetaxel [\( P = 0.019 \)] and 7.5 months for nab-paclitaxel 100 mg/m\(^2\) [\( P = 0.010 \)]).
CURRENT OPINION IN GASTROENTEROLOGY

End-stage liver disease complications
Rahimi RS, Rockey DC


Purpose of review: Chronic liver disease causes significant morbidity and mortality because of any number of complications including hepatic encephalopathy, ascites, hepatorenal syndrome (HRS), and esophageal variceal hemorrhage (EVH).

Recent findings: Predictors of response to lactulose, probiotics, and L-ornithine-L-aspartate therapy in minimal hepatic encephalopathy (MHE) have been reported. Although rifaximin was slightly more effective than lactulose in the maintenance of remission and decreased re-admission in patients with MHE, it was not as cost-effective as lactulose. Beta-blockade has been associated with paracentesis-induced circulatory dysfunction. Those who respond to nonselective beta-blockers have a predictable overall lower probability of developing ascites and HRS. Noradrenaline was as effective as terlipressin for the treatment of type 1 HRS and was less costly. Hemorrhagic ascites, defined as an ascitic fluid red blood cell (RBC) count of at least 10,000/μl, appeared to be a marker for poor outcome in patients with cirrhosis. In patients with acute EVH, band ligation, pharmacologic vasoconstrictors, and antibiotics are effective; notably, intravenous proton pump inhibitor therapy in lieu of vasoconstrictors achieved similar hemostatic effects with fewer side-effects.

Summary: Refinement in the clinical management strategies for patients with cirrhosis and its complications appear to continue to contribute to improved patient outcomes.

IMMUNITY

Human CD1c+ dendritic cells drive the differentiation of CD103+ CD8+ mucosal effector T cells via the cytokine TGF-β


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In comparison to murine dendritic cells (DCs), less is known about the function of human DCs in tissues. Here, we analyzed, by using lung tissues from humans and humanized mice, the role of human CD1c+ and CD141+ DCs in determining the type of CD8+ T cell immunity generated to live-attenuated influenza virus (LAIV) vaccine. We found that both lung DC subsets acquired influenza antigens in vivo and expanded specific cytotoxic CD8+ T cells in vitro. However, lung-tissue-resident CD1c+ DCs, but not CD141+ DCs, were able to drive CD103 expression on CD8+ T cells and promoted CD8+ T cell accumulation in lung epithelia in vitro and in vivo. CD1c+ DCs induction of CD103 expression was dependent on membrane-bound cytokine TGF-β1. Thus, CD1c+ and CD141+ DCs generate CD8+ T cells with different properties, and CD1c+ DCs specialize in the regulation of mucosal CD8+ T cells.

JACC: CARDIOVASCULAR IMAGING

Imaging of low-gradient severe aortic stenosis
Tandon A, Grayburn PA


Although most patients with severe aortic stenosis (AS) have high peak velocity and mean transvalvular gradient, there is a subset of patients with low-flow, low-gradient severe AS (LGSAS). Assessment and management of such patients can be difficult and dobutamine echocardiography has been recommended to distinguish those with pseudo-AS (low calculated AVA due to insufficient flow to fully open the valve) from those with contractile reserve and true LGSAS, who may have good outcomes with surgery. More recently, a group of patients with LGSAS and preserved LV function have been identified. These patients are often elderly with hypertension, small left ventricular cavities, and concentric left ventricular hypertrophy. Because cardiac imaging plays a vital role in hemodynamic classification of patients with suspected LGSAS and determining appropriate management, this review was undertaken to summarize the current state of knowledge of this important but complex condition.

MEDICAL CLINICS OF NORTH AMERICA

Managing and treating tension-type headache
Freitag F


Although tension-type headache is ubiquitous, only a relatively small percentage of the population has these headaches occurring with sufficient frequency and severity to cause them to seek out medical attention. This small group, however, may have substantial impact from their disease on productivity and quality of life. Assessment of the headaches includes assessment for other headache disorders that may overlap it, such as a chronic migraine. Additionally, coexisting diseases that may contribute to the process, such as mood disorders and mechanical disorders of the spine and neck, require investigation. Treatment is optimized by appropriate use of acute medications and preventive treatments that may include drugs in the antidepressant classes along with nonpharmacologic modalities and other alternative treatments ranging from biofeedback to manual therapy to the use of botulinum toxin type A injections.

