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Clinical research studies enrolling patients through Baylor Research Institute

Currently, Baylor Research Institute is conducting more than 800 research projects. Studies open to enrollment are listed in the Table. To learn more about a study or to enroll patients, please call or e-mail the contact person listed.

<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>
<td>Rose Boehm, CCRC, RRT, RLD 214-818-9405 <a href="mailto:rosebo@baylorhealth.edu">rosebo@baylorhealth.edu</a>; Jana Holloway, RRT, CRC 214-820-9888 <a href="mailto:janahol@baylorhealth.edu">janahol@baylorhealth.edu</a></td>
</tr>
<tr>
<td>Cancer</td>
<td>Breast, ovarian, endometrial, prostate, brain, lung, bladder, colorectal, pancreatic, and head and neck cancer; hematological malignancies, leukemia, multiple myeloma, non-Hodgkin’s lymphoma, melanoma vaccine; bone marrow transplant</td>
<td>Grace Townsend 214-818-8472 <a href="mailto:cancer.trials@baylorhealth.edu">cancer.trials@baylorhealth.edu</a></td>
</tr>
<tr>
<td>Diabetes (Dallas)</td>
<td>Type 1 and type 2 diabetes, cardiovascular events</td>
<td>Kris Chionh 214-820-3416 <a href="mailto:kristen.chionh@baylorhealth.edu">kristen.chionh@baylorhealth.edu</a>; Kerri Purcell, RN 817-922-4640 <a href="mailto:kerri.purcell@baylorhealth.edu">kerri.purcell@baylorhealth.edu</a></td>
</tr>
<tr>
<td>Diabetes (Fort Worth)</td>
<td>Type 2; cardiac events</td>
<td>Trista Bachand, RN 817-922-2587 <a href="mailto:trista.bachand@baylorhealth.edu">trista.bachand@baylorhealth.edu</a>; Kerri Purcell, RN 817-922-4640 <a href="mailto:kerri.purcell@baylorhealth.edu">kerri.purcell@baylorhealth.edu</a></td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>Healthy subjects needing colonoscopies</td>
<td>Allison Cox 214-820-6779 <a href="mailto:marya.cox@baylorhealth.edu">marya.cox@baylorhealth.edu</a></td>
</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, renal denervation for hypertension, diabetes in heart disease, cholesterol disorders, heart valves, thoracotomy pain, stem cells, critical limb ischemia, cardiac surgery associated with kidney injury, pulmonary hypertension</td>
<td>Merielle Boatman 214-820-2273 <a href="mailto:MeriellH@baylorhealth.edu">MeriellH@baylorhealth.edu</a></td>
</tr>
<tr>
<td>Heart and vascular disease (Fort Worth)</td>
<td>Atrial fibrillation, atrial fibrillation post PCI</td>
<td>Meagan King 817-922-2583 <a href="mailto:meagan.king@baylorhealth.edu">meagan.king@baylorhealth.edu</a></td>
</tr>
<tr>
<td>Heart and vascular disease (Legacy Heart)</td>
<td>At risk for heart attack/stroke; previous heart attack/stroke/PAD; cholesterol disorders; atrial fibrillation; overweight/obese; other heart-related conditions</td>
<td>Angela Germany 469-800-6409 <a href="mailto:lhcresearch@baylorhealth.edu">lhcresearch@baylorhealth.edu</a></td>
</tr>
<tr>
<td>Heart and vascular disease (Plano)</td>
<td>Aortic aneurysm; coronary artery disease; renal stent for uncontrolled hypertension; poor leg circulation; heart attack; heart disease; heart valve repair and replacement; critical limb ischemia; repair of aortic dissections with endografts; surgical leak repair; atrial fibrillation; heart rhythm disorders; carotid artery disease; congestive heart failure; gene profiling</td>
<td>Tina Worley 469-814-4712 <a href="mailto:c19459@baylorhealth.edu">c19459@baylorhealth.edu</a></td>
</tr>
<tr>
<td>Hepatology</td>
<td>Liver disease</td>
<td>Jonnie Edwards 214-820-6243 <a href="mailto:jonnie.edwards@baylorhealth.edu">jonnie.edwards@baylorhealth.edu</a></td>
</tr>
<tr>
<td>Infectious disease</td>
<td>HIV/AIDS</td>
<td>Bryan King, LVN 214-823-2533 <a href="mailto:bryan.king@ntidc.org">bryan.king@ntidc.org</a></td>
</tr>
<tr>
<td>Nephrology</td>
<td>Homocysteine and kidney disease, dialysis fistulas, urine/protein disorders in cancer patients</td>
<td>Dallas Clinical Trials Office 214-818-9688 <a href="mailto:Fabrienne.english@baylorhealth.edu">Fabrienne.english@baylorhealth.edu</a></td>
</tr>
<tr>
<td>Neurology</td>
<td>Stroke</td>
<td>Darlene Bunpian, MPH 214-818-2523 <a href="mailto:darlene.bunpian@baylorhealth.edu">darlene.bunpian@baylorhealth.edu</a></td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>Cerebral aneurysms</td>
<td>Kenneth Layton, MD 214-827-1600 <a href="mailto:kenl@baylorhealth.edu">kenl@baylorhealth.edu</a></td>
</tr>
<tr>
<td>Rheumatology (9900 N. Central Expressway)</td>
<td>Rheumatoid arthritis, psoriatic arthritis, lupus, gout, ankylosing spondylitis</td>
<td>Giselle Huey Krystine Cethoute 214-987-1253 214-987-1249 <a href="mailto:ruth.huet@baylorhealth.edu">ruth.huet@baylorhealth.edu</a> <a href="mailto:krystine.cethoute@baylorhealth.edu">krystine.cethoute@baylorhealth.edu</a></td>
</tr>
<tr>
<td>Transplantation</td>
<td>Bone marrow, blood stem cells, solid organs</td>
<td>Grace Townsend 214-818-8472 <a href="mailto:grace.townsend@baylorhealth.edu">grace.townsend@baylorhealth.edu</a></td>
</tr>
<tr>
<td>Weight management</td>
<td>Obesity</td>
<td>Kris Chionh 214-820-3416 <a href="mailto:kristen.chionh@baylorhealth.edu">kristen.chionh@baylorhealth.edu</a></td>
</tr>
<tr>
<td>Women’s health (Fort Worth)</td>
<td>Endometriosis and endometrial ablation</td>
<td>Theresa Cheyne, RN 817-922-2579 <a href="mailto:theresa.cheyne@baylorhealth.edu">theresa.cheyne@baylorhealth.edu</a></td>
</tr>
</tbody>
</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.
Colonoscopy is an important procedure in preventing colon cancer. The risk of colonic perforation during colonoscopy at the Baylor University Medical Center (BUMC) Gastrointestinal Laboratory was chosen as a surrogate marker for the safety of colonoscopy. A recent 2-year experience at BUMC was examined and compared with reports in the medical literature. The results are presented here along with a discussion of problems inherent with different health care systems and their ability to accurately track complications. It was concluded that colonoscopy at BUMC is as safe as that reported by comparable health care systems. The risk of perforation at BUMC was 0.57 per 1000 procedures or 1 in 1750 colonoscopies. Continued efforts to make colonoscopy safer are needed.

Colonoscopy plays an important role in the diagnosis and management of colonic diseases and in the prevention of colon cancer (1–3). However, complications associated with this procedure can be quite serious (4). The frequency of complications is dependent on the skill of physicians doing the procedure, on safeguards that are in place within the laboratory where the procedure is carried out, and whether colonoscopy is done for screening or for diagnostic or therapeutic indications. Major complications include adverse sedation or anesthetic events including aspiration pneumonia, post-polypectomy bleeding, diverticulitis, intraperitoneal hemorrhage, and colonic perforation (5–7).

Assessing the complication rate of colonoscopy is relatively easily done in countries where medical care is sponsored by the government, because complete and lifetime medical records are available on almost all patients. In some integrated health care systems, such as Kaiser-Permanente in the United States, complications from colonoscopy can also be accurately determined (8). The latter are referred to in this report as “closed” systems. However, assessing the safety of colonoscopy in private health care systems such as Baylor is much more difficult because patients may receive medical care in other hospitals with different medical records. For example, there are 27 gastroenterologists and 8 colorectal surgeons who do colonoscopies in the Baylor University Medical Center (BUMC) Gastrointestinal Laboratory. Some of these physicians practice in several hospitals and may perform colonoscopies in independent outpatient facilities within the community. Systems such as this are referred to as “open” systems in this report.

Although colonoscopy has been done at BUMC for over 40 years, there has never been a comprehensive assessment of complications. To partially rectify this deficiency, it was decided to use perforation rate as a surrogate measure of colonoscopy safety in general. Perforation was chosen because it always demands hospitalization and often requires surgery, and records of admission and surgery would be available for study. Moreover, most patients experiencing colonic perforation would be expected to return to BUMC for hospital care.

METHODS

Upon approval of the institutional review board, we reviewed the BUMC electronic health records from January 1, 2011, through December 31, 2012, and identified all patients discharged with a diagnosis of colonic perforation. We then identified those who had undergone colonoscopy at BUMC within the month prior to admission for colonic perforation. These numbers were then compared with the number of colonoscopy procedures performed in the Baylor Gastrointestinal Laboratory for any purpose. A literature search was then conducted to determine the rates of colonic perforation during colonoscopy at other “open” and “closed” health care institutions.

RESULTS

Perforation rate

A total of 10,534 colonoscopies were performed at BUMC from January 1, 2011, through December 31, 2012. Of this number, 3137 (30%) were for screening of healthy persons for colon polyps and colon cancer. During this time frame, 107 patients were discharged from BUMC with a diagnosis of colon perforation from all causes. As shown in Table 1, five patients had undergone colonoscopy at BUMC within 1 month prior to admission, and one had undergone flexible sigmoidoscopy. By
definition, these were assumed to represent colonic perforation due to colonoscopy. The calculated incidence of colonic perforation due to colonoscopy at BUMC during this 2-year period was 0.57 per 1000 procedures, or 1 per 1750 procedures. Two additional patients were admitted to BUMC with colonic perforation after colonoscopy done elsewhere. They were not included in the calculations.

Literature review

In Table 2, the average perforation rate for six “open” system reports involving 187,810 patients was 0.59 per 1000 colonoscopies (9–22). Table 3 summarizes 10 studies with 603,132 patients in “closed” systems with an average perforation rate of 0.74 per 1000 procedures. Figure 1 summarizes the average colonoscopic perforation rates in both “open” and “closed” systems. The Baylor rate of 0.57 per 1000 procedures is included; it is comparable to the 0.59 per 1000 rate in “open” systems and less than the 0.74 per 1000 rate in “closed” systems.

Clinical features of Baylor perforations:

No perforations occurred in the 3137 patients who underwent screening colonoscopy. All of the six perforations occurred in the 7347 patients examined for diagnostic or therapeutic reasons. Moreover, all of the six perforations occurred in patients who were found to have colonic disease. The diagnosis of colonic perforation was made immediately in two patients and as long as 22 days after colonoscopy in one. Three patients died and

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Procedure</th>
<th>Indication</th>
<th>Findings</th>
<th>Intervention</th>
<th>Perforation site</th>
<th>Time to diagnosis</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53</td>
<td>M</td>
<td>Flexible sigmoidoscopy</td>
<td>Hematochezia, radiation proctitis</td>
<td>Radiation proctitis</td>
<td>ERB ablation</td>
<td>? Splenic flexure on CT</td>
<td>5 days</td>
<td>No surgery</td>
<td>Multigorgan failure and died</td>
</tr>
<tr>
<td>2</td>
<td>79</td>
<td>F</td>
<td>Colonoscopy</td>
<td>Diarrhea, abdominal pain, C. difficile+</td>
<td>Ischemic colitis, perforation</td>
<td>None</td>
<td>Descending colon</td>
<td>Immediate</td>
<td>Colon resection</td>
<td>Perforated duodenal ulcer, died</td>
</tr>
<tr>
<td>3</td>
<td>68</td>
<td>F</td>
<td>Colonoscopy</td>
<td>Colonic stricture</td>
<td>Ischemic colitis</td>
<td>Biopsy</td>
<td>Multiple perforations</td>
<td>22 days</td>
<td>Colectomy, ileostomy</td>
<td>Died</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>M</td>
<td>Colonoscopy</td>
<td>Ulcerative colitis</td>
<td>Severe colitis</td>
<td>Rectal biopsies</td>
<td>Sigmoid</td>
<td>Immediate</td>
<td>Colectomy, ileostomy</td>
<td>Recovered</td>
</tr>
<tr>
<td>5</td>
<td>44</td>
<td>M</td>
<td>Colonoscopy</td>
<td>Chronic diarrhea</td>
<td>Ischemic colitis</td>
<td>Biopsies</td>
<td>Multiple sites</td>
<td>1 day</td>
<td>Colectomy, ileostomy</td>
<td>Recovered</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>F</td>
<td>Colonoscopy</td>
<td>Sigmoid stricture, radiation colitis</td>
<td>Sigmoid stricture</td>
<td>Dilation, stent placed</td>
<td>Sigmoid</td>
<td>2 days</td>
<td>Diverting colectomy</td>
<td>Recovered</td>
</tr>
</tbody>
</table>

Table 2. Cases of colonic perforation at Baylor University Medical Center at Dallas, 2011–2012

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Ref</th>
<th>Location</th>
<th>Number of colonoscopies</th>
<th>Perforations</th>
<th>Perforation rate per 1000</th>
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</thead>
<tbody>
<tr>
<td>Geenen et al</td>
<td>1975</td>
<td>9</td>
<td>Wisconsin</td>
<td>1,106</td>
<td>9</td>
<td>9</td>
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<tr>
<td>Farley et al</td>
<td>1997</td>
<td>10</td>
<td>Rochester, MN</td>
<td>57,028</td>
<td>43</td>
<td>0.7</td>
</tr>
<tr>
<td>Zubark et al</td>
<td>1998</td>
<td>11</td>
<td>Georgetown, DC</td>
<td>1,196</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anderson et al</td>
<td>2000</td>
<td>12</td>
<td>Scottsdale, AZ</td>
<td>10,486</td>
<td>20</td>
<td>1.9</td>
</tr>
<tr>
<td>Imperiale et al</td>
<td>2000</td>
<td>13</td>
<td>Indiana</td>
<td>1,994</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Korman et al</td>
<td>2002</td>
<td>14</td>
<td>USA, 45 ASCs</td>
<td>116,000</td>
<td>37</td>
<td>0.3</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td>187,810</td>
<td>110</td>
<td>0.59</td>
</tr>
</tbody>
</table>

ASC indicates endoscopic ambulatory surgical centers.

Table 2. Perforations during colonoscopy in six “open” systems

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Ref</th>
<th>Location</th>
<th>Number of colonoscopies</th>
<th>Perforations</th>
<th>Perforation rate per 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basson et al</td>
<td>1998</td>
<td>15</td>
<td>Connecticut VA</td>
<td>5,163</td>
<td>3</td>
<td>0.6</td>
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<tr>
<td>Eckardt et al</td>
<td>1999</td>
<td>16</td>
<td>German</td>
<td>2,550</td>
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<td>0.8</td>
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<td>Sieg et al</td>
<td>2001</td>
<td>17</td>
<td>German</td>
<td>82,416</td>
<td>13</td>
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<tr>
<td>Nelson et al</td>
<td>2002</td>
<td>18</td>
<td>VA</td>
<td>3,198</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Gatto et al</td>
<td>2003</td>
<td>19</td>
<td>Medicare</td>
<td>39,286</td>
<td>77</td>
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<tr>
<td>Viala et al</td>
<td>2003</td>
<td>20</td>
<td>Australia</td>
<td>23,508</td>
<td>23</td>
<td>1</td>
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<tr>
<td>Levin et al</td>
<td>2006</td>
<td>8</td>
<td>Kaiser-Permanente</td>
<td>16,318</td>
<td>15</td>
<td>0.91</td>
</tr>
<tr>
<td>Rabeneck et al</td>
<td>2008</td>
<td>21</td>
<td>Canada</td>
<td>97,091</td>
<td>54</td>
<td>0.7</td>
</tr>
<tr>
<td>Arora et al</td>
<td>2009</td>
<td>22</td>
<td>California Medicaid</td>
<td>277,434</td>
<td>228</td>
<td>0.82</td>
</tr>
<tr>
<td>Warren et al</td>
<td>2013</td>
<td>6</td>
<td>Medicare</td>
<td>53,220</td>
<td>33</td>
<td>0.6</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td>603,132</td>
<td>448</td>
<td>0.74</td>
</tr>
</tbody>
</table>

VA indicates Veterans Affairs.
three recovered. One patient had severe ulcerative colitis, three had ischemic colitis, and two had radiation colitis. Four patients underwent immediate colectomy, and one underwent a diverting colostomy. One patient developed multiorgan failure and was determined not to be an operative candidate. One patient developed a perforated duodenal ulcer postcolectomy and died. One patient with ischemic colitis died after colectomy. Two patients had a sigmoid stricture, due to ischemia in one and to radiation in the other. The latter patient had a sigmoid stent placed. Three patients were men and three were women. The age ranged from 18 to 79 years. Those who died were 53, 68, and 79 years of age. One endoscopist had two perforations. He was one of the highest-volume endoscopists on our staff.

**DISCUSSION**

The Baylor perforation rate of 0.57 per 1000 procedure is comparable to that reported in other “open” systems, which averaged 0.59 per 1000, and less than the rate of 0.74 per 1000 in “closed” systems. The higher rate in closed systems is likely due to more complete retrieval of complications.

How can the risk of colonic perforation at colonoscopy be reduced? It is important to be aware of risk factors that increase the likelihood of perforation, which include female sex, increasing age, obstruction, polypectomy, inflammatory bowel disease, stricture dilation, thermal cautery, and comorbidities (23, 24). Sedation, especially with propofol, should be kept as light as possible so that patients experiencing pain or discomfort (23, 24). Sedation, especially with propofol, should be kept as light as possible so that patients experiencing pain or discomfort can be identified and corrective maneuvers instituted. Patients with inflammatory bowel disease, including ulcerative colitis, Crohn's colitis, ischemic colitis, and radiation colitis, should be approached with special care (25).

Dilation of colonic strictures must be done cautiously. Barotrauma can result in colonic perforation and can be avoided by frequent monitoring of abdominal distention and minimal air or CO₂ insufflation during the procedure. Special care must be employed during resection of sessile or flat colon lesions with thermal cautery. The saline lift technique is indicated in resecting these lesions. Hot biopsy forceps are thought to be associated with an increased risk of perforation and should not be used (23).

Avoiding screening colonoscopy in persons over age 80 with a previous normal exam and no risk factors should be considered. Low-volume colonoscopists have an increased rate of complications and may need to be monitored. Endoscopists who have difficulty reaching the cecum may require monitoring (26). Regularly scheduled morbidity and mortality conferences where all serious complications are reviewed should help identify safety concerns and promote best practices (25).

This study indicates that colonoscopy as performed at BUMC is as safe as that reported in the literature from comparable institutions. However, we should continuously strive to reduce complications insofar as possible. The measures cited above should hopefully reduce the risks of this important procedure. Periodic monitoring of the colonoscopic perforation rate at BUMC, as done in this study, should reveal how effective our efforts are. The safety and welfare of our patients should be our primary goals.

**Acknowledgments**

I would like to acknowledge the extensive assistance of Dr. John S. Fordtran in the organization, review, and completion of this study.


*Figure 1. Colonic perforations per 1000 procedures.*
Female breast tissue is composed of variable proportions of fat and fibroglandular tissue, and in general, an increased ratio of fibroglandular tissue to fat corresponds to increased mammographic density. Studies suggest that mammographic density is an independent risk factor for breast cancer, and the sensitivity of mammography can be lower with heterogeneously dense or extremely dense breasts. Nineteen states have legal statutes requiring that patients be notified if they have dense breasts, including the state of Texas. Hendra’s law, mandated on January 1, 2012 in Texas, suggests that patients with dense breasts could benefit from additional screening tests such as breast magnetic resonance imaging (MRI). Our study examined the impact of Hendra’s law by comparing the number of screening breast MRIs performed for dense breasts before and after the law’s implementation. Results showed a 23-fold increase in the number of dense breast MRIs in the 2 years that this new legislation was in effect. This increase could have substantial implications for the health care economy, and further studies are needed to determine the cost-effectiveness of this additional screening tool.

METHODS

To determine the overall trend in the number of MRIs performed for the purpose of evaluating dense breast tissue, all breast MRIs between 2011 and 2013 were examined at Baylor University Medical Center at Dallas and were divided into three categories: 1) total number of breast MRIs; 2) total number of screening breast MRIs (defined as studies of asymptomatic patients with no personal history of breast cancer); and 3) total number of screening breast MRIs ordered for the evaluation of dense breasts (excluding high-risk patients with a strong family history of breast cancer or who were known to be BRCA positive).

RESULTS

In 2011 (pre-Hendra’s law), a total of 255 breast MRIs were performed, 32 of which were considered to be screening breast MRIs. Only 2 of the patients with screening breast MRIs received MRIs for evaluation of dense breasts (Table). After the implementation of Hendra’s law in 2012, not only was there an increase in the total number of breast MRIs, but there was also an increase in the number of screening MRIs performed for evaluation of dense breasts (Table). There was a continued increase in the number of screening breast MRIs performed in 2013, with 46 MRIs performed for the evaluation of dense breasts out of 78 total screening breast MRIs (Table). This represents a 23-fold increase in the number of MRIs ordered for dense breasts when compared to the pre-Hendra’s law data from 2011 (Figure).
DISCUSSION

Increased breast tissue density is a frequent mammographic finding, with 26% to 32% of women in the general population having a breast tissue density ≥50% (2). The sensitivity of mammography can decrease as the density of breast tissue increases, with one study showing sensitivity values ranging from 87% in breast tissue composed almost entirely of fat to 62.9% in extremely dense breast tissue (6). Henda’s law took effect in the state of Texas on January 1, 2012, to ensure that affected patients and their primary care physicians were informed of the possible limitations of mammography and the potential benefit of supplemental screening examinations such as breast MRI. Contrast-enhanced MRI has been shown to be more sensitive than mammography in the detection of early breast tumors due to the different contrast enhancement pattern of an underlying breast cancer in comparison to normal breast parenchyma (1, 7, 8).

Our analysis of the number of breast MRIs performed for the evaluation of dense breasts during the year 2011 (pre-Henda’s law) as well as during the 2 years after the implementation of Henda’s Law (2012 and 2013) showed a 23-fold increase after the law was passed, demonstrating the effect of Henda’s law on the overall course of preventive breast care.

The implications of this increase could be potentially staggering to the health care economy. To date, only one state, Connecticut, has mandated that insurance cover adjunctive screening in these higher-risk patients. Among women in their 40s, 74% have dense breasts, and the percentage decreases to 57% for women in their 50s (9). Simply put, most women over 40 are affected by this need for additional screening. Without clear guidelines and definitive measures to control costs, we could no longer engage in screening as recommended by the World Health Organization, which states that any screening

Table. Breast MRI data at Baylor University Medical Center at Dallas before and after implementation of Henda’s law

<table>
<thead>
<tr>
<th>Month</th>
<th>Total breast MRIs</th>
<th>Screening breast MRIs</th>
<th>Dense breast MRIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011: Before implementation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jan</td>
<td>19</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Feb</td>
<td>12</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Mar</td>
<td>25</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Apr</td>
<td>13</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>May</td>
<td>24</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Jun</td>
<td>20</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Jul</td>
<td>13</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Aug</td>
<td>31</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Sep</td>
<td>23</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Oct</td>
<td>26</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Nov</td>
<td>31</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Dec</td>
<td>18</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>255</td>
<td>32</td>
<td>2</td>
</tr>
<tr>
<td>2012: After implementation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jan</td>
<td>19</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Feb</td>
<td>25</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Mar</td>
<td>27</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Apr</td>
<td>37</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>May</td>
<td>35</td>
<td>10</td>
<td>3</td>
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<tr>
<td>Jun</td>
<td>39</td>
<td>4</td>
<td>0</td>
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<tr>
<td>Jul</td>
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<td>6</td>
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<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Sep</td>
<td>18</td>
<td>4</td>
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<tr>
<td>Oct</td>
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</tr>
<tr>
<td>Nov</td>
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<td>Dec</td>
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<tr>
<td>Total</td>
<td>360</td>
<td>65</td>
<td>9</td>
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<td>2013: After implementation</td>
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<td>6</td>
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<td>6</td>
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</tr>
<tr>
<td>Sep</td>
<td>34</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Oct</td>
<td>39</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Nov</td>
<td>39</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Dec</td>
<td>41</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>387</td>
<td>78</td>
<td>46</td>
</tr>
</tbody>
</table>

Total breast MRIs indicates the total number of both screening and diagnostic magnetic resonance imaging (MRI) scans divided by month; screening breast MRIs, the total number of screening breast MRIs divided by month; dense breast MRIs, the total number of dense breast screening MRIs divided by month.
examination should be not only safe and effective but also relatively inexpensive (10).