PLoS ONE

Curcumin modulates DNA methylation in colorectal cancer cells
Link A, Balaguer F, Shen Y, Lozano JJ, Leung HC, Boland CR, Goel A


Aim: Recent evidence suggests that several dietary polyphenols may exert their chemopreventive effect through epigenetic modifications. Curcumin is one of the most widely studied dietary chemopreventive agents for colon cancer prevention; however, its effects on epigenetic alterations, particularly DNA methylation, remain unclear. Using systematic genome-wide approaches, we aimed to elucidate the effect of curcumin on DNA methylation alterations in colorectal cancer cells.
Materials and methods: To evaluate the effect of curcumin on DNA methylation, three CRC cell lines, HCT116, HT29 and RKO, were treated with curcumin, 5-aza-2'-deoxycytidine (5-aza-CdR) and trichostatin A treated cells were used as positive and negative controls for DNA methylation changes, respectively. Methylation status of LINE-1 repeat elements, DNA promoter methylation microarrays and gene expression arrays were used to assess global methylation and gene expression changes. Validation was performed using independent microarrays, quantitative bisulfite pyrosequencing, and qPCR.

Results: As expected, genome-wide methylation microarrays revealed significant DNA hypomethylation in 5-aza-CdR-treated cells (mean \( \beta \)-values of 0.12); however, non-significant changes in mean \( \beta \)-values were observed in curcumin-treated cells. In comparison to mock-treated cells, curcumin-induced DNA methylation alterations occurred in a time-dependent manner. In contrast to the generalized, non-specific global hypomethylation observed with 5-aza-CdR, curcumin treatment resulted in methylation changes at selected, partially-methylated loci, instead of fully-methylated CpG sites. DNA methylation alterations were supported by corresponding changes in gene expression at both up- and down-regulated genes in various CRC cell lines.

Conclusions: Our data provide previously unrecognized evidence for curcumin-mediated DNA methylation alterations as a potential mechanism of colon cancer chemoprevention. In contrast to non-specific global hypomethylation induced by 5-aza-CdR, curcumin-induced methylation changes occurred only in a subset of partially-methylated genes, which provides additional mechanistic insights into the potent chemopreventive effect of this dietary nutraceutical.

SCIENCE TRANSLATIONAL MEDICINE

Induction of ICOS+CXCR3+CXCR5+ CD4+ T cells correlates with antibody responses to influenza vaccination


Seasonal influenza vaccine protects 60 to 90% of healthy young adults from influenza infection. The immunological events that lead to the induction of protective antibody responses remain poorly understood in humans. We identified the type of CD4+ T cells associated with protective antibody responses after seasonal influenza vaccinations. The administration of trivalent split-virus influenza vaccines induced a temporary increase of CD4+ T cells expressing ICOS, which peaked at day 7, as did plasmablasts. The induction of ICOS was largely restricted to CD4+ T cells coexpressing the chemokine receptors CXCR3 and CXCR5, a subpopulation of circulating memory T follicular helper cells. Up to 60% of these ICOS+CXCR3+CXCR5+CD4+ T cells were specific for influenza antigens and expressed interleukin-2 (IL-2), IL-10, IL-21, and interferon-\( \gamma \) upon antigen stimulation. The increase of ICOS+CXCR3+CXCR5+CD4+ T cells in blood correlated with the increase of preexisting antibody titers, but not with the induction of primary antibody responses. Consistently, purified ICOS+CXCR3+CXCR5+CD4+ T cells efficiently induced memory B cells, but not naïve B cells, to differentiate into plasma cells that produce influenza-specific antibodies ex vivo. Thus, the emergence of blood ICOS+CXCR3+CXCR5+CD4+ T cells correlates with the development of protective antibody responses generated by memory B cells upon seasonal influenza vaccination.

VASCULAR

Treatment of proximal vertebral artery disease

Shutze W, Gierman J, McQuade K, Pearl G, Smith B

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Vertebral arterial disease (VAD) is a less commonly recognized and treated source of cerebrovascular ischemia compared with carotid artery disease. Patients are often referred for treatment after they have developed symptoms in the form of transient ischemic attacks or had a posterior hemispheric stroke. Traditional treatment of VAD has been surgical. More recently, endovascular treatment of VAD has been utilized. We performed a retrospective review of our institutional experience in treating VAD from 2001 to 2010. For treatment of proximal VAD, perioperative morbidity is lower for the endovascular group than for the surgical group, but six-week mortality was higher for the endovascular group. Complete resolution of symptoms occurred more frequently with surgery than with endovascular therapy. Therefore surgical reconstruction appears to be preferable to angioplasty and stenting for treatment of proximal vertebral artery occlusive disease.
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