Comparison of length of stay and outcomes of patients with positive versus negative blood culture results

Danielle Armstrong-Briley, DO, Neda S. T. Hozhabri, PhD, Kris Armstrong, MD, Jason Puthottile, MD, Raul Benavides, MD, and Stacy Beal, MD

In the United States, sepsis is the leading cause of death in critically ill patients. The fatality rate for severe sepsis is about 40%, and treatment costs over $16 billion annually. It is critical to identify and treat the source of sepsis. While there are varying guidelines determining when to draw blood for culture, at Baylor University Medical Center at Dallas, blood cultures are ordered for patients with new onset of fever, immunosuppression, or a suspicion of an underlying infectious etiology.

We conducted a retrospective study of patients who had blood cultures after hospital admission or in the emergency department in December 2013. We compared length of stay and outcomes of patients with positive versus negative blood cultures. There was no significant difference for length of stay or outcomes among patients with positive and negative blood cultures. For patients admitted from the emergency department, there was a longer length of stay for patients with positive cultures; however, the overall prognosis was not worse.

Up to 46% of hospitalized septic patients are admitted through the emergency department (ED) (1). Since many ill patients initially present to the ED, it is of utmost importance to assess and identify the source of infection for proper and rapid treatment. Thirty to fifty percent of patients presenting with a clinical syndrome of severe sepsis or shock have positive blood cultures; therefore, the international gold standard of practice when there is suspected sepsis is blood culture analysis (2). However, incubation of blood cultures can take anywhere from 3 to 7 days, and in cases of suspected sepsis, antibiotics are usually started empirically without waiting for pathogen isolation (3). Due to the absence of published guidelines that clearly state when blood cultures should be drawn (4) and to establish if there is a correlation between positive blood cultures and outcome, we conducted a retrospective study of inpatients with the diagnosis code for sepsis and all ED patients with blood cultures performed over 1 month. We aimed to determine if a positive blood culture predicted increased morbidity and mortality among patients presenting to Baylor University Medical Center at Dallas (BUMC) who were suspected of having sepsis.

METHOD

We searched our electronic health system for two patient populations during the month of December 2013: all hospitalized patients who had blood cultures drawn if sepsis was suspected (hospital sepsis cohort) and all patients who had blood cultures performed in the ED. Patients who had cultures drawn during hospitalization may not have had cultures drawn in the ED prior to admission.

For all patients in this study, one or more blood cultures were obtained in a BacTAlert FA (30 mL) and/or FN (40 mL) blood culture bottle (bioMérieux, Durham, NC) in the ED or in the hospital at BUMC. The samples were sent via courier to the affiliated reference laboratory, med fusion (Lewisville, Texas). Upon arrival, the bottles were placed on the BacTAlert automated blood culture system. Any positive culture was flagged and reported to caregivers. Samples were defined as negative if an organism was not detected within 5 days.

Clinical information was derived from the patient’s electronic medical records. Demographic information included age and gender. Other data included type of pathogen present in blood culture, length of stay, in-hospital mortality, intensive care unit (ICU) admission, and hospital admission or readmission for those patients who presented to the ED. P values were calculated by converting the z value (from Microsoft Excel 2007) to a P value (calculated on Graphpad).

RESULTS

In December 2013, a total of 135 patients who presented to the ED at BUMC had blood cultures drawn. In addition, 54 hospitalized patients had the diagnosis code for sepsis, for a total of 189 patients. The patients’ ages ranged from 19 to 101 years (mean 64). There were 89 men and 100 women.

Hospital sepsis cohort

For the hospital sepsis cohort, the patients (n = 54) were admitted through the ED but had blood cultures drawn after
hospitalization. Thirty-four patients had negative blood cultures, and 20 patients had positive cultures. For those with positive cultures, the most common organisms recovered were *Escherichia coli* (3, 15%), alpha streptococci (viridans group) (3, 15%), and beta hemolytic streptococci (3, 15%). The remaining organisms recovered were *Staphylococcus aureus* (2), coagulase-negative staphylococci (2), *Bacteroides fragilis* (1), *Proteus mirabilis* (1), *Klebsiella pneumoniae* (1), *Streptococcus pneumoniae* (1), *Enterococcus faecalis* (1), *Propionibacterium acnes* (1), and *Capnocytophaga canimorsus* (1) (Table 1).

Our data did not show statistically significant differences in the outcomes between hospitalized patients with positive blood cultures and those with negative cultures. Twenty-five (73.5%) of the patients with negative cultures were admitted to the ICU versus 18 (90%) of the patients with positive cultures (*P* = 0.335, NS). For patients with positive cultures, the average length of stay was 5.6 days (range 0–23, SD 5.44) compared with 6.5 days (range 0–29, SD 8.28) for those with negative cultures (*P* = 0.63, NS) (Figure 1). Eleven (32%) patients with negative blood cultures and 6 (30%) patients with positive blood cultures died during their stay (*P* = 0.9998, NS). Therefore, for hospitalized patients, positive blood cultures may not be a predictor of mortality or ICU admission in patients who meet the clinical criteria for sepsis.

**ED cohort**

The second group of patients consisted of those who had blood cultures initially drawn in the ED. A total of 134 patients who presented to the ED in December 2013 had blood cultures drawn. Of this group, 124 patients (93%) had negative cultures, and 10 (7%) had positive cultures. For patients with positive cultures, the most common organisms were coagulase-negative staphylococci (3), alpha streptococci (viridans group) (2), and *S. aureus* (2). The remaining microorganisms present were *E. coli* (1), *P. acnes* (1), and *Micrococcus* sp. (1).

Of the 10 patients with positive cultures, three were directly discharged from the ED. These patients had positive cultures for coagulase-negative staphylococci, *P. acnes*, and *Micrococcus* sp., which are common contaminants (5). One patient who was positive for coagulase-negative staphylococci was transferred to an outside hospital. Of the six remaining patients with positive blood cultures who were admitted to the hospital (two with *S. aureus*, two with alpha streptococci viridans group, and one each with *E. coli* and coagulase-negative staphylococci), only one patient (17%) who was positive for alpha streptococci (viridans group) was admitted to the ICU. One admitted patient with a positive culture for coagulase-negative staphylococci died (17%) (Figure 2).

Of the 124 patients with negative blood cultures, 112 (90%) were either discharged directly from the ED or left against medical advice; one died in the ER; three were transferred to an outside hospital (2%); and eight were admitted—two (25%) to the ICU and six (75%) to the medical/surgical floor (Figure 2).

Our data showed no significant difference in ICU admission among patients with positive blood cultures compared with

---

**Table 1. The most common organisms in the hospital sepsis cohort**

<table>
<thead>
<tr>
<th>Organism</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>3</td>
</tr>
<tr>
<td>Alpha streptococci</td>
<td>3</td>
</tr>
<tr>
<td>Beta hemolytic streptococci</td>
<td>3</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>2</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>2</td>
</tr>
<tr>
<td><em>Bacteroides fragilis</em></td>
<td>1</td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td>1</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>1</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>1</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td>1</td>
</tr>
<tr>
<td><em>Propionibacterium acnes</em></td>
<td>1</td>
</tr>
<tr>
<td><em>Capnocytophaga canimorsus</em></td>
<td>1</td>
</tr>
</tbody>
</table>

![Figure 1](image-url) Outcomes for the hospitalized sepsis cohort. There were no statistically significant differences in the (a) length of hospital stay or (b) number of intensive care unit (ICU) admissions among patients who had positive or negative blood culture results.
patients with negative cultures. However, the average length of stay of patients with positive cultures was longer than that for patients with negative cultures. Of the 9 patients with negative cultures who were admitted to the hospital, the average length of stay was less than 1 day (range 0–16 days). The average length of stay for the patients with positive cultures was 5.1 days (range 0–12; $P = 0.0001$). Therefore, for patients presenting to the ED, a positive blood culture could be a predictor of an increased length of hospital stay (Figure 3).

**DISCUSSION**

Approximately 200,000 episodes of bacteremia occur in the United States each year, with an incidence of about 10 per 1000 hospital admissions (4). In fact, bacterial bloodstream infections are associated with a mortality of 14% to 37%. Bloodstream infections include infective endocarditis, primary bacteremia, and those secondary to focal infections such as pneumonia, abscesses, urinary tract infections, and osteomyelitis (4). As a result, if sepsis or any of these aforementioned illnesses are suspected in the ED, blood cultures are often liberally ordered to help direct physicians towards proper treatment. As a result, only 4% to 7% of blood cultures drawn are positive (4). Our data also show that most of the patients who are hospitalized and who present to the ED do not have positive cultures.

The presence of systemic inflammatory response syndrome (SIRS) criteria is often used to identify patients with possible sepsis and establish when to draw a blood culture. One of the most common SIRS presentations is a new fever, and most physicians have a low threshold for ordering blood cultures for patients with a newly developed fever (6). Our data indicate that most of the patients who had blood cultures drawn had a history of fever or a newly developed fever (data not shown). However, most of the patients with a history of fever did not have positive blood cultures and were discharged. Since there does not appear to be an increased incidence of positive blood cultures and worse prognosis among patients with fever, perhaps blood cultures are not needed for patients only presenting with fever when the patient is well enough to be discharged from the ED.
Among the medical community, it is generally accepted that the presence of blood pathogens can indicate a worse prognosis. However, Previsdomini et al did not show an increased length of ICU stay and mortality among patients with positive blood cultures (6). Similar to Previsdomini et al, our data also did not show a statistically significant difference in ICU admission and mortality among those with positive and negative cultures; however, our data showed that a positive blood culture trended towards longer hospital stays (6).

Skin and environmental contaminants in blood cultures can lead to unnecessary antibiotic therapy and longer hospital stays (6). It is likely that the three patients with positive cultures in the ED cohort who were directly discharged from the ED had contaminants in the culture. In fact, as many as half of the cultures that are positive represent probable contaminants (4). Bates et al found that contaminant results independently increased subsequent laboratory charges by 20% (5). Therefore, it is important to identify common pathogens that likely represent contaminants in order to prevent increased medical costs.

Limitations of this study include a sample from a single medical facility with a modest patient number due to a short study period. There may have been patients with potential infection who did not have blood cultures performed. As Shapiro et al identified, physicians have a lower threshold for ordering blood cultures for patients who have comorbidities. Therefore, our study may have bias towards finding these comorbidities as predictors of death (8). Approximately two-thirds of patients hospitalized for sepsis in the United States are 65 and older (1). Hence, a single site study could be biased towards this age group. Comparing data with multiple sites, including a longer duration for data collection and a younger patient population, could help control for confounders (1). In addition, patients may have died due to causes unrelated to infection.

Published guidelines do not clearly indicate when blood cultures should be drawn; cultures are often obtained on patients presenting with fever, chills, focal infections, leukocytosis, or suspected endocarditis (4). At BUMC, patients with a suspected underlying infectious etiology, fever, and those who are immunosuppressed routinely have blood cultures drawn in the ED. After reviewing the data for December 2013, it appears there is a statistically significant increase in the length of stay among patients with positive blood cultures drawn in the ED. However, there does not appear to be an increase in mortality or an increase in hospital admissions and ICU stay among patients with positive cultures in the ED. Although protocols recommend blood cultures to rule out an underlying infectious etiology, our data show that blood cultures may have limited utility for patients not admitted from the ED or patients solely presenting with fever who appear clinically appropriate for discharge from the ED.

Health care is evolving into a value-based reimbursement system focused on quality and outcomes. Reported outcomes from national databases are used for quality improvement projects and public reporting. This study compared reported outcomes in cardiac and thoracic surgery from two validated reporting databases—the Society of Thoracic Surgeons (STS) database and the National Surgical Quality Improvement Program (NSQIP)—from January 2011 to June 2012. Quality metrics and outcomes included mortality, wound infection, prolonged ventilation, pneumonia, renal failure, stroke, and cardiac arrest. Comparison was made by chi-square analysis. A total of 737 and 177 cardiac surgery cases and 451 and 105 thoracic surgery cases were captured by the STS database and NSQIP, respectively. Within cardiac surgery, there was a statistically significant difference in the reported rates of prolonged ventilation, renal failure, and mortality. No significant differences were found for the thoracic surgery data. In conclusion, our data indicated a significant discordance in quality reporting for cardiac surgery between the NSQIP and the STS databases. The disparity between databases and duplicate participation strongly indicates that a unified national quality reporting program is required. Consolidation of reporting databases and standardization of morbidity definitions across all databases may improve participation and reduce hospital cost.

Clinical databases are one means of determining risk-adjusted outcomes. Hospitals and health care systems participate in national databases to meet the requirements for payment, as well as to track performance. The rapidly increasing number of available databases include multispecialty or specialty-specific clinical registries and administrative claims databases. The popularity and expansion of specialty-specific databases is most likely due to the value found in disease-specific outcomes. Multispecialty databases evaluate commonly occurring outcomes such as wound infection, pneumonia, or venous thromboembolism, whereas specialty databases allow for finer discrimination of outcomes such as graft patency or anastomotic leak. Focused databases allow for advancement of our knowledge outside of formal clinical trials, giving a more accurate assessment of treatment effects in the general population, and provide significant research opportunities. The robust outcomes data from the Society for Thoracic Surgeons (STS) database has produced more than 100 peer-reviewed publications (1). However, with the added benefits of specific databases comes an increase in the time and cost of participation. Each database has specific and unique criteria and definitions for reporting. Interestingly, in the current health care climate of increased efficiency and reduced cost, the increasing number of databases with variability of reporting criteria results in duplication of work, increased cost, and possible reporting inconsistencies. The surgical department at our institution spends >$125,000 annually for database participation and an additional cost of 6.5 full-time employees for management and chart/data abstraction. Statistics from national databases are being publicly reported, but are they comparing apples to apples? This study compared reported outcomes in cardiac and thoracic surgery from two validated reporting databases at a single institution.

METHODS

Our institution is a tertiary care academic medical center that has an active quality improvement program with participation in many quality-reporting structures, including the STS database and the National Surgical Quality Improvement Program (NSQIP).

NSQIP was initiated in 1994 within Veteran Affairs hospitals as a means to compare surgical outcomes with the national standard. This program achieved a >40% reduction in mortality and was subsequently expanded to nonveteran hospitals beginning in 1998, with an open subscription program by the end of 2004 (2). Today, NSQIP reports outcomes of surgical specialties including general, vascular, and cardiothoracic surgeries. It uses validated sampling strategies and does not include 100% of cases. Data abstractors are registered nurses employed by the hospital. Program training is facilitated through the NSQIP program, and quality assurance is maintained through periodic auditing. Inter-rater reliability is robust, with disagreement rates improving since inception and reported at 1.56% in 2008 (3). Validity has been proven previously for accuracy, as well as for newly collected readmissions data (4).
The STS database was started in 1989 as an initiative for quality improvement and patient safety among cardiothoracic surgeons. It is a well-established and robust quality-reporting program that boasts 94% participation by all adult cardiac surgery centers nationally. Over 5 million cases have been captured across its three divisions: adult cardiac surgery, congenital heart surgery, and general thoracic surgery. Data managers abstract retrospective chart data, in addition to prospective clinical data collection by clinical team members (5). Annual auditing is performed at randomly selected institutions for data validation (6).

Outcomes data from our single institution for the period of January 2011 to June 2012 were compared between the two databases. Non–risk-adjusted data were compared to eliminate variability. Quality metrics included mortality, wound infection, prolonged ventilation, pneumonia, renal failure, stroke, and cardiac arrest. The rates were compared by chi-square or Fisher’s exact test, as appropriate. Statistical significance was set at \( P < 0.05 \).

RESULTS
There are fundamental differences between the two databases. As discussed above, the abstraction patterns and case inclusion are varied, but the variables collected are also not identical. As shown in Figure 1, STS collects 121 variables (59 preoperative, 45 intraoperative, and 17 postoperative), whereas NSQIP captures 75 variables (46 preoperative, 4 intraoperative, and 25 postoperative). The preoperative and intraoperative data are used for risk stratification.

During the study period, 737 and 177 cardiac surgery cases and 451 and 105 general thoracic cases were captured by the STS database and NSQIP, respectively. NSQIP captured 24% of cardiac procedures and 23% of thoracic cases performed. As shown in Table 1, for cardiac surgery there was a significant difference in the reported rates of prolonged ventilation, renal failure, and mortality; however, the rates of deep wound infection, pneumonia, stroke, and cardiac arrest were similar. In the thoracic surgery cases, no statistically significant difference was found for any category, including wound infections, prolonged ventilation, pneumonia, renal failure, stroke, and mortality rate (Table 2).

Due to the difference in outcomes within some of our measured metrics, the definitions for each were further investigated and found to often be discordant (Table 3). A diagnosis of superficial wound infection for the STS database required three components: infection within the skin and subcutaneous tissue, opening of the wound, and one of the following: purulent drainage; organism isolated from wound; or pain, tenderness, or heat. In contrast, NSQIP required only one of four possible criteria: purulent drainage; organism isolated from the wound; diagnosis by the physician; or pain, swelling, or heat and wound opening. Another difference was found in the definition of renal failure. The STS database defined renal failure by the RIFLE criteria (absolute creatinine increase by threefold or \( >4.0 \)) (7). In contrast, NSQIP defined renal failure as the patient requiring dialysis or an increase in creatinine value by 2.0 (1, 8).

DISCUSSION
Quality reporting systems are critical tools in the current health care environment. Public reporting allows patients to

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**Table 1. Cardiac surgery outcomes by database**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>STS (n = 737)</th>
<th>NSQIP (n = 177)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound infection</td>
<td>7 (0.9%)</td>
<td>2 (1.1%)</td>
<td>0.690</td>
</tr>
<tr>
<td>Prolonged ventilation</td>
<td>241 (32.7%)</td>
<td>20 (11.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>68 (9.2%)</td>
<td>10 (5.6%)</td>
<td>0.130</td>
</tr>
<tr>
<td>Renal failure</td>
<td>65 (8.8%)</td>
<td>7 (4.0%)</td>
<td>0.031</td>
</tr>
<tr>
<td>Stroke</td>
<td>26 (3.5%)</td>
<td>2 (1.1%)</td>
<td>0.096</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>41 (5.6%)</td>
<td>8 (4.5%)</td>
<td>0.580</td>
</tr>
<tr>
<td>Mortality rate</td>
<td>56 (7.6%)</td>
<td>6 (3.4%)</td>
<td>0.046</td>
</tr>
</tbody>
</table>

NSQIP indicates National Surgical Quality Improvement Program; STS, Society of Thoracic Surgeons.

**Table 2. Thoracic surgery outcomes by database**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>STS (n = 451)</th>
<th>NSQIP (n = 105)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound infection</td>
<td>10 (2.2%)</td>
<td>3 (2.9%)</td>
<td>0.720</td>
</tr>
<tr>
<td>Prolonged ventilation</td>
<td>17 (3.8%)</td>
<td>5 (4.8%)</td>
<td>0.580</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>22 (4.9%)</td>
<td>4 (3.8%)</td>
<td>0.800</td>
</tr>
<tr>
<td>Renal failure</td>
<td>8 (1.8%)</td>
<td>2 (1.9%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (0.2%)</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>Mortality rate</td>
<td>15 (3.3%)</td>
<td>5 (4.8%)</td>
<td>0.560</td>
</tr>
</tbody>
</table>

NSQIP indicates National Surgical Quality Improvement Program; STS, Society of Thoracic Surgeons.

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Figure 1. Database variables. NSQIP indicates National Surgical Quality Improvement Program; STS, Society of Thoracic Surgeons.
identify high-performing hospitals and physicians. Furthermore, the current strategy for reimbursement reform is also designed to incentivize high-quality care, which may lead to better outcomes and lower mortality (9, 10). Therefore, it is concerning that reporting metrics can appear discordant between databases. Our study clearly indicates a significant discordance in quality reporting for cardiac surgery between NSQIP and the STS database.

Many studies have shown a dramatic discrepancy between these two types of outcomes collection methods in terms of postoperative complications. In a single institution study, Meguerditchian et al (11) matched data from NSQIP with the Agency for Healthcare Research and Quality Patient Safety Indicators (AHRQ-PSI) and reported a large variance in postoperative outcomes. Using data from over 200 hospitals to compare Medicare claims and NSQIP, Lawson et al (12) also found significant differences in postoperative complications, with poor agreement between the two databases ($\kappa = 0.21–0.47$). In another study, one hospital showed that risk-adjusted postoperative mortality varied from the top third to the bottom decile between the NSQIP and University HealthSystem Consortium (UHC). Additionally, the rate of infectious complications (13% vs 1%) and the rate of readmissions (14.6% vs 17.6%) varied between NSQIP and UHC databases (13, 14).

Clinical databases are now accepted as more accurate than administrative databases, but large hospitals that participate in multiple registries still find frequent discrepancies. Koch et al (15) compared three databases—AHRQ, NSQIP, and the Cardiovascular Information Registry (CVIR)—and found that the overall concordance rates were poor ($0.02–0.60$). When Koch et al compared NSQIP and CVIR, they reported discordance for sepsis ($\kappa = 0.05$), hemorrhage ($\kappa = 0.27$), respiratory failure ($\kappa = 0.40$), and deep vein thrombosis ($\kappa = 0.51$). These results concur with our finding of variable outcomes reporting in cardiac surgery by clinical databases.

The variance in outcomes between NSQIP and the STS database demonstrated in our study is most certainly attributable to differences in metric definitions and data abstraction techniques. The STS database captures all cardiothoracic procedures; in contrast, NSQIP data are a representative sampling. Additionally, NSQIP data are collected for 30 days after the procedure, and many STS values are collected for the duration of a patient’s hospital stay or 30 days, whichever is longer.

Endeavors at combining multiple databases in order to provide a more powerful and robust data source have been previously attempted (11, 16–18). Combining patient data from multiple sources is complicated by attempts at patient de-identification in order to protect patient confidentiality. After the STS database began collecting Social Security numbers in 2008, it was matched with the Social Security Death Master File. STS database sensitivity for in-hospital death was 98.8%, whereas sensitivity for out-of-hospital 30-day death was 59.7% (17), further demonstrating the discordance between these two databases.

Limitations of this study include nonidentical patient populations within the two databases. NSQIP captures roughly 25% of case volume, compared to 100% for the STS. The cases were not matched to the STS database patients prior to comparing outcomes, to better highlight the differences in data reported. The study time of 18 months may be too short to accrue an adequate sample size, especially in the NSQIP arm, to eliminate type I error. Because the study involved only a single institution, the volume of data is also limited. We recognize that both the NSQIP and STS outcome databases continually strive to improve accuracy and clarity of patient outcomes. Therefore, there is constant evolution of measures and definitions.

This study is one more example of discordant metrics that are reported and available to our patients and payers. In the current fiscal environment, cost savings is paramount. A feasible method of data sharing and common metric definitions between databases would significantly reduce the number of man-hours required for data entry, reduce the redundancy of duplicate chart extraction, and improve consistency of reporting. This would result in greater efficiency and cost reduction of quality database reporting and participation and may allow
for smaller hospitals with ever-tightening budgets to contribute to national databases. Furthermore, standardizing definitions of morbidities and complications would result in increased clarity for outcomes research.

General multispecialty databases such as NSQIP have the advantage of lower cost and can be applied across a wide range of specialties, but the limited sampling strategy and generalized criteria may not allow for fine discrimination of outcomes to specific patient populations. Since the STS database collects a greater proportion of cases and includes specialty-specific complications and more robust risk adjustment, specialty-specific databases such as the STS database should probably be considered the gold standard. However, the increased power of specialty-specific data comes at the price of a narrow scope that must be replicated for multiple specialties.

Postextubation dysphagia (PED) is a common problem in critically ill patients with recent intubation. Although several risk factors have been identified, most of them are nonmodifiable preexisting or concurrent conditions. Early extubation, small endotracheal tube size, and small bore of nasogastric tube potentially decrease the risk of PED. The majority of patients receive treatment based on only bedside swallow evaluations, which has an uncertain diagnostic accuracy as opposed to gold standard instrumental tests. Therefore, the treatment decision for patients may not be appropriately directed for each individual. Current treatments are mainly focused on dietary modifications and postural changes/com- pensatory maneuvers rather than interventions, but recent studies have shown limited proven benefits. Direct therapies in oromotor control, such as therapeutic exercises and neuromuscular stimulations, should be considered as potential effective treatments.

INCIDENCE

Of 220,000 survivors of acute respiratory failure requiring mechanical ventilation each year in the US (5), 3% to 62% develop PED. The wide range of incidence could be explained by the differences in the population studied, differences in the sensitivity of diagnostic methods and the timing of the assessment, and the duration of intubation. The patients who required prolonged intubation from all diagnosis subtypes were found to have a higher incidence of PED compared to postoperative patients with a shorter duration of intubation (6).

MECHANISMS

The mechanisms of PED are multifactorial and include mechanical causes, cognitive disturbances, and residual effects of narcotics and anxiolytic medications (7). Mechanical causes are directly related to the duration of intubation and endotracheal tube size, since these tubes cause mucosal inflammation leading to loss of architecture, oropharyngeal muscle atrophy from disuse during intubation, diminished proprioception, decreased laryngeal sensation, and laryngeal injury (edema, granuloma, and vocal cord paralysis) (6). Traumatic brain injury or critical illness may also cause PED by damaging peripheral and bulbar nerves, altering cognition, or causing the dysregulation of the swallowing reflex (8).

RISK FACTORS

Preexisting neurological conditions, such as stroke and neuromuscular disease (2), low Glasgow Coma Scale scores (1), advanced age (9–11), prolonged mechanical ventilation (1, 2, 9, 10), preexisting congestive heart failure, forced supine position, the presence of tracheostomy, nasogastric tube placement (12–16), head and neck cancer, and recent transesophageal echocardiography (17) have been associated with a higher risk of developing PED. A study in trauma patients found that number of ventilator days and an age ≥55 years were independent risk factors. Each day of intubation increased the risk of PED by 14%, and patients older than 55 had a 37% increased risk of dysphagia compared with younger patients (9).

PED is clearly linked to preexisting neurological disorders that cause swallowing abnormalities, such as stroke, neuromuscular diseases, and low Glasgow Coma Scale scores. The increased prevalence of neurological disease in elderly patients is one of the risk factors that places elderly patients at a higher risk of PED and a poor functional status prior to admission (11).
The incidence of PED is increased in the presence of risk factors that cause laryngeal irritation and inflammation, including prolonged mechanical ventilation (>50% of patients with PED were intubated for >48 hours) (1, 2), the presence of tracheostomy, nasogastric tubes, or a recent transesophageal echocardiography study. A large-bore nasogastric tube is more likely than a small-bore nasogastric tube to be associated with the development of PED (18).

SCREENING AND EARLY DETECTION
Since PED can potentially cause life-threatening consequences, including aspiration pneumonia, malnutrition, prolonged hospital stays, massive financial costs, and increased mortality (3, 4, 19), early detection of PED is essential to reduce complication rates. However, there is no well-established standard screening protocol across institutions in the US. Most diagnostic tests are performed 18 to 24 hours after extubation (18).

Many facilities have developed screening tools for PED. A dysphagia clinical evaluation typically includes the following:
- Questions about history/risk factors
- Observation of the patient's behavioral characteristics, such as level of alertness, cooperation, and motivation
- Observation of signs of motor speech and/or voice abnormalities
- Observation of oral motor structure, sensation, and function
- Observation of signs of oral and pharyngeal dysphagia

Swallow screening evaluation is used to determine the need for further instrumental assessment. A clinical examination to evaluate the pharyngeal phase has a good correlation with fiberoptic endoscopy in swallowing evaluation and is adequate to start oral nutrition (20). About 60% of PED evaluations use only bedside swallow evaluations (18).

DIAGNOSTIC PROCEDURES
Various instrumental tests used for evaluation of PED include videofluoroscopic swallow study (VFSS) (21), fiberoptic endoscopic evaluation of swallowing (FEES) (22), ultrasonography (23), pH-manometry (24), and scintigraphy (25). Many factors, such as the presence of established screening guidelines, hospital size, type of academic affiliation, and availability of diagnostic tests, have a significant influence on the pattern of formal evaluation in PED in the US. The gold standard evaluation of oropharyngeal dysphagia is VFSS or FEES, which allows real-time imaging of all stages during swallowing.

VFSS is sometimes called a modified barium swallow exam or swallow study. It incorporates a set of modifications in various consistencies and textures, ranging from thin barium to barium-coated cookies, patient positioning, and radiographic focus, to facilitate optimum visualization of the oral-pharyngeal-laryngeal structures and their function during swallowing. The effects of compensatory maneuvers, diet modification, and bolus transport during all stages of swallowing can be studied fluoroscopically in a real-time manner to determine a safe-for-swallow diet and to maximize efficiency of the swallow.

An FEES allows a direct observation of the pharyngeal and laryngeal structures during swallowing via a fiberoptic nasopharyngolaryngoscope to evaluate the pharyngeal swallow. Detailed information regarding swallowing function and relevant functions of nearby structures within the upper aerodigestive tract are evaluated. Also, compensatory positions and therapeutic maneuvers can be attempted to determine a safe diet and to maximize the efficiency of the swallow. The advantages of FEES include its ability to be done at the bedside and its ability to assess tissue quality, such as strictures from fibrosis. It also can reduce the exposure to radiation (26).

Both VFSS and FEES are mainly used when the diagnosis is uncertain after bedside swallow evaluations, and both tests are more likely to be available at university-based hospitals than community-based hospitals (18). Other criteria for obtaining an instrumental examination include suspicion for silent aspiration, recurrent pneumonia, or right lower lobe pneumonia and the need for treatment strategy evaluation (18).

TREATMENT
Dysphagia treatment is focused on nutritional status, hydration, and reducing morbidity from pneumonia. However, treatment modalities have been relatively underappreciated. Based on most studies, there are three major therapeutic options for PED: dietary texture modifications, postural changes/compensatory maneuvers, and interventions to improve swallow function, therapeutic exercises, and neuromuscular stimulation.

The American Dietetic Association has classified diet level according to textural properties and anchor foods to four levels of semisolid/solid foods (27):
- I. National Dysphagia Diet Level 1: Dysphagia-pureed (homogenous, very cohesive, pudding-like, requiring very little chewing ability)
- II. National Dysphagia Diet Level 2: Dysphagia-mechanical altered (cohesive, moist, semisolid foods, requiring some chewing)
- III. National Dysphagia Diet Level 3: Dysphagia-advanced (soft foods that require more chewing ability)
- IV. Regular (all foods allowed)

The level of liquid viscosity is labeled based on correlating viscosity ranges:
- I. Thin: 1–50 centiPoise (cP)
- II. Nectar-like: 51–350 cP
- III. Honey-like: 351–1750 cP
- IV. Spoon-thick: >1750 cP

The patients will receive treatment based on the level of severity and the pattern of dysphagia after swallowing function assessment.

Without changing swallowing function, postural techniques such as 90° upright, 45° reclining sitting posture, and chin down position, and swallowing maneuvers, such as a small amount of intake per swallow and multiple swallows, are used to change the patients’ environment to overcome anatomical and physiological deficiencies. Postural methods can reduce airway aspiration by changing the passage and speed of ingested food.

Therapeutic exercises and neuromuscular stimulation are focused on improving swallowing function. A speech pathologist can prescribe an oral-pharyngeal regimen to improve oromotor...
control and to decrease the risk of aspiration (26). More recent interventions, such as neuromuscular electrical stimulation, cricopharyngeal botulinum toxin injection, and surface electromyography biofeedback, have also shown benefits in alleviating underlying neuromuscular disorders in dysphagia (28, 29).

Paul Revere Osler: the other child

Richard L. Golden, MD

Sir William Osler (1849–1919) is among the most honored and esteemed physicians of our time. His life, and that of his wife Grace Revere Osler (1854–1928), has been examined in great detail by historians and biographers and continues to be the subject of intensive scrutiny. Their son “Revere” (Edward Revere Osler) (1895–1917), who died in the Great War, is often mistakenly referred to as their only child. Grace had two previous pregnancies, having given birth to Paul Revere Osler, who lived but a week, early in their marriage in 1893 and to a stillborn infant during her first marriage to Dr. Samuel W. Gross in 1877. Information regarding these two events is often ill defined, cursory, or incorrect. New research provides further knowledge of these events and their impact, giving a fuller understanding and a more lucid historiography of the Oslers.

Sir William Osler was the most celebrated physician of his time, still renowned today for his achievements as a clinician, educator, philosopher, humanist, and author. He held professorships at McGill, Pennsylvania, and Johns Hopkins universities, capping his career as Regius Professor of Medicine at Oxford.

Even in a life as carefully examined as that of William Osler, there are inevitably obscure or unknown areas that defy further scrutiny as a result of lack of documentation, correspondence, or historical commentary, as well as others that can be further explored and elucidated. The short life of Paul Revere Osler, the firstborn child of William and Grace Osler, is such an example, as well as the scant information regarding Grace’s pregnancy during her first marriage to Dr. Samuel W. Gross. Details are frequently absent or incorrect and their second child, Edward Revere Osler (“Revere”) (1896–1917), who died in the Great War, is often referred to as their only child. The knowledge of these events and their impact contributes to our fuller understanding and a more lucid historiography of the Oslers (Figure 1).

Grace Linzee Revere Gross, the great-granddaughter of the illustrious midnight rider Paul Revere and the widow of the well-known Philadelphia surgeon Samuel W. Gross, had apparently refused Osler’s early proposal. He had been writing his textbook at the time and had threatened to let the book “go hang”; she had sagely advised the shoemaker to “stick to his last.” Osler received the first copy of The Principles and Practice of Medicine on February 24, 1892, and the next day, according to the time-honored story, he tossed the book into her lap, exclaiming, “There, take the darn thing; now what are you going to do with the man?” (1). This was the successful forerunner to their secretive marriage in Philadelphia on May 7, 1892 (2).

Only a few cryptic remarks have been recorded of Grace’s pregnancy. In November 1892, he wrote casually to a colleague: “I did not care to leave madam (who has by the way a young Professor under contract) in all the wrack and ruin of painters plasterers and paper-hangers” (3). In January his mother Ellen wrote with perspicacity to her daughter Charlotte “Chattie” (Gwyn): “I had a scrap from Willie this morning. . . . He puts on a good show of spirits but in his heart of hearts I know he must have an anxious time as to the coming event” (4). Paul was born in Baltimore on February 6, 1896, delivered at home by Howard A. Kelly almost exactly 9 months after the wedding (5, 6). Osler was delighted and, in somewhat dubious taste, boasted that he had put something over on Gross (7). On February 11, Osler wrote to John H. Musser that the “young doctor looked

Figure 1. The Osler Family, 7 Norham Gardens, Oxford, June 1905. From the William Osler Photo Collection, CUS_064-001_P, with permission of the Osler Library, McGill University, Montreal.

From The State University of New York at Stony Brook; The Osler Library, McGill University; and the American Osler Society.

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very touchy; tho fine & strong he has developed a bad jaundice which has benumbed his nerve centres more than usual” (8). To his great sorrow, the small boy died at the end of a week. To his colleague Lafleur, Osler explained: “He seemed all right for five or six days and then developed a sudden coma.” In addition he commented: “Though the birth was an exceedingly easy one, he was a little asphyxiated, and I suppose there was slight meningeal hemorrhage, and subsequent clotting in the veins or sinuses” (9). The death certificate (Figure 2) signed by John Hewetson, assistant resident physician at The Johns Hopkins Hospital, listed meningeal hemorrhage as the cause and noted that both birth and death had occurred at the Osler residence at One West Franklin Street. The baby was entombed in the Egyptian revival style public mausoleum at Green Mount Cemetery, Baltimore (no doubt with an appropriate plaque) on February 14, 1893 (5). The name is variously misspelled “Oslier” on the interment card and “Oslen” on the death certificate.

In 1929 the original mausoleum (erected in 1840 with an 80-tomb capacity [10]) was replaced for unknown reasons by a new, larger structure on the same site (11, 12), and “the remains of the deceased were placed in single graves throughout the cemetery” (personal communication, Mary Murray, June 26, 2014, Green Mount Cemetery, Baltimore). Green Mount Cemetery unfortunately neglected to make the usual notations on the permit information and is currently unable to locate the burial site. In view of the fact that the family was deceased by that time and unable to provide a headstone, there is the probability that this is an unmarked grave.

Although no correspondence from Grace mentioning her pregnancy can be found, there is no doubt that she was devastated. Although it is not commonly known, this was not her first pregnancy. As late as 1979 a reputable source declared that there were no birth or death records of the earlier event and that the sex and place of burial of the child remained unknown (8). New research reveals that on August 31, 1877 (during her first marriage to Dr. Samuel W. Gross), she delivered a premature stillborn male while visiting her parents (John Revere and Susan Tilden [Torrey] Revere) at 40 Commonwealth Avenue, in the fashionable Back Bay area of Boston (13, 14) (Figures 3 and 4). Grace was then 23, and if it is assumed that conception
Heaven July 14 [1893]

My dear Mother

I for one am good & get on nicely with our singing and if our earthly parents continue to show an interest in us by remembering us in their prayers, we are allowed to write about every three or four tatma’s (i.e. months). I got here safely with very little inconvenience. I scarcely knew anything until I awoke in a lovely, green spot, with fountains & trees & soft couches & such nice young girls to tend us. You would have been amused to see the hundreds which came the same day. But I must tell you first how we are all arranged; it took me several days to find out about it. Heaven is the exact counterpart of earth so far as its dwellers are concerned; thus all from the U.S. go to one place—all from Maryland to one district & even all from the cities & townships get corresponding places. This enables the guardian angels to keep the lists more carefully & it facilitates communication between relatives. They are most particular in this respect and have a beautifully simple arrangement by which the new arrivals can find out at once whether they have connections in heaven. I never was more surprised in my time—we say that here not life & not eternity, for that has not started for us—when the day after my arrival Althea brought me two quill feathers on one of which was written Julius Caesar & the other Emma Osler. I knew at once about the former as I had often heard you and father talk of him and had so longed to wear his little cap; but the latter I did not know at all but she said she had been father’s little sister & she had been sent to make me feel happy and comfortable.

You must know that all the souls coming here are grouped in 6 divisions

(1) Those who have never lived and have not seen the sun. The angels have no end of trouble with them, largely Althea says because they are so stupid and learn so slowly, not having seen the sun-light. They are allowed to grow until equal to the size of the body of a 2 year old child & at which point they stop. They never obtain a full knowledge but always remain childlike. This is their great attraction & in their gardens may be seen hundreds of thousands of middle aged & old soul-bodies refreshing their memories of happy days on earth by playing with these angel children.

2. Those who have not lived a full year are also in a separate division and we are gradually taught and within a very short space of time have beautiful soul-bodies about the size of an earthly child of five. We have however full knowledge and have not many childish ways.

3. Children between 1 & 5 years look here about 10 years in earthly-size; & though they say that their voices are better & their education more perfect than ours we do not think so.

4. From 5 to 15 years the children who come attain in their soul-bodies the earthly size of about 15 and are of great use to the angels in helping with the younger ones & in showing all the beauties of the place and in tuning harps in the great days of the chorus.

5. The grown soul-bodies—about which we do not know very much only seeing those very nearly related to us by earthly ties. We play all day & talk so much with each other about earth and take a great interest in all that you do. We cannot always see you, why I do not know, but at intervals we have such clear and definite sights of our earthly homes. Julius Caesar is very well and a great favorite. He looks a dear little fellow of about two years old (earthly count) and he told me when his guardian angel was not near that he felt a little badly that I should have been in the Amarathyn (18) division—i.e. the one in advance of his. He and Aunt Emma are to come very often and we know now all about our many relatives. Unlike the real angels we have no fore-knowledge and cannot tell what is to happen to our dear ones on Earth. Next to the great feast days, when we sing choruses by divisions in the upper heavens, our chief delight is in watching the soul bodies as they arrive in our divisions. I am helping the angels to get them in order & properly trained. In the children’s divisions not a friad (i.e. about an hour of earthly time) passes without the excitement of a father, a mother, a brother or a sister united to one of us. We know about 1000 of each other so that it is great fun to see our comrades & friends making their relatives feel at home.

The other day my kind Althea said there was a baby-soul in the 1st division from New Hampshire, which had left her kind regards for me at the general intelligence office of the heavenly United States (19). It was chorus day so I could not go, but I am to see her tomorrow if she is advanced enough to receive visitors. It takes about ten days to get our beautiful plumage in order.

If you keep as you are I shall be able (Althea says) to write again in three months. I send you much love—also to pop!

Your loving son
Paul Revere
We use the word ‘pop’ here for papa or father very much

Figure 7. The letter William Osler wrote to his wife, Grace, in the voice of his child, Paul Revere Osler, from heaven.
occurred shortly after marriage (December 19, 1876), she would have been in the eighth month of her pregnancy. The infant was buried in a family lot (Torrey) in the historic Forest Hills Cemetery of Boston (Section 7, Lot 684, Chrysanthemum Path) (Figure 5). The grave bears no memorial stone or marker, which was not uncommon under certain circumstances. While the exact location within the family plot is uncertain, it appears most likely that he (“Baby” Gross) is interred between the graves designated as numbers 4 and 6 (personal communication, Sally Alves, June 20, 2014, Forest Hills Cemetery, Boston) (Figure 6).

After the death of Paul, Osler observed, perhaps in stoic fashion: “One must take the rough with the smooth” (6). However, his true feelings may be ascertained in the letter (with its celestial postmark) signed “Paul Revere” that Grace found on her dressing table (16, 17). Written to comfort Grace and no doubt to give vent to his own feelings, Osler exhibits great sensitivity, humor, and fertile imagination, with references to “Emma,” his little sister who had died long ago in her third year, and to “Julius Caesar,” the stillborn Gross child whose cap (5) Grace had plaintively kept (Figure 7).

In 1896, Grace was again pregnant and Osler wrote that “she expects in January. We hope for better luck” (20). She was 42 years old and he 46; this was perhaps a last-chance baby. On December 28, Edward Revere Osler (“Revere”) was born and brought exquisite joy to his parents. Osler, traumatized by his previous experience, did not allow himself to kiss the baby until the fifth day (21). The story of Revere’s life is not within the scope of this paper, but suffice it to say that throughout his few years, cut short in the charnel house of the Great War, he was surrounded by the endless devotion and affection of his parents. Tragedy enters every life, and the devastating loss of Revere, compounded by their previous experiences, changed their lives forever. Osler poignantly observed: “The Fates do not allow the good fortune that has followed me to go with me to their lives forever. Osler poignantly observed: “The Fates do not allow the good fortune that has followed me to go with me to the grave—call no man happy until he dies” (22).

To reiterate, the final resting places of “Baby’ Gross within Boston’s Forest Hills Cemetery and Paul Revere Osler in Baltimore’s Green Mount Cemetery have not been precisely located. Yet, as Sir Thomas Browne, whom Osler called “his lifelong mentor” (23), observed: “The greater part [of men] must be content . . . to be found in the Register of God, not in the record of man” (24).

Acknowledgments

Thanks to Christopher Lyons, Lily Szczrygiel, and Bozena Latinic of the Osler Library and Joel Nathanblut of the McGill University Library for their valued assistance.

4. Ellen Free Pickton Osler to Charlotte Gwyn, Toronto, January 24, 1893, William Osler Letter Index, Osler Library, McGill University, CUS417/89.5.
10. No photographs of the original mausoleum can be found. It is seen on a striking 1869 “bird’s eye view” perspective map of Baltimore by E. Sachse & Co. as a tiny structure essentially devoid of detail. Library of Congress Geography and Map Division, Washington, DC; available at http://hdl.loc.gov/loc.gmd/g3844b.pm0002540.
13. Registry of “Still-Born Infants in Boston, 1877.”
15. John G. Torrey (1791–1863) and Susan Linzee (Tilden) Torrey (1804–1863) were the maternal grandparents of Grace Linzee Revere Osler.
16. Fictional letter from Heaven; Paul Revere Osler to Grace Osler, July 14, 1893. William Osler Letter Index, Osler Library, McGill University, CUS417/89.25. Minor editing has been performed.
18. Amaranth: This appears to be an Osler neologism possibly related to amaranth or amaranthine, a plant genus or color. The amaranth was a mystical flower that never faded; it was undying or everlasting. He may also be remembering John Milton’s Paradise Lost:

   Immortal amaranth, a flower that once
   In Paradise, fast by the tree of life
   Began to bloom; but soon for man’s offences
   To heaven removed where first it grew, there grows,
   And flowers aloft, shading the fount of life,
   And where the river of bliss through mist of heaven
   Rolls o’er Elysian flowers her amber stream;
   With these that never fade the spirit elect
   Bind their resplendent locks . . . (III, 353)
19. An enigmatic reference to an unidentified female child from New Hampshire, stillborn in 1893. (Grace Osler’s mother had friends, Roland and Edith Baker from New Hampshire [Cushing H. Life II, 159], but no definitive association could be found.)
We present two patients with a high viral load of HIV-1 who developed symptoms of ascending paralysis leading to respiratory failure and autonomic instability. One patient had symptom improvement with highly active antiretroviral therapy (HAART) and a subsequent decrease in viral load. The other patient improved with intravenous immunoglobulin therapy and did not show much improvement on HAART alone. There are several proposed mechanisms for peripheral neuropathies seen in HIV-infected patients, including a direct action of HIV on the nerve by neurotropic strains or formation of autoantibodies against nerve elements. The comparison of the response to different therapies in these two cases highlights the importance of understanding different pathophysiologies, as the treatment modality may differ.

About 34 million people are affected with HIV worldwide as of 2010, including more than 1.1 million in the United States (1). The immune impairment manifests clinically in multiple organ systems including the nervous system. Since the introduction of highly active antiretroviral therapy (HAART), HIV has evolved into a chronic condition with an increase in related complications (2). Neurologic complications occur in more than 40% of patients with HIV infection, and the prevalence of neuropathologic findings at autopsy is about 80% (3, 4). Central and peripheral nervous system involvement in HIV-infected patients occurs due to various causes, including opportunistic infections, immune reconstitution, a side effect of antiretroviral medication, or the effect of the virus (5). The variations might be due to a difference in age, disease stage, treatment history, timing of the study (i.e., pre- or post-HAART era), and the diagnostic criteria used in different studies. We present two cases of ascending paralysis in HIV-positive patients. Not only was the autoimmune nature of Guillain-Barré syndrome (GBS) in the setting of an immunocompromised patient remarkable, but more importantly the improvement seen in both patients required different treatment approaches.

**CASE 1**

A 33-year-old white man presented with a 1-day history of bilateral lower-extremity weakness, numbness, and a tingling sensation that started in his feet and progressed to his knees and very soon involved his fingertips bilaterally. The patient was diagnosed with HIV 1 week earlier during evaluation of a flulike illness including fever, chills, and maculopapular rash with diarrhea. His HIV viral load was 2,095,380 copies/mL, with a CD4 count of 526 cells/μL (Table 1). Baseline genotype testing done at that time showed no drug resistance. His past medical history was unremarkable. Examination disclosed intact cognition, intact cranial nerves, decreased sensation in the lower extremities bilaterally up to the knees, along with decreased sensation on the palmar aspect of the hands bilaterally. Muscle strength was slightly decreased bilaterally in the...
The patient's ascending paralysis worsened over the next 3 days with paresthesias, loss of all deep tendon reflexes, and involvement of cranial nerves. He completed a full course of IVIG of 2 g/kg over 3 days but continued to deteriorate and was started on a five-cycle regimen of plasmapheresis on day 5. Despite aggressive daily plasmapheresis for three cycles, he continued to worsen with autonomic instability, flaccid quadriplegia, and respiratory failure requiring endotracheal intubation and mechanical ventilation 8 days after admission. Four days after intubation, the patient fairly quickly recovered his respiratory muscle strength and was extubated. A repeat HIV viral load test after 1 week of HAART showed only 3590 copies/mL.

A nerve conduction study (NCS) and electromyogram (EMG) performed 15 days after presentation showed evidence of an acquired sensory and motor peripheral neuropathy with mixed axonal and demyelinating features. There was also diffuse early denervation indicating secondary axonal loss. The relative paucity of denervation seen on the EMG/NCS exam likely reflected the short time lapse since the onset of symptoms.

The patient continued to gradually regain his muscular function and was transferred to a skilled nursing facility for continuing physical therapy. After a 4-week stay at the facility, his muscle strength was close to baseline, and he was discharged home.

### CASE 2

A 37-year-old white man with a history of HIV/AIDS with a last CD4 count of 22 cells/μL (Table 1) presented to the emergency department with 4 weeks of progressively worsening ascending weakness, tingling, and numbness of his lower extremities, with gradual involvement of his upper extremities. He had a history of recurrent lower-extremity weakness and decreased sensation that had required previous hospitalizations. His past medical history was significant for anemia, several episodes of gastritis, asthma, past hepatitis B infection, and anxiety. His family history was not significant for any neurological diseases. Examination disclosed a cognitively intact man with intact cranial nerves. There was a lack of sensation to light touch in the feet and numbness in the hand bilaterally. Grip strength was weak in both hands with trace finger abduction. Elbow flexion and extension was 3/5 and shoulder flexion was 2/5. Reflexes were absent in both upper and lower extremities. MRI scans of the brain and spine were unremarkable. CSF evaluation revealed classic albuminocytologic dissociation without any signs of active infection (Table 2).

NCS and EMG tests 20 days after hospitalization showed diffuse sensory motor polyneuropathy with both demyelinating and axonal features. The patient was started on HAART with Stribild (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate) and given 2 days of IVIG. Soon after starting IVIG, the patient showed clinical improvement. He was transferred for rehabilitation after a 1-week hospital stay for aggressive physical therapy. Since his initial presentation about a year ago, he has been rehospitalized twice with similar symptoms despite being on continual HAART, during which his viral load has been very low (varying from <20 copies/mL up to 1510 copies/mL). His symptoms continue to respond to treatment with IVIG. Repeated CSF evaluations reveal cytologic dissociation at varying degrees (white cells range from 2 to 8 /μL, and protein ranges from 114 to 331 mg/dL). Although the patient started out with AIDP with axonal features, he now carries the diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP).

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**Table 2. Initial cerebrospinal fluid data**

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein (mg/dL)</td>
<td>109</td>
<td>331</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>52</td>
<td>54</td>
</tr>
<tr>
<td>White blood cells (cells/μL)</td>
<td>35 (89%)</td>
<td>8 (52%)</td>
</tr>
<tr>
<td>Red blood cells (cells/μL)</td>
<td>N/A</td>
<td>4000</td>
</tr>
<tr>
<td>Gram stain</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>IgG synthesis</td>
<td>Elevated</td>
<td>N/A</td>
</tr>
<tr>
<td>Oligoclonal bands</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>Negative</td>
<td>N/A</td>
</tr>
<tr>
<td>Epstein-Barr virus IgM</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Varicella zoster virus PCR</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Herpes simplex virus PCR</td>
<td>N/A</td>
<td>Negative</td>
</tr>
<tr>
<td>Cocksackie A/B PCR</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Cytomegalovirus PCR</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Cryptococcal antigen</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>West Nile antibody</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Cytology</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Venereal Disease Research Laboratory</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Bacterial culture</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>HIV PCR (copies/mL)</td>
<td>N/A</td>
<td>2142</td>
</tr>
<tr>
<td>Mycoplasma IgG</td>
<td>1:4</td>
<td>N/A</td>
</tr>
<tr>
<td>Mycoplasma IgM</td>
<td>Negative</td>
<td>N/A</td>
</tr>
</tbody>
</table>

PCR indicates polymerase chain reaction; Ig, immunoglobulin.
DISCUSSION

These two cases of HIV illustrate very similar clinical presentations with very different pathophysiologies and long-term outcomes. The CSF and HIV status findings dictated very different treatment regimens. In case 1, the patient had aseptic meningitis with multiple possible etiologies (HIV, mycoplasma, seroconversion) and improved only after his HIV RNA titers came down in a monophasic pattern of illness. In the second case, the patient did not have meningitis but rather had what is now known to be CIDP with recurrent symptoms responding very well to IVIG.

HIV can be neuroinvasive, neurotropic, and neuroviral. Many peripheral neuropathic syndromes have been reported in the context of HIV infection, including HIV-associated distal sensory neuropathy, neurotropic nucleoside neuropathy, and inflammatory demyelinating neuropathy. HIV-associated distal sensory polyneuropathy (also called predominantly sensory neuropathy, or distal symmetrical peripheral neuropathy) is the most common neurological problem in AIDS, with variable incidences in different reports ranging from 19% to 66% (6, 7). The risk factors for HIV-associated distal sensory polyneuropathy are older age, history of alcohol abuse, advanced HIV disease, prior use of a neurotropic antiretroviral drug, and diabetes mellitus (8, 9). Inflammatory demyelinating neuropathy, on the other hand, is less common and can occur at various stages of the disease, requiring different therapeutic approaches.

Both patients presented with an ascending paralysis typically described with clinical GBS. GBS generally follows an infectious prodrome, resulting in an augmented immune response, which cross-reacts with axolemmal or Schwann cell antigens, leading to peripheral nerve damage believed to be due to molecular mimicry. The clinical features of GBS are progressive, ascending, fairly symmetric muscle weakness, typically with absent reflexes. The severity of symptoms can vary from mild to profound weakness of all extremities and involving respiratory muscles, resulting in respiratory failure requiring intubation. Respiratory failure requiring ventilator support occurs in 10% to 30% of the cases (10). Symptoms can also include tachycardia, urinary retention, labile blood pressure, arrhythmias, and paresthesias more commonly seen on fingertips and feet and can include autonomic instability in severe cases. The hallmark laboratory finding is albuminocytologic dissociation on the CSF with a near normal white blood cell count seen in up to 66% of patients (11). Treatment for GBS typically involves IVIG or plasmapheresis, which have been shown to have similar outcomes. In our first case, intrathecal IgG synthesis was dramatically elevated, suggesting an ongoing immune-mediated process, which did not improve until his viral load came down. Notably, he recovered very rapidly (walking within a week after tetraplegia). This was much faster than could be expected in typical GBS patients who have significant changes, both demyelinating and axonal, on NCS/EMG.

GBS in an HIV/AIDS patient was first described in 1985 (12). GBS may occur in HIV-infected patients at the time of seroconversion, even with normal CD4 counts, and can be the presenting symptom or seen in the setting of the immune reconstitution syndrome (13–16). Nucleoside analogue reverse transcriptase inhibitors (NRTIs), a backbone component of HAART, have also been related to GBS in HIV-infected individuals in association with the immune reconstitution syndrome. Twenty-two cases of GBS associated with stavudine (NRTI) therapy have been reported (17–19).

Several mechanisms have been proposed regarding GBS in HIV-infected patients. Proposed mechanisms include a direct action of HIV on the nerve by neurotropic strains or formation of autoantibodies against myelin secondary to the abnormal immunoregulation caused by the HIV infection (20). In the setting of immune reconstitution syndrome, there is a reemergence of previously anergic lymphocytes upon viral suppression with HAART (13–16). Cell-mediated immunity is known to play a major role in the pathogenesis of GBS. The clinical features of GBS in HIV-infected patients are similar to those in HIV-negative people. However, HIV GBS may be associated with more frequent recurrent episodes and progression to CIDP (21).

In our first case, the onset of rapidly progressive ascending paralysis coincided with the acute retroviral syndrome of HIV. This patient continued to worsen despite IVIG therapy and plasma exchange and only improved with the initiation of HAART and reduction in the viral load. We have not found any previous reports specifically addressing the efficacy of either IVIG or plasmapheresis in the setting of acute retroviral syndrome, but previously reported cases and our first case suggest that antiretroviral treatment is preferable especially if CSF findings show the presence of meningeal inflammation. In our second case, the patient with chronic HIV infection had clinical symptoms consistent with AIDP and ultimately CIDP with modest recovery only seen with IVIG. IVIG has been shown to speed the course of recovery in patients with GBS and HIV seropositivity. Reports of efficacy range from ineffective or mild benefit to a great response (22). In the first case, mycoplasma tested positive and in the second case cytomegalovirus was positive. Both cytomegalovirus and mycoplasma have been implicated in ascending paralysis. It is fairly common to have several potential causes for similar presentations in HIV patients with neurological complications, which exemplifies the complexity of HIV patients.


Hypothermia is a multifactorial process that results from decreased heat production or increased heat loss, with the former due to, but not limited to, endocrine dysfunction, malnutrition, and central nervous system pathologies. We report an HIV-1 patient with transient hypothermia secondary to severe protein calorie malnutrition and elevated HIV viral load. In this patient, it is hypothesized that the etiology of the hypothermia was multifactorial due to severe protein calorie malnutrition, evidenced by decreased insulin-like growth factor-1 levels, severe hypothyroidism, and an elevated HIV viral load, since the patient began to improve with the initiation of highly active antiretroviral therapy, improved nutrition, and continuation of thyroid supplementation.

CASE PRESENTATION

A 49-year-old African American man with prior chronic kidney disease, systemic hypertension, heart failure, HIV-1, and hepatitis C was admitted for respiratory distress secondary to pharyngeal and mediastinal abscesses. The patient had an initial CD4 count of 265 and an HIV viral load of 4.9 million copies. The CD4 count soon decreased to 125 with the viral load increasing to 9 million over a 1-month duration. The patient was started on atovaquone for *Pneumocystis jirovecii* prophylaxis.

During his hospital course, the patient became hypothermic with rectal temperatures of 91°F to 93°F. On examination, he was cachectic with coarse rhonchi diffusely over the lungs. Thyroid-stimulating hormone was elevated with nondetectable free T3 levels. Intravenous levothyroxine was initiated. A cosynotropin stimulation test, T4, reverse T3 levels, prolactin, thyroid antibodies, and transglutaminase IgA and IgG levels were all within normal limits. Insulin-like growth factor-1 (IGF-1) levels were significantly decreased. A purified protein derivative test was negative, and immunologic studies were positive for cytomegalovirus IgG indicating past infection.

The white blood cell count was $2.5 \times 10^9/L$, hemoglobin was 7.2 mg/dL, and platelet count was $60 \times 10^9/L$. The prealbumin level was decreased at 11 mg/dL. Magnetic resonance imaging without contrast showed mild chronic small vessel ischemic disease in the periventricular and subcortical white matter. A few days after starting highly active antiretroviral therapy (HAART), the patient’s rectal temperature began to improve to his baseline of 95°F to 97°F with intermittent use of an external body warmer. The patient’s nutritional status also improved with the initiation of percutaneous endoscopic gastrostomy tube feedings.

DISCUSSION

There are few published reports on hypothermia in HIV patients. Several hypotheses have centered on the dysfunction of the hypothalamic-pituitary-thyroid axis since the hypothalamus is the basal metabolic center of the body. Several have suggested that this phenomenon may be due to HIV-induced neurodegenerative processes of thermoregulatory centers of the brain. In 2003, a case was reported of an HIV patient with episodic hyperhidrosis-hypothermia and HIV-induced CNS damage consisting of brain atrophy and myelopathy (1). Anderson et al suggested that HIV viral load and the infection itself acted as a “catalyst” that increased the production of neurotoxins that impaired synaptic transmission of neurotransmitters such as neuropeptide Y and glutamate (2). An animal study in 2007 by Huitron-Resendiz et al hypothesized that HIV caused a circadian impairment leading to disruptions in several functions such as body temperature and other basal metabolic activities (3). Our patient only exhibited hypothermia, which can be multifactorial in the HIV population. It is important to evaluate other coinfections such as cytomegalovirus (4) and fungemia. Nutritional status, endocrine abnormalities such as decreased IGF-1 levels (5), and CNS pathologies such as spinal cord and hypothalamic lesions can also contribute.
In this patient, it is hypothesized that the etiology of the hypothermia was multifactorial due to severe protein calorie malnutrition, evidenced by the decreased IGF-1 levels, severe hypothyroidism, and an elevated HIV viral load since the patient began to improve with the initiation of HAART, improved nutrition, and continuation of thyroid supplementation.

The presence of an anion gap in a diabetic patient, especially if associated with evidence of compromised renal function, should prompt clinicians to consider metformin as a contributing factor. This consideration is especially important in patients with severe anion gaps associated with lactic acidosis out of proportion to the patient’s clinical presentation.

Measurement of serum electrolytes and determination of acid-base status is beyond routine in today’s clinical practice. The importance of recognizing and treating disturbances in normal physiology cannot be overstated, as this information can provide clues to the existence of many reversible, yet if left untreated fatal, disease processes. The most commonly used scenario for calculating the serum anion gap (AG) is determining the etiology of metabolic acidosis (Table 1). Disturbances of the AG can be seen in a variety of conditions, and if accurately recognized can yield critical diagnostic information. Presented is a case of compound AG acidosis.

**CASE PRESENTATION**

A 71-year-old woman with type 2 diabetes mellitus, hypertension, and coronary artery disease presented to the emergency department because of altered mental status. She had been seen in an emergency department 9 days earlier for nausea, emesis, diarrhea, and abdominal pain when her creatinine was 1.8 mg/dL and AG was 20 mEq/L. She was discharged home with antiemetics. Her symptoms persisted and she returned via paramedic transport. She was intubated shortly upon arrival secondary to a decreased level of consciousness and concern for airway protection. Her family denied knowledge of hematemesis, melena, fevers, or chills. Her home medications included potassium 20 mEq daily, Lasix 80 mg twice a day, metformin 850 mg twice a day, Novolin R sliding scale, and metoprolol tartrate 100 mg daily.

On examination, her blood pressure was 100/54 mm Hg; heart rate, 123 beats per minute; respiratory rate, 22 breaths per minute; and temperature, 97.9°F. She was intubated and sedated. She was tachycardic without precordial murmurs and tachypneic on the ventilator with coarse breath sounds bilaterally. Her abdomen was soft with hypoactive bowel sounds and without masses. She had palpable pulses that were equal bilaterally. Key laboratory data are outlined in Table 2. A trans-thoracic echocardiogram showed an ejection fraction of 75%, a dilated pulmonary artery, and a suggestion of moderate pulmonary hypertension with a right ventricular systolic pressure of 44.4 mm Hg.

The patient was admitted to the intensive care unit for refractory shock, acute respiratory failure, oliguric acute kidney injury, severe AG metabolic acidosis, and presumed Metformin-induced lactic acidosis with emphasis on the anion gap

**Britton Blough, MD, Amber Moreland, MD, and Adan Mora Jr., MD**

**Table 1. Causes of increased anion gap metabolic acidosis**

<table>
<thead>
<tr>
<th>Acidosis Type</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-lactic acidosis</td>
<td>Propylene glycol</td>
</tr>
<tr>
<td>D-lactic acidosis</td>
<td>Aspirin overdose</td>
</tr>
<tr>
<td>Ketoadidosis</td>
<td>Toluene</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Pyroglutamic acid</td>
</tr>
<tr>
<td>Methanol</td>
<td>Ethylene glycol</td>
</tr>
</tbody>
</table>

**Table 2. Principal laboratory findings**

<table>
<thead>
<tr>
<th>Test Result</th>
<th>Test Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mEq/L)</td>
<td>142</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>3.6</td>
</tr>
<tr>
<td>Chloride (mEq/L)</td>
<td>87</td>
</tr>
<tr>
<td>CO₂ (mEq/L)</td>
<td>8</td>
</tr>
<tr>
<td>BUN (mg/L)</td>
<td>53</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>3.0</td>
</tr>
<tr>
<td>Anion gap (mEq/L)</td>
<td>47</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.7</td>
</tr>
</tbody>
</table>

**Hematology**

<table>
<thead>
<tr>
<th>Test Result</th>
<th>Test Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (K/uL)</td>
<td>8.1</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>11.3</td>
</tr>
<tr>
<td>Arterial blood gas</td>
<td>pCO₂ (mm Hg)</td>
</tr>
<tr>
<td>pH</td>
<td>6.85</td>
</tr>
<tr>
<td>pCO₂ (mm Hg)</td>
<td>30.5</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>3.4</td>
</tr>
<tr>
<td>Lipase (U/L)</td>
<td>3211</td>
</tr>
</tbody>
</table>

BUN indicates blood urea nitrogen; CO₂, carbon dioxide; pCO₂, partial pressure of carbon dioxide; pO₂, partial pressure of oxygen; WBC, white blood cells.

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pancreatitis. Her blood was cultured, and she was started on empiric antibiotics. After fluid resuscitation, her mean arterial pressure remained low, requiring norepinephrine and stress dose steroids. Her severe lactic acidosis was refractory to a bicarbonate drip. She required an elevated compensatory high minute ventilation and eventually continuous veno-venous hemodialysis. While her lactic acidosis slowly down-trended, it remained abnormally high relative to the degree of her hypoperfused state. A metformin level ordered on admission returned as 2.7 mcg/mL. The usual therapeutic metformin blood level is in the range of 0.5 to 2.5 mcg/mL (1).

The patient became progressively hypotensive despite aggressive measures. No source of infection could ever be identified and all cultures remained negative. A mesenteric Doppler was unable to visualize vascular structures due to body habitus, and a contrast study could not be performed due to the patient’s severe iodine allergy. Her respiratory status deteriorated with decreasing lung compliance. On day 6 of her hospitalization, she remained unstable and a decision was made by the family to withdraw life-sustaining therapy. The family declined a postmortem examination.

**DISCUSSION**

In their article initially describing the clinical implications of the AG, Emmett and Narins defined the AG and detailed its utility in evaluating a patient’s acid-base status (2). The serum AG is calculated from the laboratory measurement of electrolytes and provides important information regarding a patient’s acid-base status. By definition, the AG is the difference between the measured serum cations and anions: \((\text{Na}^+ + \text{K}^+) - (\text{Cl}^- + \text{HCO}_3^-)\).

Since the influence of potassium in regards to the AG is minimal, the equation is accepted as simply the following: \((\text{Na}^+) - (\text{Cl}^- + \text{HCO}_3^-)\).

In the hospitalized patient, one of the most common causes of metabolic acidosis is lactic acidosis, which produces an unmeasured anion resulting in an elevated AG. Lactate is formed during gluconeogenesis as a product of pyruvate metabolism. This formation requires the presence of the catalytic enzyme lactate dehydrogenase to convert nicotinamide adenine dinucleotide hydrate into nicotinamide adenine dinucleotide. Lactic acid in the serum is buffered by bicarbonate to lactate, which in turn is converted back to pyruvate in the liver and kidney. An increase in lactic acid can thus be thought of as either an overproduction of lactate in the serum or an underutilization of lactate by the liver. The former most commonly results from an inhibition of oxidative metabolism that decreases the available ATP and shunts the reaction to formation of additional lactate. The types of lactic acidosis can further be broken down into types A and B (Table 3). In general, type A can be attributed to tissue hypoxia or global hypoperfusion, as seen in circulatory collapse or in the setting of increased anaerobic activity (3). Type B lactic acidosis occurs in the absence of tissue hypoperfusion and comprises a heterogeneous group of etiologies, including intoxications, liver failure, malignancy, rare hereditary enzyme deficiencies, and certain medications, as seen in our patient (4).

<table>
<thead>
<tr>
<th>Type</th>
<th>Etiology</th>
</tr>
</thead>
</table>
| A    | Shock (septic, cardiogenic, hypovolemic)  
      | Hypoxemia  
      | Severe anemia  
      | Carbon monoxide |
| B    | Mitochondrial defects  
      | Cyanide toxicity  
      | Beriberi (thiamine deficiency)  
      | Drugs (metformin, salicylates, nucleoside reverse transcriptase inhibitors)  
      | Liver failure  
      | Ethanol intoxication |

Metformin-associated lactic acidosis can occur acutely in an overdose but typically has a more gradual onset in patients with hepatic or renal dysfunction due to decreased excretion. It often presents with nausea, abdominal pain, tachycardia, hypotension, and tachypnea (5). The lactic acidosis from metformin is primarily type B. In an overdose, the lactic acidosis can be compounded by type A when the drug’s lactic acid accumulation leads to cardiovascular collapse, tissue hypoperfusion, and hepatic dysfunction.

In 1918, guanidine, the active ingredient of the plant *Galega officinalis*, demonstrated hypoglycemic effects in animals and led to the development of the class of drugs known as biguanides. These drugs act to reduce blood glucose levels and insulin concentrations by suppressing basal hepatic gluconeogenesis and improving peripheral tissue insulin sensitivity; however, their association with the development of lactic acidosis has been well reported (5). The biguanides contain two guanide molecules linked together with an elimination of an amino group. In the 1920s, several synthetic biguanides were used clinically, but their toxicities limited their use (6, 7). Metformin, currently the only biguanide available in the United States, is less associated with lactic acidosis and was not approved until 1995 by the US Food and Drug Administration (8). Several other more potent biguanides were also developed, including phenformin and buformin, but these were discontinued in many countries by the late 1970s secondary to the development of lactic acidosis (6, 7).

Metformin lowers blood glucose in multiple ways, including suppression of hepatic gluconeogenesis, increased peripheral insulin-mediated glucose uptake, decreased fatty acid oxidation, and increased intestinal glucose consumption (7). Metformin reaches maximal plasma concentration approximately 2 hours after ingestion, and its half-life ranges from 2.5 to 4.9 hours. Approximately 90% of it is eliminated in the urine in 12 hours (7). The most common side effects of metformin use are gastrointestinal, including diarrhea, nausea, vomiting, abdominal bloating, and anorexia. These side effects may occur in 20% to 30% of patients receiving this drug, usually at the onset of therapy, but rarely persist (9). Current contraindications for metformin use include chronic kidney disease (creatinine levels >1.5 mg/dL.)
in men and >1.4 mg/dL in women), liver disease, heart failure, age >65, pulmonary disease, use of intravenous contrast agents within 48 hours, or any condition with relative tissue hypoxia (9).

Lactic acidosis is a rare but serious side effect of metformin use. The estimated incidence is 6 cases per 100,000 patient-years (9). The presence of metformin-associated hyperlactatemia in critical care patients has been associated with a mortality >30% (10).

Metformin inhibits mitochondrial cellular respiration, which increases anaerobic metabolism and lactate levels (3). This effect is most profound in the gut due to its affinity for intracellular proteins in the gastrointestinal tract (11). The pathophysiology of lactic acidosis from metformin is likely due to inhibition of gluconeogenesis by blocking pyruvate carboxylase, the first step of gluconeogenesis, which converts pyruvate to oxaloacetate. Blocking this enzyme leads to accumulation of lactic acid. Biguanides also decrease hepatic metabolism of lactate and have a negative ionotropic effect on the heart, both of which elevate lactate levels (11). Metformin dose, along with the duration of exposure from accumulation in patients with decreased renal clearance, can cause lactic acidosis (3). Gradual toxicity, as demonstrated in our patient, is usually multifactorial and related to the drug’s decreased renal excretion. The lipophilic nature of the drug allows for its accumulation, causing a severe lactic acidosis but only minimally elevated serum drug levels (12). As previously mentioned, while there is an accepted therapeutic range of metformin, the amount of drug required to cause toxicity is unclear (3). A study by Lalau et al demonstrated that the lactic acidosis seen is not necessarily due exclusively to metformin accumulation (13). This leads to the conclusion that a mixed type of lactic acidosis (A and B) is seen in most cases, and it is the severity of the underlying disease process that determines the overall prognosis (14).

Hemodialysis continues to be the definitive treatment for metformin accumulation leading to toxicity, as 90% of the drug is eliminated via the kidneys. A report by Pearlman et al demonstrated through serial measurements of metformin levels during hemodialysis that the drug can be dialyzed; however, there can be a rebound phenomenon due to its lipophilic properties and increased tissue binding (15). Despite metformin having minimal protein binding, hemodialysis does not remove large amounts of the drug due to its large volume of distribution. However, hemodialysis does improve acid-base status and clinical outcomes in patients with severe lactic acidosis due to metformin.

Our patient did not have extremely high plasma concentrations of metformin in the setting of profound shock. This leads us to the conclusion that she likely had a slow accumulation over a period of days and likely stopped taking the medication at some point prior to her arrival due to her illness. Her severe lactic acidosis was likely of a mixed type from the combination of tissue hypoxia as well as metformin toxicity, both of which contributed to her overall mortality. Although metformin does cause a lactic acidosis, this by itself is not an independent predictor of mortality in these patients.

Gastrostomy tubes are frequently used to provide enteral access in a variety of patient populations. Long-term complications are usually minor and include ulceration of the surrounding skin, clogging or dislodgment of the feeding tube, and superficial abscess; severe long-term complications are rare. Here we report a case of a life-threatening complication from an indwelling gastrostomy tube, specifically retrograde jejunoduodenogastric intussusception. Computed tomography and intraoperative images, as well as a review of literature, provide a detailed picture for diagnosis and treatment. Although feeding tubes are now routine and associated with low morbidity, physicians should remain aware of this potentially lethal complication in order to minimize the increased morbidity and mortality from intussusception and subsequent bowel ischemia.

**CASE DISCUSSION**

A 61-year-old white woman with a medical history of severe mental retardation, epilepsy, and cerebral palsy presented with 24 hours of hematemesis. She had a gastrostomy tube that was placed a number of years earlier for feeding purposes. The patient appeared agitated on exam but was nonverbal secondary to cerebral palsy. Her abdominal exam revealed upper abdominal discomfort with distention but no evidence of peritonitis, rebound tenderness, or guarding. Her serum lipase was 9648 units/L; total bilirubin, 2.3 mg/dL; alkaline phosphatase, 440 units/L; aspartate transaminase, 686 units/L; and alanine transaminase, 589 units/L. Her white blood cell count was elevated at 15.3 x 10⁹/L.

A computed tomography (CT) scan of the abdomen and pelvis (Figures 1 and 2) demonstrated intra- and extrahepatic biliary dilatation secondary to an obstructive process and duodenal and gastric wall thickening with pneumatoasis involving the stomach and most of the duodenum. The patient was taken emergently to the operating room for upper endoscopy and exploratory celiotomy. The anesthesia team performed rapid sequence intubation.

Esophagogastroduodenoscopy was performed first to evaluate the gastric mucosa and the gastric mass. The gastric mucosa in the fundus appeared normal, but there was a large necrotic-appearing mass in the body of the stomach that extended down through the pylorus. The esophagogastroduodenoscopy scope could not be advanced through the pylorus. A celiotomy was performed. After an upper midline incision was made, initial inspection revealed that the entire anterior stomach was viable. She had a dense mass in the stomach that extended down into the duodenum. The stomach was mobilized along the greater curvature until the entire posterior wall was visualized, which also appeared normal. There was no evidence of gastric ischemia.

The exploration continued with a Kocher maneuver, and the duodenal wall was ischemic and thickened. The transverse colon was lifted superiorly to examine the ligament of Treitz, and this maneuver revealed that the proximal jejunum had intussuscepted into the duodenum and stomach (Figure 3). Approximately 2 ft of jejunum was “milked out” of the duodenum and stomach. Evaluation of this intussuscepted segment of bowel revealed diffuse ischemia with patchy areas of full-thickness necrosis (Figure 4). The balloon for the gastrostomy tube had migrated from the stomach through the duodenum.
and into the proximal jejunum. At this point, the stomach and duodenum both appeared healthy, and repeat upper endoscopy was performed to confirm that there was no mucosal necrosis. Approximately 2 ft of jejunum was resected. A bowel anastomosis was not performed and the patient was transferred to the surgical intensive care unit with an open abdomen for further resuscitation.

The patient returned to the operating room 24 hours later for reevaluation of the bowel. A short segment of the proximal jejunum was resected for persistent ischemia, after which a duodenjejunalostomy hand-sewn anastomosis was performed to the fourth portion of the duodenum. The mesenteric defects were reapproximated. A feeding jejunostomy and gastrostomy were placed. The abdomen was closed, and the patient was returned to the surgical intensive care unit for further care. The patient was initiated on enteral nutrition per the feeding jejunostomy, and the remainder of the postoperative course was uncomplicated. The pathology of the resected jejunum did not reveal any further causes of intussusception such as webs, strictures, tumors, or polyps.

DISCUSSION

The unique case presented in this report describes an adult patient with a retrograde jejunojejunostomy intussusception secondary to a gastrostomy feeding tube. Intussusception commonly presents in the pediatric population but is rare in an adult population as a complication of a long-term indwelling gastrostomy tube.
adult and can involve any part of the bowel from the stomach to the rectum (4). Most adult cases of intussusception have an underlying pathologic etiology, with only 8% to 20% being idiopathic (primary). It is imperative to identify the etiology (5). There are only a few documented cases of retrograde jejunal intussusceptions caused by feeding tubes. A Medline literature search provided only four other documented cases in adults that were attributed to a gastric feeding tube (6–9).

Our patient suffered a potentially lethal injury followed by multiple abdominal surgeries due to a preventable complication involving a gastric feeding tube. The balloon migrated through the antrum of the stomach, past the pylorus and into the small intestine. Once in the small intestine, the balloon served as the lead point with peristalsis generating the intussusception. This intussusception continued until ischemia, obstruction, and pain prompted the patient’s caregivers to seek further medical evaluation.

Gastrostomy tubes can be over 30 cm in length and are typically secured at 2 to 4 cm from the balloon or flange to the skin, depending on the thickness of the subcutaneous tissues. During placement, not only should the positioning disc be secured to the skin, but it is of utmost importance that the tube be secured to the positioning disc. If the gastrostomy tube is not anchored appropriately, there is risk of migration and, as our case report exemplifies, intussusception and necrosis of the small bowel. Conversely, constant tension placed on the gastrostomy tube can cause erosion of the tube through the stomach, muscle, or abdominal wall.

If balloon migration is discovered, an attempt at repositioning the gastrostomy tube should be made by first deflating the balloon and then, with gentle traction, pulling the tube and the balloon into the stomach. The balloon should only be inflated once in the gastric lumen and then secured against the abdominal wall at the originally dictated distance. Aspiration of gastric contents or injection of radiographic contrast with subsequent radiologic imaging can verify appropriate gastric placement.

If the patient remains symptomatic, further workup may be required, such as CT imaging, upper endoscopy, or radiologic contrast studies. Our patient presented with hematemesis and pancreatitis, but was able to continue to tolerate feeds since the balloon was distal to the obstruction. Typical signs of intussusception include nausea, vomiting, abdominal pain, a palpable abdominal lump, melena, hematemesis, weight loss, fever, feeding intolerance or high residual, and constipation (4, 10). In this particular case, the CT scan suggested gastric necrosis due to pneumatosis of the stomach wall and concern for a duodenal internal hernia. Other case reports have documented CT findings such as foreshortening and narrowing of the gastric antrum, converging or telescoping of mucosal folds in the antrum or duodenum, prepyloric outpouchings, widening of the pylorus and duodenum, or an intragastric filling defect (4, 10). Upper endoscopy is imperative to assist with the diagnosis of gastrojejunal intussusception, evaluate ischemia, and provide a complete evaluation of the upper GI tract to ensure that a
more common source such as a tumor is not the lead point. If a short-segment intussusception is demonstrated on endoscopy, reduction can be attempted, but if reduction is unsuccessful or the intussusception comprises a large segment, as seen in this case, exploratory surgery should be performed. If there is any uncertainty concerning the accuracy of the reduction, it is our recommendation that exploratory surgery be performed.

In the operating room, specific steps should be performed to assist with the reduction of the intussusception. First and foremost, jejunoduodenogastric intussusception is a surgical emergency, and operative intervention should not be delayed. Celiotomy is performed to allow gentle manual exploration and reduction. The lesser sac should be entered to facilitate complete mobilization of the stomach. A Kocher maneuver will enable extensive exposure and evaluation of the duodenum. Once these two areas are fully inspected, the intussusception can be reduced by gentle proximal, sequential, and circumferential pressure, coercing the intussuscepted segment out of the stomach. No attempt should be made to pull the intussuscepted bowel distally, as this often results in transmural tears and perforation. The viability of the intussuscepted segment can then be evaluated with subsequent resection of the necrotic areas. Further resuscitation in the intensive care unit will allow the bowel time to fully demarcate by the “second-look” celiotomy 24 to 36 hours later.

Another option would be to use indocyanine green (ICG) fluorescence imaging to assess the remaining bowel’s viability intraoperatively. ICG fluorescence can be given as an intravenous bolus, and the tissue or intestine can be assessed with the SPY Intraoperative Perfusion Assessment System (distributed in North America by LifeCell Corp., Branchburg, NJ; manufactured by Novadaq Technologies Inc., Richmond, British Columbia, Canada). This system provides real-time assessment of tissue viability as verified in ophthalmology, plastic surgery flaps, and transplant surgery. However, this technology may not be available at all institutions (11). A feeding jejunostomy can be placed prior to abdominal closure and feeds initiated distal to the anastomosis.

Although feeding tubes are routine, serious complications can occur, and the importance of proper tube care by the staff should be emphasized throughout the life of the patient and the gastric tube. Awareness of these complications and the appearance on radiologic imaging is necessary to facilitate early treatment and correction.

Diagnosing placenta percreta can be difficult. We describe a 41-year-old woman presenting at 21 weeks’ gestation with intraabdominal bleeding and no signs of placental abnormality on ultrasound. The disagreement between results of the ultrasound and magnetic resonance imaging made definitive diagnosis difficult. The bleeding resolved spontaneously after a blood transfusion, and the patient was hospitalized for the remainder of the pregnancy. Delivery was by scheduled repeat cesarean at 34 weeks’ gestation. Spontaneous rupture of the entire fundus occurred at the time of delivery. Placenta percreta was confirmed by histologic examination of the operatively excised uterus.

Placenta percreta is becoming more common as cesarean section and other uterine surgeries increase. Clinical diagnosis can be difficult. Both ultrasound and magnetic resonance imaging (MRI) may have misleading results. This case demonstrates how an unusual presentation can be well managed with multidisciplinary cooperation between obstetricians, perinatologists, and radiologists.

CASE DESCRIPTION

A 41-year-old G3P1011 African American woman at 20 weeks 6/7 days’ gestation presented to labor and delivery triage with the acute onset of abdominal pain beginning approximately 17 hours prior to presentation. The pain had progressively increased in intensity. Her past medical history included hypothyroidism and Asherman’s syndrome. Previous surgical history included one low transverse cesarean section and operative hysteroscopic lysis of adhesions complicated by uterine perforation.

On admission, the patient’s blood pressure was 101/55 mm Hg and her heart rate was 88 beats per minute. Abdominal exam revealed diffuse tenderness with rebound. During the first 24 hours after admission, her heart rate increased to 112 beats per minute, blood pressure fell to 95/50 mm Hg, and blood hematocrit fell from 33.4% to 22.5%. After receiving 2 units of packed red blood cells, her hematocrit rose to 29%. A dedicated obstetric sonogram showed a posterior fundal placenta and a normal uteroplacental interface with normal color Doppler images, without any evidence of abnormal placentation. MRI revealed deep invasion of placental tissue at the fundal area of the uterus (Figure 1). Complex free fluid compatible with hemoperitoneum also was visualized in the pelvis and right upper quadrant.

The patient was transferred to the antepartum unit where she and her fetus remained on inpatient bedrest. Antenatal corticosteroids were administered at 29 weeks’ gestation for fetal lung maturation after increased abdominal pain and uterine contractions. She had no further intraabdominal bleeding episodes, and blood counts remained stable.

A scheduled cesarean section was performed at 34 weeks 2 days’ gestation with delivery of a liveborn female infant weighing 4 pounds 13 ounces with an APGAR score of 9 and 9 at 1 and 5 minutes, respectively. Examination of the uterus in situ disclosed a 2 cm defect in the uterine serosa in the posterior fundal location with palpable placenta. There was minimal bleeding from the area and no invasion of surrounding organs. After exteriorization of the uterus, the thin serosal layer covering the remainder of the placenta splayed open (Figure 2). Excessive bleeding from the placental bed was then encountered, and a supracervical hysterectomy was performed. The patient’s total estimated blood loss from the procedure was 2 L; she was appropriately volume resuscitated with intravenous fluids and blood products intraoperatively. She had an uncomplicated postoperative course and was discharged home in stable condition on postoperative day 4. Her infant was discharged on day 7 of life in good condition. Histologic examination confirmed the clinical diagnosis of placenta percreta with placental tissue deeply invading the myometrium to the uterine serosal surface associated with hemorrhage and fibrin deposition.

DISCUSSION

Placenta percreta is characterized by the invasion of the chorionic villi through the myometrial and serosal layer of the uterus, typically in the absence of normal decidualized endometrial stroma. This absence of the decidua basalis leads to a clinically adherent placenta. Uterine instrumentation, previous cesarean section, and other procedures causing myometrial...
Placenta percreta is one of the most devastating obstetric diseases associated with abnormal placentation. Complications associated with the condition include uterine rupture, massive blood transfusion, ureteral ligation or fistula formation, infection, perinatal death, and maternal death (4). There is no recommended management strategy for intraabdominal bleeding due to placenta percreta diagnosed in the previable period in a stable patient. Possible options include hysterectomy with or without embolization of uterine or internal iliac arteries to prevent a potential life-threatening hemorrhage without consideration of fetus or uterus; embolization and hysterotomy with removal of fetus and placenta in hopes of preserving the uterus; feticide combined with methotrexate possibly resulting in a spontaneous vaginal abortion or, if needed, vaginal or abdominal removal; and an expectant management approach within a clinical setting with all precautions of adequate intervention available in case of recurrent bleeding (5). With expectant management, the timing of delivery for placenta percreta needs to be individualized to optimize both maternal and fetal outcomes. A recent decision analysis states that in a stable patient, planned delivery at 34 weeks’ gestation without amniocentesis for fetal lung maturity is acceptable (6).

The incidence of placenta percreta has gradually increased coinciding with the increasing rate of cesarean delivery: the incidence was 1/70,000 (7) in the 1970s and 1/533 (1) in 2005. Not surprisingly, previous cesarean section is one of the strongest risk factors for development of abnormal placentation. Additional risk factors for the development of placenta percreta include advanced maternal age, placenta previa, and other previous uterine procedures (1, 2).

We describe a 46-year-old Hispanic woman who was incidentally found to have hyperpigmentation of the oral mucosa and nails during a routine full body skin examination. The patient reported having these changes for years with no symptoms. A diagnosis of the Laugier-Hunziker syndrome (LHS) was made. LHS is an acquired, benign condition characterized by pigmented skin changes involving the oral mucosa and is often associated with longitudinal melanonychia.

The Laugier-Hunziker syndrome (LHS) is an acquired, benign pigmentary skin condition involving the oral mucosa, often associated with longitudinal melanonychia. It is a diagnosis of exclusion, and other systemic conditions should be excluded prior to making a diagnosis. We describe the case of a patient who was diagnosed with LHS during a routine skin examination.

CASE DESCRIPTION

A 46-year-old Hispanic woman was incidentally noted to have four asymptomatic, hyperpigmented macules on the inner aspect of the lower lip (Figure 1) and one hyperpigmented macule on the inner aspect of the upper lip during a routine total body skin exam. The patient denied any symptoms related to any of these lesions. She was also found to have longitudinal hyperpigmented changes of the fingernails extending to the cuticle, more common on the lateral aspect of the nails (Figure 2). Similar findings were also present on the fifth digit of the right foot. The patient reported that she had had these nail changes for several years. There was no associated nail dystrophy, and she denied any symptoms related to the nail findings. The remainder of the physical exam showed no evidence of other pigmented lesions. She was otherwise healthy and not currently taking any medications.

DISCUSSION

LHS, also known as idiopathic lenticular mucocutaneous pigmentation, was first described in 1970 (1). It is characterized by a number of asymptomatic, hyperpigmented mucocutaneous macules whose color ranges from brown to black (1). Lesions most commonly involve the buccal mucosa and lips, but the gums, tongue, palate, fingers, toes, neck, and abdomen can also be involved. Nails are affected in about 60% of cases, and findings include longitudinal stripes affecting the nail plate (2). The diagnosis of LHS is frequently made clinically and is a diagnosis of exclusion (3). Biopsy of the lesions can be performed to confirm the diagnosis, and histopathologic changes

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associated with LHS show increased basal layer pigmentation with a normal number and morphologic appearance of melanocytes (2).

Prior to making the diagnosis of LHS, it is important to exclude other associated systemic conditions including the Peutz-Jeghers syndrome (PJS) and Addison’s disease. PJS is an autosomal dominant genetic disorder that shares clinical features with LHS and is an important differential diagnosis to exclude due to its increased risk of malignancy (4). PJS is characterized by hamartomatous gastrointestinal polyposis and hyperpigmentation of the skin and mucous membranes and is associated with an increased risk of both intestinal and extraintestinal malignancies. Diagnosis of PJS is made based on the presence of polyps in the gastrointestinal tract and a family history of the disorder, neither of which was present in our patient. Addison’s disease, an endocrine disorder caused by insufficient production of cortisol and aldosterone, is characterized by increased pigmentation of the knuckles, skin creases, and mucous membranes and should also be considered in the differential (5). Other systemic findings include hypotension, dehydration, and abdominal pain, which were all absent in our patient. Other less common conditions that should be considered in the differential for hyperpigmentation include the McCune-Albright syndrome, drug-induced hyperpigmentation (tetracyclines, antimalarials, and chemotherapy), and the Gardner syndrome (2).

Our patient presented with the characteristic features of LHS. With the lack of systemic symptoms and a prior colonoscopy showing no evidence of polyps, PJS and Addison’s disease were ruled out. LHS is known to be a benign disorder with no systemic manifestations and no increased risk for malignancy (5). Treatment for LHS is usually sought for cosmetic reasons, and possible therapeutic options include laser therapy and cryosurgery (2). Our patient did not have any cosmetic concerns, and as such, no treatment was given.

Intracranial germinoma

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Pineal region tumors make up less than 1% of all intracranial neoplasms, with the majority being of germ cell origin. We describe the diagnostic evaluation and treatment of a patient presenting with neurological deficits who was found to have a germinoma of the pineal gland.

CASE REPORT

A 28-year-old woman with an unremarkable past medical history presented to the emergency department with a 6-month history of headaches and the insidious onset of neurologic deficits including hearing loss, slowed speech, fatigue, loss of appetite, hair loss, and presyncopal episodes. She described parietal region headaches that worsened during the day with slight improvement at night. She had previously been seen by her primary physician with complaints of excessive thirst, frequent urination, and abnormal menses and was found to have diminished thyroid function. Neurological examination revealed subtle left face and arm weakness, slight left pronator drift, right-sided tremor, and left-sided dysmetria. Extraocular muscles were abnormal on far leftward gaze, with the left eye demonstrating a mild lateral rectus palsy.

An unenhanced head computed tomography (CT) scan and subsequent gadolinium-enhanced magnetic resonance imaging (MRI) revealed a large midline mass centered in the pineal region with moderate to severe obstructive hydrocephalus (Figure 1). The MRI demonstrated a solid and cystic-enhancing mass with imaging findings suggestive of a pineal germinoma, although there were a number of alternative, albeit less likely, differential pathologic considerations for the appearance of this mass.

Dexamethasone was initiated for cerebral edema in addition to levetiracetam for seizure prophylaxis. The patient underwent an endoscopic third ventriculostomy with tumor biopsy. Histological analysis was compatible with a germinoma (Figure 2). Initial cerebrospinal fluid (CSF) cytological testing was negative for malignant cells and showed CSF tumor marker levels of 2.5 mIU/mL for beta-human chorionic gonadotropin (beta-HCG) and <0.5 ng/mL for alpha-fetoprotein (AFP). Follow-up serum screening results 1 month later revealed a beta-HCG of 5 mIU/mL and AFP of 1.5 ng/mL. MRI of the spinal axis was negative for drop metastases.

The patient's postoperative course was complicated by diabetes insipidus treated with intranasal desmopressin. The patient received whole ventricular radiation therapy followed by a boost to the tumor and its margin to a total dose of 4500 cGy using intensity-modulated radiation therapy over the course of 5 weeks. Early posttreatment imaging demonstrated considerable interval improvement in the appearance of the tumor bed (Figure 3); however, surveillance imaging will be needed to confirm complete resolution of the neoplasm.

DISCUSSION

Pineal region tumors are rare and make up <1% of all intracranial neoplasms (1). Germ cell tumors (GCTs) account for 50% of tumors found in the pineal region, with the majority being pure germinomas (1, 2). Germinomas may be found in the pineal recess (50%–65%), suprasellar region (25%–35%), and basal ganglia/thalamus (5%–10%) (3). The median age of diagnosis for a CNS GCT is 10 to 12 years, with a male predominance of up to 3:1 (1, 4, 5). In individuals with a GCT in the pineal region, male predominance is 12:1 (1, 4, 5). The clinical presentation of a pineal germinoma includes findings of increased intracranial pressure and/or hydrocephalus: headache, nausea, vomiting, papilledema, lethargy, and somnolence. Parinaud syndrome can be found in patients with pineal GCTs and is characterized by paralysis of upward gaze in addition to loss of accommodation, convergence, and pupillary light reflex (3).

The differential diagnosis for neoplastic masses in the pineal region includes GCT (pure germinoma, World Health Organization [WHO] grade 2) and nongerminomatous cell tumors, including pineal parenchymal tumors such as pineocytomas (WHO grade 1), pineoblastomas (WHO grade 4), pineal parenchymal tumors of intermediate differentiation (no current WHO grade), and papillary tumors of the pineal region (WHO grade 2–3). Germinomas typically demonstrate...
increased attenuation relative to gray matter on CT as well as a draped configuration with respect to the posterior third ventricle (6, 7). Lesions are typically isodense to hyperintense to gray matter on T1- and T2-weighted MRI, with cystic and necrotic changes seen in larger masses (6, 7). Avid enhancement is seen following intravenous contrast administration. MRI of the entire neuroaxis and lumbar puncture is recommended to assess for CSF seeding and drop metastases (6). Other lesions encountered in the pineal region include, but are not limited to, exophytic tectal astrocytomas, pineal cysts, epidermoids/dermoids, neurocysticercosis, and tentorial incisure meningiomas.

Establishing a definitive diagnosis of a germinoma is quite important due to the pronounced differences in treatment options compared with other histological subtypes found in this area. Germinomas are particularly sensitive to radiation therapy, and long-term survival rates between 79% and 90% have been routinely achieved (8). External-beam radiation therapy distributes ionizing radiation from a source outside the patient to produce permanent cancer cell DNA strand breaks. The current standard of care predicates the use of whole ventricular radiation therapy with an additional boost to the tumor versus craniospinal irradiation (9). Whole ventricular radiation therapy achieves reduced recurrence rates and decreased spinal failure compared with craniospinal irradiation (9). The addition of neoadjuvant chemotherapy can

Figure 1. (a) Axial noncontrast CT image demonstrates a pineal region mass (white arrow) with intrinsic hyperdensity and associated obstructive hydrocephalus. (b) Axial T2-weighted, (c) axial, and (d) coronal postcontrast T1-weighted MR images reveal a T2 signal isointense to gray matter with intermixed cystic foci (white arrow in b) and avid enhancement following contrast administration (large white arrows in c and d). A separate T2 hypointense (small black arrow in b) and enhancing (small white arrow in c) nodule is seen at the interface of the septum pellucidum and left fornical body, which suggests local cerebrospinal fluid dissemination of tumor. Additional, peripherally enhancing cystic foci are present within the midbrain tectum (black arrows in d).

Figure 2. (a) Histologic examination of the biopsy specimen reveals predominantly monotonous polygonal shaped cells with prominent nucleoli and cytoplasm ranging from clear to eosinophilic. Immunohistochemical stains for (b) OCT3/4 and (c) CD117 reveal strong reactivity. CD117 marker may also be found in other tumors such as gastrointestinal stromal tumors, whereas OCT4 is relatively specific for germ cells. When CD117 and OCT4 are used together, they are quite specific for a germinoma.

Figure 3. MR images following radiotherapy show a marked improvement in the appearance of the tumor bed. Near complete resolution of the large mass in the pineal fossa is seen with minimal residual enhancement along the margin of the splenium of the corpus callosum (arrows in c and d). There is considerable reduction in the extent of the previously seen peripheral enhancement involving the cystic components within the tectum of the midbrain (arrows in a and b).
lead to a reduced radiation dose and volume with localized germinomas, which is of particular importance in pediatric patients (10). Efforts to minimize toxicity may lead to a reduced side effect profile without sacrificing tumor regression (10).


We describe a 71-year-old man who presented with abdominal pain, lower-extremity edema, recent unintentional weight loss, hypertension, hyperglycemia, hypokalemia, and metabolic alkalosis. Serum cortisol levels remained elevated after overnight high-dose dexamethasone suppression. Magnetic resonance imaging revealed a small mass in the head of the pancreas with scattered liver metastases. Both endoscopic ultrasound-guided pancreatic biopsy and liver biopsy revealed a well-differentiated neuroendocrine tumor. These lesions did not show significant uptake on octreotide scan. Medical management and hepatic artery chemoembolization were attempted. Ultimately, the patient underwent bilateral adrenalectomy, but died within 4 months of symptom onset secondary to postoperative complications.

Ectopic adrenocorticotropic hormone (ACTH) production outside the pituitary gland occurs in approximately 10% of patients presenting with Cushing’s syndrome (1). Pancreatic neuroendocrine tumors (NET) are a rare cause of ectopic ACTH syndrome. Herein, we present a case of metastatic pancreatic NET with ectopic ACTH production refractory to medical and surgical management.

CASE DESCRIPTION

A 71-year-old white man originally from Ireland with known hypertension, hyperlipidemia, and hypothyroidism was in his usual state of health until 2 months before admission when he experienced progressive functional decline. His ambulation was limited to less than half a mile on level ground and less than one flight of stairs. Over this time, he reported abdominal distension, moderate nonspecific abdominal discomfort, anorexia, and a 25-pound unintentional weight loss. Evaluation by his primary care physician included a normal colonoscopy. During these office visits, his blood pressure and blood sugar were elevated. Over the 2 weeks before admission, he developed progressive lower-extremity edema and was started on hydrochlorothiazide and spironolactone. Despite this, his abdominal distension and lower-extremity edema progressed, prompting admission to our hospital. Prior to this admission, he was taking aspirin, calcium, vitamin D, fluticasone nasal spray, lisinopril, and simvastatin. He was started on potassium citrate within the month prior to admission for persistent hypokalemia. He reported an 80-pack year tobacco history and former heavy alcohol use (up to 12 beers daily). His mother and sister both died of gastric carcinoma at 57 and 38 years of age, respectively.

On presentation, he was afebrile, with a heart rate of 111 beats/minute, blood pressure of 155/86 mm Hg, and oxygen saturation of 94% on room air. He was in no apparent distress. He had a round, ruddy face with slight exophthalmos and right-sided facial droop (both of which preceded his current illness). Preconal exam revealed a soft systolic ejection murmur at the left upper sternal border. His lungs were clear to auscultation. His abdomen was protuberant and nontender to palpation. He had symmetric 2+ to 3+ lower-extremity edema that extended to the knees. No striae, moon facies, or proximal muscle weakness were appreciated.

Initial laboratory results disclosed potassium 1.8 mEq/L, bicarbonate 38.4 mEq/L, aspartate transaminase 124 U/L, alanine transaminase 189 U/L, alkaline phosphatase 157 U/L, and lipase 94 U/L. A contrast computed tomography (CT) scan of the abdomen disclosed multiple hypodense liver lesions (Figure 1), small 2- to 3-mm scattered pulmonary nodules, and a lumbar compression fracture.

His serum cortisol at 5:00 AM was 38.9 μg/dL with an ACTH level of 84 pg/mL. After overnight high-dose dexamethasone suppression, his 8:00 AM cortisol level remained elevated at 38.8 μg/dL. His initial 24-hour urine free cortisol was 371.5 mcg. Renin and aldosterone were below the detectable limits of testing. Analysis of tumor markers revealed a carbohydrate antigen (CA) 19-9 284 U/mL, beta-human chorionic gonadotropin 7.2 mIU/mL, carcinoembryonic antigen 8.7 ng/mL, and prostate-specific antigen 6.77 ng/mL.

Magnetic resonance imaging (MRI) of the brain revealed no pituitary abnormalities. An MRI of the abdomen showed a pancreatic head mass and multiple hepatic lesions. Endoscopic ultrasound-guided biopsy of the pancreatic mass showed predominantly nonneoplastic pancreatic and gastrointestinal tissue.

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with rare groups of atypical epithelioid to plasmacytoid cells, suspicious for well-differentiated NET (Figure 2a). Liver biopsy revealed a uniform population of plasmacytoid neoplastic cells with characteristic “salt and pepper” chromatin (Figure 2b). Cell block preparation of the liver mass showed neoplastic cells demonstrating positive immunohistochemical staining for synaptophysin (Figure 2c) and chromogranin. The ki-67 proliferative index was 35%. Stains for Pax-8, TTF-1, CDX-2, ACTH, and gastrin were negative. Octreotide scan did not show significant uptake within these lesions.

He was started on ketoconazole with improvement in serum cortisol, but this drug was discontinued due to worsening liver function. He was switched to metyrapone with urine free cortisol downtrending to a nadir of 67.9 mcg/day (range 17–47 mcg/day); however, this drug was also stopped for cost and insurance concerns. Despite continued high cortisol levels, the patient became symptomatic from steroid withdrawal, manifesting as fatigue and malaise, for which he received 1 mg of dexamethasone. The patient was maintained on octreotide acetate despite lack of uptake on octreotide scan. He underwent hepatic artery embolization on hospital day 18 without a significant effect on cortisol secretion. Due to persistently elevated cortisol levels, he underwent bilateral adrenalectomy.

Figure 1. CT of the abdomen showing innumerable small hypodense hepatic lesions suggestive of metastatic disease.

Figure 2. (a) Pancreatic biopsy reveals occasional groups of atypical epithelioid to plasmacytoid cells, suspicious for well-differentiated neuroendocrine tumor (Papanicolaou stain). (b) Liver biopsy shows a monomorphic population of similar-appearing neoplastic cells with round to oval nuclei and dispersed, finely stippled chromatin that are arranged as dispersed single cells with scattered pseudorosette formations (Papanicolaou stain). (c) Cell block preparation from the liver biopsy demonstrates strong immunoreactivity for synaptophysin in tumor cells (hematoxylin-eosin; inset: synaptophysin immunohistochemical stain). (d) Bilateral adrenalectomy specimens show multifocal metastatic neuroendocrine tumor in a background of diffuse adrenal cortical hyperplasia (hematoxylin-eosin).
on day 28 of hospitalization (Figure 2d). Figures 3a to 3c depict the erratic, uncontrolled levels of urine free cortisol, serum cortisol, and serum ACTH during his treatment course. His labile blood pressure and volume overload were controlled with escalating doses of spironolactone, captopril, labetalol, and furosemide.

Postoperatively, the patient was started on stress-dose steroids with intravenous hydrocortisone 100 mg every 8 hours. Following surgery, he experienced a number of postoperative complications including delirium, acute pancreatitis, enterococcal urinary tract infection, peripherally inserted central catheter-associated deep venous thrombosis, gastrointestinal hemorrhage, and atrial fibrillation. Due to his rapid functional decline, the patient and his family chose to transition to a comfort-oriented care approach and he passed away on hospital day 42.

**DISCUSSION**

Ectopic ACTH production secondary to a pancreatic NET may have variable presentations, ranging from vague, nonspecific symptoms to more dramatic cases of diabetic ketoacidosis or hypertensive crisis (2). Many patients lack the traditional phenotypic features of Cushing's syndrome, but have prominent biochemical abnormalities, specifically hypokalemia, metabolic alkalosis, and hyperglycemia (3). The majority of patients are middle-aged women with limited comorbid diseases.

Pancreatic NET often presents with advanced, metastatic disease, similar to our case. Approximately 75% of cases of midgut or hindgut NET have known liver metastases (4). These cases are difficult to manage given early and aggressive tumor recurrence despite resection of the primary lesion. A minority of cases may respond to targeted medical therapies based on biochemical profiling of the tumor pathology (5–7). These indolent tumors are slower growing, and their localization often precedes ACTH secretion and the Cushingoid phenotype. Variations in clinical course can be ascribed to aggressive transformation of the tumor upon disease recurrence or liver metastases. NET may be biochemically heterogeneous and secrete multiple different hormones to produce distinct clinical phenotypes (8). We note that the pathology specimen in our patient did not stain positive for ACTH, which may be due to sampling error. Alternatively, cases of pancreatic NET secreting corticotropin-releasing hormone (CRH) have been described (9). The clinical picture is still one of Cushing's syndrome, though specific CRH staining must be sought.

Finding the source of ectopic ACTH production can be challenging, as these tumors are typically small and radiographically covert on routine CT imaging (10). Primary sites include the lung (bronchial carcinoids or small cell carcinomas), but can more rarely include the pancreas, thymus, gastrointestinal tract, and prostate (1, 10). In our case, MRI detected a pancreatic head mass, not seen on initial CT imaging. Somatostatin receptor imaging with tagged octreotide (11) and combined positron emission tomography/CT (12, 13) can further localize ectopic ACTH-producing tumors.

Managing ectopic ACTH production includes pharmacologic control of hypercortisolemia, bilateral adrenalectomy, and/or interventional or surgical resection of the secreting tumor or associated metastases. Resection of the primary tumor can be performed, but reported surgical success has been only modest (30%–50%) (1). Limited experiences support the safety and efficacy of early bilateral adrenalectomy in refractory cases (14). Thus, medical therapies represent the mainstay of initial management. Steroidogenesis can be directly inhibited by agents such as ketoconazole, metyrapone, mitotane, amino-glutethimide, ortho-paradichlorodiphenyldichloroethane, and etomidate (15). Ketoconazole has been effective in small case series; however, the majority of patients died of ketoconazole-refractory cortisol production within a median of 19 weeks.
Pancreatic NET may have specific treatment approaches. Somatostatin analogues (octreotide and lanreotide) target somatostatin receptors commonly expressed in pancreatic NET and can lead to decreased hormone production, although they often have limited tumor regression effects (18). Advanced pancreatic NET may be amenable to chemotherapeutic intervention, and early clinical data favor the use of everolimus (rapamycin inhibitor) (19) and sunitinib (tyrosine kinase inhibitor) for improvement in progression-free survival, although response rates are in the single-digit range (20). Streptozocin in conjunction with doxorubicin or 5-fluorouracil is approved for pancreatic NET, but is limited by its toxicity profile (21, 22). There are several small series testing capicitabine and temozolomide with response rates in the 40% to 70% range. Palliation of unresectable tumors may be achieved with hepatic arterial embolization with improvement in symptoms and reduction in overall tumor burden (4). Unfortunately in our patient, hypercortisolemia persisted despite available medical and surgical interventions.

Pancreatic NET can have variable, often aggressive endocrinologic manifestations. A high index of suspicion is required for early diagnosis given the vague, undifferentiated initial presentation. Tumor heterogeneity and a rapidly progressive course can pose significant management challenges. A multidisciplinary team can tailor treatment strategies to target biochemical tumor features.
Lobular carcinoma of the breast with gastrointestinal metastasis

Catherine Jones, MD, Alex W. Tong, PhD, Mariam Mir, MD, and Yvonne Coyle, MD

We present the case of a 74-year-old woman with metastatic lobular carcinoma with an occult breast primary presenting as a suspected ampullary tumor due to its ampullary metastasis. The patient's clinical presentation is of interest in two aspects. First, lobular carcinoma of the breast metastatic to the ampulla is extremely rare. Second, in the absence of a detectable primary lesion, prior history of malignancy, or distinguishing clinical, radiological, and endoscopic features, histopathological assessments are pivotal for arriving at the appropriate diagnosis and for optimizing treatment.

Invasive lobular carcinoma (ILC) of the breast accounts for about 15% of breast carcinomas and is the second most common histologic type of invasive breast cancer after invasive ductal carcinoma (IDC). ILC is both clinically and biologically distinct from IDC, particularly in its predilection for metastasis to the gastrointestinal (GI) tract. We present here a case of metastatic lobular carcinoma with an occult breast primary presenting as a suspected ampullary tumor due to its ampullary metastasis.

CASE DESCRIPTION

A 74-year-old woman presented to the emergency department for right hip pain after a fall. She was found to have a closed fracture of the right femoral neck and was taken for repair via right hip hemiarthroplasty the following day. The patient complained of persistent, generalized weakness associated with malaise and anorexia. She presented with hypokalemia and markedly elevated liver function test values (Table). Her white blood cell count was also elevated with reduced hemoglobin and hematocrit levels. Her bilirubin was normal on presentation but became elevated on hospital day 1 and further increased during her stay to a high of 7.5 mg/dL on hospital day 9. Abdominal ultrasound revealed dilatation of the intrahepatic, extrahepatic, common bile, and main pancreatic ducts suspicious for an ampullary malignancy.

Esophagogastroduodenoscopy was attempted. Due to duodenal narrowing, it was not possible to pass the endoscope. Biopsies of the narrowed portion of the duodenum were obtained. Computed tomography scans of the abdomen and pelvis showed marked dilatation and obstruction of both the common duct and pancreatic ducts near the ampulla. A percutaneous biliary drain was placed with subsequent improvement in her liver function tests.

Table. Laboratory findings*

<table>
<thead>
<tr>
<th>Observed value</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium (mEq/L)</td>
<td>3.5–5.1</td>
</tr>
<tr>
<td>Liver function</td>
<td></td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>0.2–1.0</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/L)</td>
<td>50–136</td>
</tr>
<tr>
<td>Aspartate aminotransferase (U/L)</td>
<td>15–36</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/L)</td>
<td>12–78</td>
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</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>12–16</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>36–47</td>
</tr>
<tr>
<td>Carcinoembryonic antigen (ng/mL)</td>
<td>0.5–2.4</td>
</tr>
<tr>
<td>CA 19-9 (U/mL)</td>
<td>&lt;37</td>
</tr>
<tr>
<td>CA-125 (U/mL)</td>
<td>&lt;35</td>
</tr>
<tr>
<td>CA 27-29 (U/mL)</td>
<td>0.0–38.6</td>
</tr>
</tbody>
</table>

*Values constitute findings prebiopsy unless otherwise stated.
†Bilirubin was normal at 1.0 mg/dL at presentation but became elevated on hospital day 1 (as shown); bilirubin further increased to 7.5 mg/dL on hospital day 9.
‡Obtained after initial biopsy.

From the Departments of Hematology/Oncology (Jones) and Clinical Oncology Research (Tong), Charles A. Sammons Cancer Center at Dallas; Baylor Research Institute, Dallas, Texas (Tong); the Departments of Internal Medicine (Jones, Coyle) and Pathology (Mir), Baylor University Medical Center at Dallas; and Texas Oncology PA, Dallas, Texas (Coyle).

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Histology results demonstrated a poorly differentiated carcinoma with highly atypical cells, some of which were present in cohesive clusters, with others invading in a single file manner (Figure 1). The cells were positive for cytokeratin (CK) 7, estrogen receptor (ER; 40%), BRST-2/GCDFP-15 (gross cystic disease fluid protein-15), mammoglobin, and the transcription factor GATA-3 (trans-acting T-cell–specific transcription factor GATA-3). Positron emission tomography showed activity around the distal bile duct, duodenum, and in one left axillary lymph node. The patient’s final pathology confirmed the presence of a poorly differentiated adenocarcinoma with an immunophenotype of CK7+, CK19+, GATA3+; CK20−, and CDX2+, consistent with a poorly differentiated adenocarcinoma of breast primary (Figure 2). Fifty percent
of the tumor was ER-positive. Progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2/neu) were negative by immunohistochemistry (Figure 3) with a proliferative fraction of 20%. E-cadherin staining was also performed and was negative within the tumor (Figure 4).

Approximately 1 month after the patient’s original admission and diagnosis, she was readmitted with a small bowel obstruction requiring surgical intervention. Intraoperatively a wedge biopsy of one of the liver lesions was obtained. This biopsy was consistent with the prior biopsy, staining positive for CK7, ER (40%), BRST-2/GCDFP-15, and GATA-3. Furthermore, HER2/neu evaluation by fluorescence in situ hybridization was negative.

The patient did not have a family history of breast cancer. She did not have a prior history of lobular carcinoma in situ and had not been on hormonal replacement therapy. Serum levels of carcinoembryonic antigen and CA-125 prior to her initial biopsy were within normal range (Table). CA 19-9 was elevated (Table) with concomitantly increased bilirubin (6.7 mg/dL), a finding that is not uncommon within the context of bile duct obstruction. Serum CA 27-29 determined after initial biopsy was also elevated. Morphologically, the tumor was consistent with a breast primary. There was no evidence of ovarian malignancy by transvaginal ultrasound.

DISCUSSION
An estimated 232,670 new cases of invasive breast cancer are expected to be diagnosed among US women in 2014 (1). ILCs, the second most common histological subset after IDCs, constitute up to 15% of all invasive breast carcinomas, and their incidence has been increasing in the last two decades (2). The higher incidence may be attributable to the increased use of combined hormonal replacement therapy (2). As a whole, primary breast cancers that metastasize to the GI tract are rare, particularly so at the time of initial diagnosis (3).

The clinical manifestations of breast cancer patients who present with GI metastasis are typically vague. The stomach is a commonly reported site of lobular carcinoma metastasis presenting as “linitis plastica” and mimicking primary gastric carcinomas (4), as exemplified by the proband, clinical, radiological, and endoscopic findings overlapping extensively with those found with primary GI malignancies. In these cases, correct identification of the primary tumor origin is essential, with immunohistochemical findings becoming pivotal for an accurate differential diagnosis.

Treatment varies considerably for a primary GI malignancy versus a metastatic breast carcinoma. Surgery would most likely be pursued in the case of a primary GI malignancy, but is not considered as clinically beneficial for patients with a metastatic breast malignancy (4). Treatment of metastatic breast cancer is generally nonsurgical, requiring some form of systemic therapy with cytotoxic chemotherapy, biologic agents in the setting of HER2-neu positivity, or antiestrogen–targeted treatment (5). Given the noncurative nature of the disease, selection of systemic therapy is based on prolonging survival while minimizing toxicities (5). For this reason, endocrine therapy is the preferred initial treatment.

Most ILCs express estrogen receptor and lack HER2/neu expression/gene amplification, hence falling into the
“luminal” molecular subgroup (6, 7). Hormonal receptor expression by the proband is consistent with this profile. However, increased ER and PR have also been described in gastric adenocarcinomas in limited series (8). CK7 and CK20 are among the most useful cytokeratin biomarkers for distinguishing carcinomas of unknown origin (9). The CK7+/CK20− phenotype is expressed in most breast, lung, and ovarian adenocarcinomas, whereas most intestinal adenocarcinomas and Merkel cell carcinomas are CK7+/CK20− (9). Metastatic breast cancer cells also express CK19, a biomarker that is of high sensitivity but limited specificity for breast cancers (10). Conversely, homeobox protein CDX2 expression commonly favors a GI cancer phenotype, as seen in 97% of colorectal cancers, 61% of gastric cancers, and 16% of pancreatic cancers (9), although adenocarcinomas of the ampulla of Vater may also be CDX2-negative (11). BRST-2 has been shown in multiple studies to be expressed primarily in breast cancers and not in GI cancers (12).

In a recent systemic review of 2500 epithelial and nonepithelial tumors, Miettinen (13) showed that >90% of primary and metastatic breast ductal and lobular carcinomas express the multispecific transcription factor GATA3. To a lesser extent, pancreatic ductal carcinomas (37%) and adenocarcinomas of the lung, stomach, and colon (<10%) are GATA3+. Since >90% of invasive lobular breast carcinomas are ER+ and neuroendocrine tumors of GI origin are not (14), the findings of CK7+/CK19+/CDX2− with positive ER, BRST-2, and GATA-3 expression support the diagnosis of metastatic breast adenocarcinoma, as opposed to a primary adenocarcinoma of ampullary origin (15). Biopsy morphology and a normal serum CA-125 level in the proband were not consistent with a metastatic ovarian malignancy.

PR expression is also supportive of a non-GI primary; however, in the case of our patient, this was negative. While a negative PR phenotype did not assist in confirming the breast origin of the patient's malignancy, there is some evidence to support its prognostic value, as PR expression is inversely associated with breast cancer stage at diagnosis (7) and a higher risk of relapse and death (16). Additionally, PR status is predictive of potential benefit from endocrine therapy (16, 17), where PR-positive breast cancer patients demonstrate a reduced risk for disease recurrence and death compared to PR-negative patients (16).

Negative expression of the epithelial calcium-dependent adhesion molecule E-cadherin has been shown to be a sensitive and specific biomarker to confirm the invasive lobular carcinoma subtype among tumors with histologically equivocal features (18, 19). Aberrant expression of the E-cadherin-β-catenin complex is an early event that affects typical lobular hyperplasia as well as lobular carcinoma in situ (19). Invasive lobular breast carcinomas are typically E-cadherin-negative, which indicates that loss of cell-cell adhesion promotes lobular carcinoma metastases (18, 19). In contrast, aberrancy in E-cadherin gene expression appears to manifest epigenetically among IDCs. IDCs generally demonstrate positive immunohistochemical staining related to E-cadherin, albeit weaker as compared with the primary tumor (20).


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Lobular carcinoma of the breast with gastrointestinal metastasis 53
We present a case of hepatic angiosarcoma that presented with disseminated intravascular coagulopathy to highlight the difficulty in diagnosing this disease due to its aggressive clinical course, the overlapping features of various coagulopathies, and the nonspecific appearance of angiosarcomas on imaging.

Hepatic angiosarcoma is a rare neoplasm that develops from endothelial cells in the liver. It presents with generalized, nonspecific symptoms such as weight loss, fatigue, and abdominal pain, but on rare occasions coagulopathies may result (1–3). Here we present a case of hepatic angiosarcoma that presented with disseminated intravascular coagulopathy (DIC).

CASE REPORT

An 81-year-old woman was admitted for anemia, thrombocytopenia, and jaundice. Three weeks earlier, she had presented with generalized pruritus and jaundice. She was found to have a hemoglobin level of 4.6 g/dL, hematocrit of 13%, and platelet count of 25,000 μL. She was initially diagnosed with thrombotic thrombocytopenic purpura and was treated with plasma exchange, methylprednisolone, and rituximab without improvement before being transferred to Baylor University Medical Center at Dallas (BUMC). Two years earlier, abdominal computed tomography (CT) disclosed a nodular-appearing liver. A biopsy did not reveal any signs of malignancy or cirrhosis, but noted focal dilatation of the sinusoidal spaces.

On presentation at BUMC, the patient had marked jaundice and diffuse purpura on her extremities. Her abdomen was distended with a positive fluid wave. Hepatosplenomegaly was not appreciated. Laboratory results showed a hemoglobin of 8.9 g/dL; hematocrit of 27.3%; platelet count of 30 μL; schistocytes on the blood smear; total bilirubin of 14.6 mg/dL; direct bilirubin of 8.5 mg/dL; alkaline phosphatase of 109 U/L; fibrinogen of 50 mg/dL (normal 200–400 mg/dL); D-dimer of 34.6 mg/L (normal <5.9 mg/L); prothrombin time of 20.7 seconds; and activated thromboplastin time of 30.2 seconds. The patient was given cryoprecipitate and a heparin infusion, and her fibrinogen transiently rose to 153 mg/dL. Magnetic resonance imaging (MRI) of her abdomen showed extensive abnormal patchy enhancement throughout the liver (Figure 1). A transjugular liver biopsy revealed spindle cells suspicious for but not diagnostic of malignancy. The night following the biopsy, swelling and tightness in her right lower extremity was found. CT revealed an expanding hematoma in the right vastus muscle. She was managed with blood products and a reduced concentration of heparin until the family decided to pursue comfort care measures only. She died within 24 hours.

Autopsy revealed a spongy liver with diffuse congestion (Figure 2a). Multiple large cystic spaces contained thrombus. Microscopically, groups of spindle cells with pleomorphic nuclei and eosinophilic cytoplasm formed small vascular channels within the cystic spaces (Figure 2b). Tumor cells also infiltrated the liver parenchyma and the sinusoids. The lining of some cystic spaces suggested venous walls, and portal tract veins also contained infiltrating tumor. No metastatic tumor was present outside of the liver. The tumor cells were immunohistochemically reactive for Factor VIII, FLI-1, and CD34, consistent with hepatic angiosarcoma.

Figure 1. MRI of the liver reveals extensive abnormal patchy enhancement throughout the liver which is favored to relate to intrahepatic shunts/collaterals consistent with possible Budd-Chiari syndrome.

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Several theories have been proposed to explain how angiosarcomas may trigger DIC, including the malignancy exposing the basement membrane of the endothelium; a decreased blood supply flow inducing blood cell trapping and lysis, triggering the release of clotting factors; and local inflammation or malignant endothelial cells inducing thromboplastin and tissue factor release. Benign capillary and visceral hemangio- mas may also be associated with DIC, as in Kasabach-Merritt syndrome (6).

In this case report, the associated DIC was initially mistaken for thrombotic thrombocytopenic purpura associated with coagulopathy of liver disease. These three hematologic disorders have many overlapping features, and distinguishing between them can be challenging. Thrombotic thrombocytopenic purpura is characterized by a microangiopathic hemolytic anemia (confirmed by the presence of schistocytes on the blood smear) and thrombocytopenia, but typically no other coagulopathy. DIC includes not just anemia and thrombocytopenia, but a coagulopathy associated with thrombin generation, including prolonged prothrombin and activated thromboplastin times, a low fibrinogen, and an increased D-dimer. Hemolysis with schistocytosis is present in 50% of cases. Liver disease can manifest a coagulopathy similar to that of DIC, including anemia, thrombocytopenia, and an abnormal coagulation profile, since most clotting factors are synthesized in the liver. Our patient’s blood smear revealed schistocytes most consistent with a microangiopathic hemolytic anemia related to DIC, rather than acanthocytes and target cells more typically noted with liver disease.

Another confounding factor that made the diagnosis elusive was the appearance of the liver on imaging. Classically on T2-weighted MRI, liver angiosarcomas are characterized as multiple lesions of high signal intensity with central regions of low signal intensity. In our case, the MRI showed diffuse abnormal patchy enhancements in the liver, which relates to intrahepatic shunts and collateral vasculature. This finding was more consistent with Budd-Chiari syndrome than malignancy. This imaging appearance, along with the nondiagnostic biopsy...
sample obtained, prevented the diagnosis of a discrete liver malignancy until autopsy.


Avocations

Sleepless

In the dark and quiet still,
Deep in mind, a nagging, stirs.
A constant drip, drop by drop:
Ripples play, hula-hoop,
In the ocean of recall.

As if this is not enough,
Pings of drops penetrate,
Sending deep prodding charges,
Tripping cells, from cell to cell.
A dissident storm pervades the grid.

In this upheaval of the mind,
Distant pledges and resolves,
Pronounced in the faded years,
Rise against incarceration
Tearing down the walls.

Remind of oath: “I shall . . . consecrate my life
To the service of humanity.”
And summon escapee conscience to the
Pen of misery:
Grimacing human figures.

Life’s quality measured in cups,
The cup needing pills,
Empty for the want of means.
Reprieve from the physical ills,
Competing with the famished den.

A distant voice asks the wind:
“Where stands the opulent village,
Promised to these weary bones?
Is it branded as utopian?
So the village remains imagined.”

—Amanullah Khan, MD, PhD

Dr. Khan (e-mail: aman1963@gmail.com) is an oncologist on the medical staff of Baylor Medical Center at McKinney. In addition to publishing over 100 research articles, he is an award-winning poet who has written poems in three languages.
Chromophobe renal cell carcinoma is a distinct subtype of renal cell carcinoma that accounts for 5% of all renal tumors. This subtype is further subdivided into two variants, classic and eosinophilic, with the latter variant being less frequent. We report two cases of the eosinophilic variant of chromophobe renal cell carcinoma diagnosed at our institution between January 2008 and December 2012.

Chromophobe renal cell carcinoma accounts for approximately 5% of all renal neoplasms and is a distinct subtype of renal cell carcinoma. This tumor is subdivided into two subtypes: classic and eosinophilic. Microscopically, the classic variant is characterized by large pale cells with thickened cell membranes resembling plant cell walls. However, making a correct diagnosis can be difficult in cases of the eosinophilic variant, where the tumor is purely composed of oncocytic cells. We present the gross, histologic, and immunohistochemical findings of two cases of the eosinophilic variant of chromophobe renal cell carcinoma (EVCRCC) diagnosed at our institution from January 2008 to December 2012.

CASE 1
A 73-year-old black woman with a complicated past medical history presented to the Baylor University Medical Center emergency department with weakness, dizziness, and left lower quadrant abdominal pain for the past 3 days. Laboratory results were significant for creatinine 1.2 mg/dL, calcium 7.8 mg/dL, white blood cell count 7500/mm³, hemoglobin 9.7 mg/dL, hematocrit 29.9%, and platelets 129,000/mm³. Computed tomography revealed a 1.8 cm mass in the upper pole of the left kidney, and a left partial nephrectomy was subsequently performed.

Grossly, the partial nephrectomy specimen contained a 1.8 cm well-circumscribed, mahogany-colored mass. Microscopically, the tumor comprised nests of granular eosinophilic (oncocytic) cells in a trabecular network with wrinkled nuclei, minimal nuclear atypia, and areas with perinuclear halos (Figure). The tumor was limited to the kidney. The tumor cells were immunohistochemically reactive for CK7 and were negative for vimentin. This mass was classified as an EVCRCC. No sarcomatoid features or necrosis was identified. The margins of resection were negative for carcinoma.

CASE 2
A 67-year-old Caucasian man presented to the emergency room after a syncopal episode. Further workup with carotid and magnetic resonance imaging evaluation was planned; however, a lower pole renal mass was incidentally discovered in the right kidney on computed tomography. A right radical nephrectomy was subsequently performed.

Sectioning through the right kidney revealed a light tan homogeneous mass measuring 3.0 cm in greatest dimension. Microscopically, the tumor was composed of nests to sheets of polygonal cells with eosinophilic granular cytoplasm and very sharp, distinct cell borders. The nuclei were small and slightly irregular, with vesicular chromatin and indistinct nucleoli with halo formation around the nuclei. The tumor cells were immunohistochemically positive for CK7, CD117, and Hale’s colloidal iron. This tumor was diagnosed as an EVCRCC. The margins of resection were negative for tumor. No sarcomatoid features or necrosis was identified.
DISCUSSION

Chromophobe renal cell carcinoma was first described in 1985 (1) and is thought to be derived from the intercalated cells of the collecting ducts (2). This neoplasm occurs in the second to eighth decades of life. Multifocality occurs in 8% of cases. Tumors can be present in bilateral kidneys 3% of the time. Grossly, the tumors are typically well circumscribed with a homogenous light brown cut surface (3). The prognosis is good and the mortality rate is <10%. Tumors that are larger in size, have areas of necrosis, and have sarcomatoid change have a worse prognosis (3, 4). Most cases are sporadic, but familial cases can be associated with Birt-Hogg-Dubè syndrome, an autosomal dominant disorder that includes benign skin tumors (skin tags, fibrofolliculomas), renal epithelial neoplasms (chromophobe renal cell carcinoma, oncocytoma), and spontaneous pneumothorax (5). Chromophobe renal cell carcinoma is associated with multiple losses of whole chromosomes, most frequently Y, 1, 2, 6, 10, 13, 17, and 21 (6).

The neoplasm is divided into two variants: classic and eosinophilic. The classic type is the most common of the two and consists of large and polygonal cells with fine, pale, foamy, reticulated cytoplasm, a prominent “plant cell wall–like” membrane, and irregular nuclei with perinuclear clearing. The classic variant comprises type 3 cells, which are large polygonal cells with abundant pale, reticulated cytoplasm and with well-defined cytoplasm borders (7). The eosinophilic variant is made up of type 1 cells (small, solid, and slightly granular cytoplasm without significant translucent areas) and type 2 cells (abundant eosinophilic cytoplasm denser at the periphery with perinuclear clearing) (7). The prognosis for EVCRCC does not differ from that of the classic type. At our institution, 791 renal cell carcinomas were diagnosed from January 2008 to December 2012. Only 36 of these cases were chromophobe renal cell carcinomas, and only two of the latter cases were the eosinophilic variant.

The main differential diagnosis of an EVCRCC is an oncocytoma, which is a benign entity. Several histologic and immunohistochemical features are helpful in distinguishing an oncocytoma from an EVCRCC. EVCRCC have tumor cells arranged in sheets with well-defined cell borders with wrinkled or raisinoid nuclei. In contrast, oncocytomas only have eosinophilic cells with round, hyperchromatic nuclei arranged in a nested or tubular pattern.

Immunohistochemically, EVCRCC is reactive for CK7 and negative for vimentin. Additionally, Hale’s colloidal iron stain shows diffuse reticular cytoplasmic positivity in EVCRCC, whereas oncocytomas display focal positive staining confined to the luminal borders (8). Ultrastructurally, the cells of an oncocytoma are packed with mitochondria, whereas the cells in EVCRCC have numerous microvesicles in the cytoplasm (8).

Pulmonary involvement of peripheral T-cell lymphoma manifesting as crazy paving pattern

Traci Fraser, MD, and Amulya Nagarur, MD

Crazy paving pattern is a finding on computed tomography of the chest that is characterized by interlobular septal thickening and ground-glass opacities. Though classically associated with pulmonary alveolar proteinosis, the differential diagnosis for this pattern is broad, and initial workup includes bronchoscopy with bronchoalveolar lavage to evaluate for malignancy, diffuse alveolar hemorrhage, pulmonary alveolar proteinosis, infection, and eosinophilic pneumonia. Herein we present an unusual case of peripheral T-cell lymphoma not otherwise specified (PTCL NOS) with pulmonary involvement that demonstrated crazy paving pattern. The diagnosis was confirmed after cytology from bronchoalveolar lavage revealed atypical lymphocytes with an immunologic profile consistent with the patient’s known PTCL NOS.

Crazy paving pattern is the appearance of ground-glass opacities with superimposed linear thickening on computed tomography (CT) of the chest that resembles irregularly shaped paving stones (1). Although classically associated with pulmonary alveolar proteinosis (PAP), the differential diagnosis for this finding is broad (1). Workup should include bronchoscopy with bronchoalveolar lavage (BAL).

CASE DESCRIPTION

A 77-year-old man with peripheral T-cell lymphoma not otherwise specified (PTCL NOS) presented with 5 months of dyspnea on exertion and cough productive of yellow sputum with occasional streaks of blood. He had been diagnosed with PTCL NOS 4 years prior when routine labs revealed a white-cell count of 28,000/mm³, with 77% lymphocytes. Peripheral smear revealed a predominance of lymphocytes with mature, clumped chromatin and frequent nuclear convolutions and lobulations. Peripheral flow cytometry demonstrated a predominant population of immunophenotypically aberrant T cells with a “double-negative” immunophenotype (CD3⁺, CD5⁺, CD7⁺, CD4⁻, CD8⁻, CD20⁻). Markers for human T-cell lymphotropic virus-1 were negative. Subsequent bone marrow biopsy was negative. Subsequent bone marrow biopsy was performed, with flow cytometry demonstrating abnormal T cells that were CD4⁻ and CD8⁻ by flow cytometry; immunohistochemistry revealed that the atypical T cells were negative for markers associated with angioimmunoblastic T-cell lymphoma and anaplastic large cell lymphoma. CT of the chest, abdomen, and pelvis revealed enlarged axillary, mediastinal, and inguinal lymph nodes, all of which were <2 cm, and small pulmonary nodules in the right upper lobe with a tree-in-bud configuration. The patient was ultimately diagnosed with an atypical PTCL NOS. Given the absence of symptoms and a stable white blood cell count, the patient and his medical team elected to pursue expectant management without chemotherapy. His lymphocytosis was monitored serially over the 4 years prior to admission and remained stable. He did not have repeat chest imaging over that interval.

He was in his usual state of health until 5 months prior to admission when he developed cough, fever, and dyspnea on exertion. He was seen in an urgent care clinic and was treated with a course of levofloxacin, after which his symptoms improved. Three months later, his cough returned and was newly productive of blood-tinged sputum and several small blood clots. He received cefpodoxime and azithromycin for presumed community-acquired pneumonia. Despite this treatment, his symptoms persisted and the following month a CT of the chest was obtained, which revealed ground-glass opacities in the lower lobes. He was again treated with cefpodoxime and azithromycin, which temporarily improved his symptoms. One week prior to the current admission, he attempted a 4-mile hike, which he was previously able to complete without difficulty, and noted significant dyspnea throughout the hike. On the day prior to admission, he experienced shortness of breath with minimal exertion that limited his ability to ambulate, prompting his presentation to the emergency department.

In the emergency department, his temperature was 98.2°F; heart rate, 83 beats per minute; blood pressure, 137/79 mm Hg; and oxygen saturation, 88% on room air. His jugular venous pulse was 6 cm, fine crackles were heard in the bilateral lower lung fields, and lower extremities were not swollen. Laboratory results were notable for a white-cell count of 34,000/mm³, with 68% lymphocytes. Chest x-ray revealed bilateral patchy opacities in the lower lung zones, and CT of the chest showed intralobular septal thickening superimposed on ground-glass opacities. Bronchoscopy with bronchoalveolar lavage revealed atypical lymphocytes with an immunologic profile consistent with the patient’s known PTCL NOS.
opacities consistent with crazy paving pattern (Figure 1). A bronchoscopy with BAL revealed clear, frothy secretions in the airways. Gram stain and culture from the BAL did not reveal microorganisms. Cytology disclosed atypical lymphocytes with an immunoprofile consistent with the patient’s prior T-cell lymphoma (Figure 2). Positron emission tomography-CT was remarkable for moderate uptake in the right upper lobe and mild diffuse bilateral low level uptake compatible with BAL findings of T-cell lymphoma. While his lymphoma had previously been managed expectantly, the severity of his pulmonary symptoms prompted initiation of chemotherapy. He was discharged with oxygen therapy and treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) as an outpatient. After his first round of chemotherapy, his cough and dyspnea improved.

DISCUSSION

Crazy paving refers to a pattern of linear thickening and ground-glass opacities on CT of the chest, resembling irregularly shaped paving stones (1). The linear thickening can manifest as thickening of interlobular septa with or without thickening of the intralobular interstitium or the linear deposition of material at the borders of the acini (1).

The differential diagnosis for crazy paving pattern is broad, and etiologies can be classified based on the duration of the patient’s symptoms. For patients who present acutely, potential diagnoses include pulmonary edema, acute interstitial pneumonitis or adult respiratory distress syndrome, diffuse alveolar hemorrhage (DAH), infection, radiation pneumonitis, and eosinophilic pneumonia (1). For those with subacute or chronic presentations, one should consider interstitial lung disease with a usual interstitial pneumonia or nonspecific interstitial pneumonia pattern, PAP, organizing pneumonia, chronic eosinophilic pneumonia, and malignancy (1). In the absence of a clear diagnosis, patients with crazy paving pattern should be evaluated with bronchoscopy with BAL to distinguish between these etiologies. Some patients will need a surgical lung biopsy if the diagnosis remains unclear following BAL.

In our patient, DAH was initially considered given his hemoptysis. DAH is a clinicopathologic syndrome in which disruption of the alveolar and capillary basement membranes allows red blood cells to enter the alveolar space (2). DAH can present with hemoptysis, anemia, diffuse pulmonary infiltrates, and hypoxemic respiratory failure. The diagnosis is made when serial BALs reveal progressively more hemorrhagic fluid (2). Given the absence of bloody fluid seen on BAL, DAH was excluded in this patient.

BAL is also helpful in the diagnosis of pulmonary infection, eosinophilic pneumonia, PAP, and malignancy. The diagnosis of PAP, however, may require transbronchial or open surgical biopsy. The diagnosis is confirmed with a positive periodic
acid-Schiff (PAS) stain from BAL washings or lung biopsies (3). Because PAS staining may not be routinely performed on BAL washings, clinicians should specifically request PAS staining when suspecting the diagnosis of PAP.

PTCL is a subgroup within T-cell non-Hodgkin’s lymphoma with an incidence of <1 per 100,000 people in the United States. The classification of the subtypes of PTCL is complex (4). PTCL NOS is the most common group of PTCL, accounting for 25.9% of cases (5). Eighty-seven percent of patients with PTCL NOS present with nodal disease, while extranodal disease involving the lungs and pleura occurs in 21% of cases (6, 7). The prognosis in PTCL NOS is generally poor, with a 10-year overall survival rate of approximately 10% (5). However, the prognostic index for PTCL (PIT) can further risk-stratify patients. The PIT includes age >60 years, normal or elevated lactate dehydrogenase levels, performance status, and bone marrow involvement; the 5-year overall survival is 62% for those with no adverse prognostic factors and 18% for those with 3 or 4 adverse prognostic factors (8).

First-line therapy of PTCL NOS is CHOP, which in a meta-analysis of 2912 patients had a 5-year overall survival of 37% (9). While more aggressive chemotherapy regimens including autologous stem cell transplantation have been attempted, they are typically reserved for more aggressive T-cell lymphomas, and further studies are needed to determine which subgroups of PTCL would benefit from these therapies (10).


Sweet syndrome and its association with hematopoietic neoplasms

Rodrigo Soto, MD, Yair Levy, MD, and John R. Krause, MD

The Sweet syndrome, or acute febrile neutrophilic dermatosis, is rare and has characteristic clinical, physical, and pathologic findings: abrupt onset of pyrexia, elevated neutrophil count, tender erythematous skin lesions, and a diffuse infiltrate of mature neutrophils in the reticular dermis with edema in the papillary dermis. The Sweet syndrome can be further classified based on the clinical setting: classical, malignancy-associated, and drug-induced. Diagnosis can alert the clinician to the presence of an underlying malignancy or the recurrence of a malignancy. The most commonly associated malignancy is acute myelogenous leukemia. We present three cases of Sweet syndrome associated with hematopoietic neoplasms.

Case Reports

Case 1

A 52-year-old man developed a nonpruritic erythematous rash over both upper extremities, the neck, and upper back accompanied by a fever of 102°F. Table 1 provides the laboratory values. Anemia, thrombocytopenia, and the presence of blasts in the peripheral blood prompted a bone marrow examination that revealed 45% blasts and trilineage dysplasia. A diagnosis of acute myelogenous leukemia was made, possibly arising from a myelodysplastic disorder (Figure 1a). Cytogenetics revealed a deletion of 5q that supported the diagnosis. A biopsy of one of the erythematous nodules was considered to be consistent with Sweet syndrome. These resolved after steroid treatment. Concomitantly his leukemia was treated with cytarabine and daunorubicin, and remission was obtained. His postremission therapy was high-dose cytosine arabinoside, and he is currently being monitored.

Case 2

A 65-year-old man had a 2-year history of a skin rash that was suspected to be scabies, as he is a veterinarian’s assistant. Scrapings, however, were negative. He was treated with ivermec-tin and the rash disappeared but reoccurred. Recently the rash worsened and involved the face, upper back, and extremities. The patient also had a fever of 102°F with flulike symptoms. The rash was described as edematous and erythematous with 1 to 2 cm plaques and was nonpruritic. Other important findings included pancytopenia (Table 1). A skin biopsy was obtained and interpreted as Sweet syndrome. A significant physical finding was splenomegaly. A bone marrow biopsy revealed hairy cell leukemia (Figure 1b). The patient was started on a 7-day course of cladribine 0.1 mg/kg per day by continuous intravenous infusion. The skin lesions were treated with corticosteroids (prednisone) and resolved over a 7-day period. A repeat bone marrow biopsy 8 weeks later revealed no evidence of leukemia.

Case 3

A 74-year-old woman was admitted in 2009 with several erythematous lesions on the dorsum of the left hand and bilateral lower extremities. The lesions were suspicious for pyoderma gangrenosum, and she was treated with mupirocin and predni-sone. In April 2011 she was admitted with painful dark bullae on the dorsum of her fingers and bilateral upper and lower extremities. Table 1 lists her blood counts. A right thigh lesion was biopsied, and findings were consistent with Sweet syndrome. Intravenous steroids were initiated, and she was discharged on oral prednisone. In October 2012 she again developed erythematous lesions over her extremities. A shave biopsy of a toe lesion was considered to be a recurrence of Sweet syndrome (Figure 1c). The patient was again treated with steroids with resolution of the lesions.

A hematology/oncology consult was obtained, as neoplastic lesions are known to occur with the Sweet syndrome. Flow cytometry found a 5% population of clonal B cells that expressed CD5 and a 2% population of clonal plasma cells. Both populations of cells expressed kappa light chain. She subsequently...
was found to have a small 0.7 g/dL IgG monoclonal protein. At this time she is considered to have a monoclonal B cell lymphocytosis with the immunophenotype of chronic lymphocytic leukemia/lymphoma and a plasma cell dyscrasia that may represent monoclonal gammopathy of uncertain significance. She is being followed on a regular basis.

DISCUSSION

Sweet syndrome was originally described by Robert Douglas Sweet in 1964 (1). The syndrome is characterized by pyrexia, elevated neutrophil count, painful red papules or plaques, and an infiltrate of predominantly mature neutrophils diffusely distributed in the upper dermis. Sweet syndrome can be classified based upon the clinical setting in which it occurs: classical or idiopathic, malignancy-associated, and drug-induced (2).

Sweet syndrome is believed to be a reactive phenomenon and should be considered a cutaneous marker of systemic disease (3). Careful systemic evaluation is indicated, especially when cutaneous lesions are severe or hematologic values are abnormal. Approximately 20% of cases are associated with malignancy, particularly hematologic malignancy (3–5). Moreover, an underlying condition such as streptococcal infection, inflammatory bowel disease, solid tumors, or pregnancy is found in up to 50% of cases of Sweet syndrome (6–8). Sweet syndrome may precede the hematologic diagnosis by months to years, so close evaluation of individuals in the idiopathic type is necessary.

There is now some evidence that treatment with hematopoietic growth factors can cause Sweet syndrome due to induction of stem cell proliferation, differentiation of neutrophils, and prolonged neutrophil survival (9, 10). Evidence supporting an immune phenomenon includes the dramatic response to steroids and similarities with hypersensitivity reactions like erythema nodosum and erythema multiforme (3). The use of steroids results in a dramatic response in the majority of patients with either idiopathic or malignancy-associated Sweet syndrome (3). Patients with hematologic malignancy–associated Sweet syndrome usually receive cytotoxic chemotherapeutic agents and/or antimetabolic drugs for the treatment of their underlying disorder.

Systemic corticosteroids (prednisone) produce rapid improvement and are considered the "gold standard" for treatment of Sweet syndrome. The skin lesions usually clear within 3 to 9 days. Topical and/or intralesional corticosteroids may be effective as either monotherapy or adjuvant therapy.

Table 1. Clinical findings in the three patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52 (male)</td>
<td>65 (male)</td>
<td>74 (female)</td>
</tr>
<tr>
<td>Location of rash</td>
<td>B, E, N</td>
<td>B, E, F</td>
<td>E</td>
</tr>
<tr>
<td>Duration of rash (days)</td>
<td>0.2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Body temperature (°F)</td>
<td>102*</td>
<td>102.2*</td>
<td>98.0*</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>9.2</td>
<td>9.5</td>
<td>9.5</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>28.4%</td>
<td>28.9%</td>
<td>28.5%</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>35.4*</td>
<td>1.2</td>
<td>9.4–&gt;19.2</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>92%</td>
<td>54%</td>
<td>76%–&gt;83%</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>4%</td>
<td>46%</td>
<td>16%</td>
</tr>
<tr>
<td>Blasts</td>
<td>2%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Platelet count (×10⁹/L)</td>
<td>70</td>
<td>113</td>
<td>300</td>
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<tr>
<td>Bone marrow blasts</td>
<td>45%</td>
<td>0%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Dermal biopsy</td>
<td>Sweet syndrome</td>
<td>Sweet syndrome</td>
<td>Sweet syndrome</td>
</tr>
<tr>
<td>Associated malignancy</td>
<td>AML</td>
<td>Hairy cell leukemia</td>
<td>MGUS, CLL/SLL</td>
</tr>
</tbody>
</table>

B indicates back; E, extremity; F, face; N, neck; AML, acute myelogenous leukemia; MGUS, monoclonal gammopathy of uncertain significance; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma.

Figure 1. (a) Bone marrow aspirate in case 1 showing acute myelogenous leukemia with dysplastic changes. Wright stain ×970. (b) Bone marrow biopsy in case 2 showing an infiltrate of hairy cell leukemia. Hematoxylin and eosin (H&E), ×400. (c) Skin biopsy in case 3 showing a neutrophilic infiltrate consistent with a diagnosis of Sweet syndrome. H&E ×400.
iodide or colchicine may induce rapid resolution (11). Individuals who have a potential systemic infection or in whom corticosteroids are contraindicated can use the above agents as first-line therapy. Other alternatives to corticosteroid treatment include dapsone, doxycycline, clofazimine, and cyclosporine (2). All of these agents influence neutrophil migration and function.

Corticosteroids were used for the skin lesions in our patients. In cases 1 and 2, chemotherapeutic agents were also used for the hematologic malignancy. The third patient is being monitored, as she has two clonal populations of cells (lymphocytes and plasma cells) that have not yet manifested into treatable diseases.

Hairy cell leukemia (HCL) is an indolent neoplasm of small mature B lymphoid cells with characteristic morphologic features usually involving the peripheral blood, bone marrow, and spleen. It constitutes approximately 2% of adult leukemias and has a male predominance. Patients usually present with weakness, splenomegaly, and pancytopenia. The overall prognosis is favorable with appropriate treatment including purine analogs, interferon-alpha, and radiation. We report a patient with a history of breast cancer who presented with a left femoral lytic bone lesion that was subsequently diagnosed as HCL by morphology, immunohistochemistry, flow cytometry, and molecular genetic techniques. It was important to biopsy the lesion to establish the correct diagnosis, as HCL is a highly treatment-responsive malignancy.

**Hairy cell leukemia** (HCL) is an indolent neoplasm composed of small mature B lymphocytes (1). The disease has a male predominance and generally affects the blood, bone marrow, and spleen. We report an unusual case of HCL that presented with a lytic lesion of the femur in a woman with a past history of breast carcinoma.

**CASE REPORT**

An 88-year-old woman with a history of breast cancer was transferred to Baylor University Medical Center at Dallas with a pathologic fracture of the left femur. Her breast cancer had been treated with chemotherapy, radiation, and surgery and had been in remission for 11 years. She presented originally to an outside hospital after suffering trauma from being hit by a scooter at a grocery store and was found to have a pathologic fracture of the left femoral neck on radiograph. On admission, her white blood cell count was 6.8 K/μL, hemoglobin 12.1 g/dL, and platelet count 270 K/μL. A monocytopenia was present, but hairy cells were not described. Further imaging showed a lytic osseous lesion of the left femoral neck (Figure 1a). The lesion was thought to represent metastatic breast cancer, so a fluoroscopic-guided biopsy of the left femoral neck was performed. Examination of the tissue showed small lymphoid-appearing cells with abundant clear cytoplasm and well-defined cell membranes (Figure 1b). Immunohistochemistry showed positivity with CD20, annexin A1, and DBA44 (B lymphocyte markers). Flow cytometry showed a 96% variable size, clonal B cell population expressing CD10, CD11c, CD19, CD20, CD22, CD45, CD52, CD103, CD123, BCL2, and Kappa. The lesion was negative for CD5, CD11b, CD23, CD25, CD38, CD56, and FMC7. Molecular genetics was positive for the BRAF V600E mutation. These results are diagnostic for HCL. A subsequent bone marrow biopsy showed 90% involvement by HCL with a grade 2/3 reticulin fibrosis. The patient underwent orthopedic stabilization and has received a course of cladribine therapy.

**DISCUSSION**

HCL is an uncommon chronic B-cell lymphoid neoplasm constituting about 2% of adult leukemias. Characteristic features include pancytopenia, splenomegaly, and marrow reticulin fibrosis. The disease has distinct morphologic, immunohistochemical, flow cytometric, and molecular findings (1). HCL is characterized by expression of B-cell markers (CD19, CD20, CD22) as well as CD11c, CD25, CD103, DBA44, and annexin A1 (2). HCL has a male predominance and usually occurs in patients over 50 years old (3). With appropriate treatment, the 10-year survival exceeds 90% (1). The most frequent complications include infection, autoimmune disorders, and secondary malignancy (3). The major sites of leukemic involvement are the spleen, bone marrow, and peripheral blood (4). The diagnosis can sometimes be difficult to make, as the disease may mimic or coexist with other disorders (5). The correct diagnosis is important to establish early, as HCL has a good prognosis when appropriate treatment is given.

This case is unusual in three aspects. First, the patient did not have splenomegaly. Splenomegaly is the most common physical finding in HCL and is reported in 70% to 100% of cases (6). There is a previous case report of 4 patients with HCL without splenomegaly who also had lytic bone lesions (7). Second, the patient did not present with pancytopenia, which is common at presentation and reported in 50% to 70% of patients with HCL (1, 2). Third, HCL presenting as a lytic lesion...
A bone lesion is very unusual (2, 8). Skeletal complications can occur as a consequence of HCL, with a reported incidence of 3% and presentation about 20 months after initial diagnosis, but to present with skeletal abnormalities is very rare (9). Lytic bone lesions at presentation have been infrequently reported, with only a small number of case reports noted (6, 10). The lytic lesions usually involve the proximal femur (10). Less frequent sites include the vertebrae, pelvis, humerus, skull, and distal tibia (10). Most of these lytic lesions respond favorably to localized radiotherapy (10). The postulated mechanism by which HCL affects the bone involves tumor necrosis factor alpha, which is a growth mediator in HCL and possibly leads to bone resorption (10).

Because HCL is a treatment-responsive disease, it is important that the correct diagnosis be made in a timely fashion so proper treatment can be instituted. In this case, it was essential to obtain a biopsy even though metastatic breast disease was suspected clinically.

Benign neoplasms in the right ventricular outflow tract

K. Jayaprakash, MD, DM, Suresh Madhavan, MD, DM, V. Sudha Kumary, MD, DM, P. G. Anish, MD, and Raju George, MD, DM

We describe benign neoplasms in the right ventricular outflow tract in two patients: one, a 2-month-old male with a rhabdomyoma, and the other, a 48-year-old woman with a myxoma. Each of these tumors is rare in that location.

Herein we report an infant with rhabdomyoma associated with tuberous sclerosis and an adult with myxoma, both arising from the right ventricular outflow tract (RVOT), a rare site for both tumors.

CASE 1
A 2-month-old male infant without any cardiac symptoms or signs was referred for cardiac evaluation. The child’s mother was 26 years old and was diagnosed with tuberous sclerosis based on the presence of multiple major and minor diagnostic criteria including adenoma sebaceum, Shagreen patches, and Koenen’s tumors (periungual fibroma). She had undergone left nephrectomy 6 years earlier for angiomyolipoma of the left kidney. Her first child had cardiac rhabdomyoma diagnosed by fetal and neonatal echocardiography and died suddenly at the age of 5 months.

Examination revealed no arrhythmias, murmurs, or heart failure. An electrocardiogram and chest radiograph were normal. Subependymal nodules were seen in the computed tomography (CT) scan. Echocardiographic examination revealed a mobile mass of $1.4 \times 1$ cm in the RVOT (Figure 1). In view of the positive family history of tuberous sclerosis and supportive neurological findings in the CT scan, the tumor was presumed to be a rhabdomyoma. There was no evidence of valvular damage, ventricular dysfunction, or RVOT obstruction. Since there was no indication for surgical intervention, the child was followed up. At 6 and 9 months, the child was stable, and the repeat echocardiogram after 9 months revealed a mild reduction in tumor size ($1.3 \times 0.9$ cm).

CASE 2
A 48-year-old woman without significant previous medical illness presented with vague discomfort in the chest of 2 months’ duration. A transthoracic echocardiogram revealed a 2.9 cm globular mass in the RVOT attached to the anterior free wall, with limited mobility (Figure 2). Valves and cardiac chambers were normal without any evidence of RVOT obstruction on Doppler interrogation. Spotty calcific deposits were noted within the tumor. The tumor was surgically removed, and the histologic examination was consistent with myxoma (Figure 3). The patient recovered uneventfully.

DISCUSSION
The two case reports demonstrate two common cardiac tumors in children and adults, respectively, but situated in relatively uncommon locations in the heart. The reports also show the utility of transthoracic echocardiography, a widely available, simple, noninvasive tool that aids in the bedside diagnosis, management, and follow up of cardiac tumors.

Cardiac rhabdomyoma, the most common primary tumor of the heart in the pediatric population, accounts for over...
60% of all primary cardiac tumors (1) and is usually detected before birth or during the first year of life. Most of these tumors spontaneously regress without clinical consequence. About 50% of patients with tuberous sclerosis develop a cardiac rhabdomyoma. Similarly, approximately 65% of children diagnosed with cardiac rhabdomyomas demonstrate clinical or radiologic evidence of tuberous sclerosis or have a positive family history of it (2).

Myxomas, the most common primary heart tumors, occur in the atria with a ventricular location in only 5% of cases. They are usually asymptomatic but may be characterized by a triad including constitutional symptoms or symptoms related to valvular obstruction or embolic events. Once a presumptive diagnosis of myxoma has been made on imaging studies, prompt resection is required.

Figure 2. The echocardiogram in case 2. (a) A parasternal long-axis view and (b) a modified apical four-chamber view showing the globular mass in the right ventricular outflow tract attached to the anterior free wall. Spotty calcific deposits may be noted within the tumor.

Figure 3. Case 2. (a) The right ventricular outflow tract tumor at the time of surgery showing an irregular mass with myxoid and gelatinous surface. (b) Histopathology demonstrating myxoid stroma with stellate cells typical of myxoma.

Acute pulmonary embolism masquerading as acute myocardial infarction

Abhijit Ghatak, MD, Ali Alsulaimi, MD, Yvan Maque Acosta, MD, and Alexander Ferreira, MD

Pulmonary embolism (PE) can be extremely difficult to diagnose based on clinical presentation. An electrocardiogram (ECG) is commonly used to evaluate patients with suspected pulmonary embolism. Many studies have demonstrated certain ECG patterns commonly seen in PE, but few have described changes consistent with ST segment elevation myocardial infarction (STEMI).

CASE REPORT

A 63-year-old man was brought to the emergency department in cardiac arrest. He had a history of systemic hypertension, hyperlipidemia, and coronary artery disease, with percutaneous coronary intervention and a stent to his left anterior descending coronary artery placed 3 years earlier. The patient complained of dizziness and dyspnea prior to his syncope. Emergency services found him in pulseless electrical activity and initiated successful cardiopulmonary resuscitation, and the patient was subsequently intubated. His initial blood pressure was 70/40 mm Hg, heart rate 68 beats/min, and pulse oximetry 80% on 100% oxygen via endotracheal tube.

The initial 12-lead ECG done in the emergency department showed anteroseptal ST segment elevation (Figure 1). Based on his clinical presentation and ECG findings, the patient was taken for an emergent cardiac catheterization. He was hemodynamically supported by norepinephrine and an intra-aortic balloon pump. His coronary angiogram showed nonobstructive epicardial coronary arteries and a patent left anterior descending artery stent.

A bedside echocardiography was performed emergently, and it revealed a dilated right ventricle and hyperdynamic left ventricle. These findings raised a suspicion of massive pulmonary embolism. Right-sided heart catheterization revealed a right ventricular pressure of 80/30 mm Hg, and a pulmonary angiogram disclosed massive filling defects suggesting bilateral pulmonary embolism (Figure 2). The patient was fully anticoagulated during the procedure with intravenous heparin with an activated clotting time of >500 sec. He was considered too unstable to be sent for a computed tomographic angiogram. Based on the massive clot burden, as diagnosed by the pulmonary angiogram, surgical intervention was considered to be most appropriate.

A pulmonary embolectomy was performed, and thromboembolic material was removed. During the surgical intervention, the patient was placed on an extracorporeal membrane oxygenator for cardiopulmonary support. Unfortunately, his condition deteriorated and he died the following day. Autopsy showed multiple residual emboli (Figure 3).

DISCUSSION

This case highlights the fact that pulmonary embolism still remains one of the biggest masqueraders in medicine. It has an estimated annual incidence of 600,000 and is believed to cause between 50,000 and 200,000 deaths annually (1).

The ECG changes associated with PE include sinus tachycardia (the most common abnormality), complete or incomplete right bundle branch block, a right ventricular strain pattern (T wave inversions in the right precordial leads [V1–4] ± the inferior leads [II, III, aVF]), a right axis deviation, or an SI QIII TIII pattern (a deep S wave in lead I, Q wave in III, and inverted T wave in III) (2). The presence of ST elevation is rare and usually suggests massive emboli.

There are a few suggested mechanisms for the presence of ST elevation in massive PE (3–5). The sudden elevation of right ventricular pressure and consequently increased right ventricular outflow obstruction results in right ventricular failure and dilatation.
inducing myocardial ischemia. These ST elevations could also be explained by a sudden increase in pressure on the right ventricle resulting in stretching of the myocardial cells leading to ischemia, and acute coronary vasospasm, resulting in ST elevation. The severe hypoxemia that accompanies massive PE induces a catecholamine surge and further increases myocardial workload, worsening the ischemia.


Invited Commentary

The masquerading pulmonary embolism: why a high index of suspicion remains even today

Pulmonary embolism (PE) remains a persistent entity of morbidity and mortality. Despite advances in treatment, diagnosis, and education, pulmonary embolisms can remain a challenge to diagnose. The Centers for Disease Control and Prevention reported that an estimated 300,000 to 600,000 people are affected each year in the United States by deep vein thrombosis (DVT)/PE, with 60,000 to 100,000 dying from DVT/PE (1, 2). Sudden death is the first symptom in about one-quarter of those who sustain a PE, and another 10% to 30% will die within 30 days of diagnosis (2). As such, early diagnosis and intervention is crucial. However, as reported by Dr. Ghatak et al (3), the presentation is not always straightforward, and there can be challenges in the diagnosis.

The initial features of cardiac arrest and the elevated 12-lead electrocardiographic findings were suggestive of a primary cardiac etiology in the patient’s presentation, which led to evaluation by cardiac catheterization. As his primary insult was a PE, his coronary arteries did not yield an answer, and further evaluation and diagnostic studies not typical of a PE evaluation were promoted. Unfortunately for the patient, the finding of PE was corroborated in a postmortem evaluation. This case serves as a reminder that disease processes even as common as PE may still have atypical presentations.

Despite multiple tools for assessing the probability of patients having a PE, such as the Wells Score for PE, PREP Score for PE, and Geneva Prognostic Score for PE, atypical presentations may hinder the clinician’s ability to proceed down the PE diagnostic pathway. Beyond tachypnea and dyspnea, there have been historical atypical presentations of PE such as hemoptysis, syncope, wheezing, and even abdominal pain (4). Relying on imperfect diagnostic studies to diagnose PE can further add to a clinician’s challenge. The patient in this case was too unstable for additional diagnostic evaluation, such as a computed tomographic angiogram. However, such imaging would not have guaranteed a diagnosis. Presently, hospitals rely on chest computed tomography for a diagnosis of PE, but there are estimates that 1 in 6 cases will be missed with this diagnostic modality (5). This particular method can have further reduced reliability, with discrepancies of up to 11% in initial interpretation (6).

This case illustrates the potential for misdiagnosis and mortality related to PE. In a study by Stein et al evaluating patients who died from PE, 70% (14 out of 20) were not suspected of having a PE (7). It is clear that challenges remain in diagnosing a prevalent entity such as PE which requires treatment to reduce the significant associated morbidity and mortality. Atypical presentations and imperfect diagnostic evaluations continue to produce missed diagnosis. The case presented serves as a great reminder that the index of suspicion should remain high and that nonconventional evaluations may still lead to the diagnosis.

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Cryoglobulinemic vasculitis is a small vessel vasculitis that has been associated with chronic infections and autoimmune, lymphoproliferative, and neoplastic disorders. When no significant etiological factors are identified, it is called essential mixed cryoglobulinemia. A detailed and thorough laboratory investigation is required to exclude all possible causes of cryoglobulin formation. Although cryoglobulin testing is simple, careful temperature regulation is needed to avoid false-negative results. Consensus diagnosis should be developed and implemented for appropriate cryoglobulin detection and accurate clinical diagnosis for cryoglobulinemic vasculitis. Here we present an interesting, first-ever case report of a 54-year-old Hispanic-American woman with essential mixed cryoglobulinemia presenting with significant digital necrosis in association with membranous nephropathy.

**CASE PRESENTATION**

A 54-year-old Hispanic-American female architect presented to our institution with the chief complaint of pain at the distal tip of her right little finger. Her symptoms started 6 weeks prior to presentation, getting progressively worse over the previous 4 days. Her past medical history was significant for systemic hypertension, diabetes mellitus, primary hypothyroidism, and chronic kidney disease with histopathological confirmation of MN 8 weeks prior to her admission. She received initial immunosuppressive treatment with prednisone, cyclophosphamide, and mycophenolate mofetil for MN; however, cyclophosphamide was discontinued after 3 weeks, as she had an episode of rectal bleeding and complaint of finger pain and numbness. Her review of systems was significant for a 20 kg unintentional weight loss, generalized fatigue, weakness, and arthralgias of both hands.

On physical examination, the patient was pale and had dry gangrene at the tip of her right little finger and black discoloration at the tip of the left index finger. Also noted was the purplish discoloration at the distal phalanx of both hands (Figure 1). Allen’s maneuver was normal in both hands, and her radial and ulnar pulses were palpable bilaterally. Blood pressure measurements were similar in both arms, and ultrasonographic Doppler revealed patent vessels from the subclavian to the radial and ulnar arteries. The erythrocyte sedimentation rate, C-reactive protein, serum creatinine, and blood urea nitrogen were elevated with a decreased glomerular filtration rate (GFR). She was mildly anemic with significant proteinuria. Hepatitis serologies, serum cryoglobulins, an HIV screen, and a hypercoagulable workup were negative. An extensive workup for systemic vasculitis was negative, including antinuclear antibody, double-stranded DNA, serum complement, rheumatoid factor, anticardiolipin, anti SS-A and SS-B, anticentromere, anti-Scl-70, anti-C3, and anti-myeloperoxidase antibodies (Table 1).
A punch biopsy with immunofluorescence of the necrotic lesion in the right little finger was performed and revealed granular IgM, C3, IgG, C5b-9, and fibrinogen depositions in and around superficial and middermal small blood vessels, supporting the diagnosis of CV type II (Figure 2). A workup to rule out infection and malignancy was negative and included a transesophageal echocardiogram, chest x-ray, computed tomography of abdomen and pelvis, mammogram, colonoscopy, and endovaginal ultrasonography.

Her hospital treatment included prednisone, mycophenolate mofetil, aspirin, and low-molecular-weight heparin. When the biopsy results suggested CV, the heparin was discontinued. Symptomatic and clinical improvement were achieved, kidney function predominantly normalized, and the patient was discharged home. On follow-up, she developed a purpuric rash over the upper back, which resolved over a 2-week period; her serum creatinine and GFR normalized; and the black discoloration in her left index finger resolved.

**DISCUSSION**

CV is classified into three serological categories. Type I is composed of a monoclonal immunoglobulin that is always linked to a B-cell lymphoproliferative disorder such as Waldenström's macroglobulinemia or multiple myeloma. Type II or mixed CV contains a mixture of polyclonal IgG and monoclonal IgM with rheumatoid factor activity. Type III comprises polyclonal IgM and IgG with rheumatoid factor activity as well (3, 6). Types II and III most often produce constitutional symptoms, as well as palpable purpura with cutaneous vasculitis; the female-to-male ratio is often reported as 2–3:1, with waxing and waning of clinical features and spontaneous remissions and

<table>
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<th>Result</th>
<th>Test</th>
<th>Result</th>
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</tr>
<tr>
<td>Anti-dsDNA</td>
<td>Negative</td>
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Ab indicates antibody; ANA, antinuclear antibody; anti-dsDNA, anti-double-stranded DNA antibody; cANCA, cytoplasmic antineutrophil cytoplasmic antibody; BUN, blood urea nitrogen; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GFR, glomerular filtration rate; Ig, immunoglobulin; pANCA, perinuclear antineutrophil cytoplasmic antibodies; RNP, ribonucleoprotein.
exacerbations (3). CV can be classified as “essential” in the absence of other well-defined infectious disorders (e.g., hepatitis C virus [HCV], which accounts for approximately 80% of all cases of CV), immunological disorders, or neoplastic disorders (2, 6). Two pathophysiological mechanisms are mainly involved in the development of various degrees of CV: 1) cryoglobulin precipitation in the microcirculation, causing vascular occlusion, and 2) immune complex–mediated deposition within blood vessels, causing subsequent systemic vasculitis (1, 2).

The so-called “essential” mixed CV is characterized by a clinical triad (Meltzer’s triad): purpura, weakness, and arthralgias with multisystem organ involvement, representing nearly 10% of all CV, a percentage that rises to 25% in HCV-negative patients (2, 5, 6). According to Stone, non-HCV and rheumatoid factor–negative CV is a rare finding (7). Unfortunately, there are no validated classification/diagnostic criteria for CV. A patient series involving 231 patients from Italy proposed preliminary criteria for CV based on clinical, serological, and pathological features (8). In this series, the female-to-male ratio was 3:1, Meltzer’s triad was present in almost 80%, palpable purpura was present in 98%, and Raynaud’s phenomenon was present in 36%, with renal involvement present in 20%; however, 30% developed renal complications over time (8). A more recent European-based diagnostic/classification criteria for CV has been studied based on questionnaire, clinical findings, and laboratory criteria. In HCV-negative patients, the sensitivity and specificity of the classification were 89.5% and 90.3%, respectively (9).

Since the diagnosis of CV requires the presence of cryoglobulins in serum, appropriate sample collection and handling is crucial. Blood should be collected in prewarmed syringes and tubes, transported, clotted, and centrifuged at 37 °C, ensuring that the temperature never falls below 37 °C (10). A negative test for cryoglobulins does not exclude the diagnosis of CV, because of the possibility of false-negative results due to improper collection and handling of laboratory samples or inconsistent laboratory techniques (11).

Renal involvement in non-HCV–related CV patients has been poorly described. Matignon et al (12) retrospectively studied kidney biopsies in 20 patients, with 10 classified as idiopathic or “essential” CV. The most common clinical presentation was nephrotic-range proteinuria (85%), microscopic hematuria (100%), and renal failure (85%). Interestingly, 100% exhibited membranoproliferative glomerulonephritis, with immunofluorescence demonstrating subendothelial and intraglomerular deposits of IgG, IgM, and C3. A review article by Sethi and Fervenza examined the conditions associated with membranoproliferative glomerulonephritis in which hepatitis C or E with or without cryoglobulinemia was an important cause (13). Our case represents the first report of non-HCV–related CV in the setting of MN.

A 55-year-old powerlifter in Tennessee learned about the sport-specific, high-intensity cardiac rehabilitation training available in Dallas, Texas, and contacted the staff by phone. He was recovering from quadruple coronary artery bypass grafting (CABG) and had completed several weeks of traditional cardiac rehabilitation in his hometown, but the exercise program no longer met his needs. He wanted help in returning both to his normal training regimen and to powerlifting competition but was unable to attend the Dallas program in person. An exercise physiologist with the program devised a virtual coaching model in which the patient was sent a wrist blood pressure cuff for self-monitoring and was advised about exercises that would not harm his healing sternum, even as the weight loads were gradually increased. After 17 weeks of symptom-limited, high-intensity training that was complemented by phone and e-mail support, the patient was lifting heavier loads than he had before CABG. At a powerlifting competition 10 months after CABG, he placed first in his age group. This case report exemplifies the need for alternative approaches to the delivery of cardiac rehabilitation services.

Patients recovering from coronary artery bypass grafting (CABG) are routinely given weight and activity restrictions to protect the sternum. Instead of cautioning these patients about what they cannot do, the cardiac rehabilitation (CR) program at Baylor Heart and Vascular Hospital in Dallas, Texas, teaches them to modify their desired movements and activities in a way that minimizes shoulder joint abduction, extension, and flexion. We present the case of a powerlifter who, with long-distance coaching by the Dallas CR staff, returned to his sport after CABG.

CASE PRESENTATION

A 55-year-old man presented with unstable angina pectoris at an emergency department in Memphis, Tennessee, in June 2013. Cardiac catheterization revealed severe three-vessel coronary artery disease with well-preserved left ventricular function, and the patient underwent quadruple CABG. He had always been physically active, was not diabetic, and did not smoke. His body mass index was 33.4 kg/m², and his waist circumference was 38 inches. Medications included amlodipine besylate, modafinil, clonazepam, and testosterone cypionate. His father had a myocardial infarction at age 55 and was found to have an aortic arch aneurysm at that time.

Before CABG, the patient exercised 10 to 12 times per week, including four sessions per week of resistance training appropriate for powerlifting—a sport that consists of three events: squat, bench press, and deadlift. At 3 weeks post-CABG he began attending CR sessions, spending 10 minutes each on a treadmill, recumbent bike, and upper body ergometer, followed by weightlifting that was restricted to 2-pound dumbbells. After completing 10 CR sessions at the hospital, he chose to continue the regimen on his own, using heavier dumbbells that were within the 10-pound weight restriction imposed by his surgeon. He also began researching how to sensibly return to his normal exercise program and especially how to resume powerlifting.

An Internet search on the phrase “recovery from CABG powerlifting” eventually led the patient to a Wall Street Journal article about the Dallas CR program for “industrial athletes,” which allows patients to use specificity of training to achieve their goals (1). He called the department and told the exercise physiologist that he wanted to lift heavy weights again and perform at powerlifting competitions (the next of which would occur 44 weeks post-CABG). The patient’s location and work schedule made it impossible for him to attend the Dallas program in person, so the exercise physiologist proposed a virtual coaching model: a sport-specific, symptom-limited exercise program with long-distance support that would enable the patient to train at a higher intensity than is typically allowed in traditional CR.

From the Cardiac Rehabilitation Department, Baylor Jack and Jane Hamilton Heart and Vascular Hospital (R. Adams, J. Adams, Bilbrey, Schussler); the Quantitative Science Department, Baylor Scott & White Health (Qin); and the Division of Cardiology, Department of Internal Medicine, Baylor University Medical Center at Dallas and Baylor Heart and Vascular Hospital, and the Texas A&M Health Science Center, College of Medicine (Schussler). Grant support was provided by the Harry S. Moss Heart Trust and the Baylor Health Care System Foundation, Dallas, Texas, through the Cardiovascular Research Review Committee and in cooperation with the Baylor Heart and Vascular Institute. The authors thank the committee for their continued support of cardiovascular rehabilitation research projects.

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The patient was sent a wrist blood pressure cuff for heart rate and blood pressure monitoring and was advised to keep his rate-pressure product (heart rate multiplied by systolic blood pressure) below 36,000 (2). He was also taught about exercises that would not negatively affect the sternum. Through e-mail, he was sent the Athletic Identity Measurement Scale–Plus (3, 4); his score of 1660 confirmed the importance of powerlifting in his life, as high scores for athletic identity range from 1467 to 2200.

The patient and the Dallas CR staff kept in touch by e-mail and phone; together they developed a powerlifting exercise regimen that he did from week 11 post-CABG (when he was cleared to lift >10 pounds) to week 27 (after which, he had been told, his sternum would be completely healed). The core of this training program consisted of exercises that were similar to powerlifting exercises but safer for a healing sternum. Safety bar squats were substituted for low-bar back squats; overhead presses, which had always been part of his training, were substituted for bench presses; and glute-ham raises were substituted for deadlifts. The patient performed 41 workouts over the 17-week period, and the weight loads were increased incrementally. By week 26 post-CABG, he had returned to his pre-CABG exercise loads.

Training was symptom limited, meaning that no specific blood pressure or heart rate limits were used to restrict exercise intensity. The patient monitored himself for elevated rate-pressure product (≥36,000), angina, dizziness, pain, and shortness of breath. He had no adverse events that required him to discontinue any powerlifting exercise session.

Peak heart rate and blood pressure were successfully recorded a total of 35 times during the virtual coaching period, and the resulting rate-pressure product values were calculated. Because the wrist cuff instructions recommend use of the device with the wrist at chest level, the measurements taken during the overhead press were deemed inaccurate, so those calculations are not reported here. The rate-pressure product values that were calculated for the other two exercises were well below the threshold of 36,000. During the glute-ham raises, the maximum rate-pressure product was 28,566; the mean peak value was 20,369 (SD, 3723). During the safety bar squats, the maximum was 29,328 and the mean peak value was 23,231 (SD, 3782).

**DISCUSSION**

In weight training, the amount of work done is expressed as volume and can be calculated as the number of repetitions multiplied by the amount of weight lifted. Figure 1 tracks the patient’s average volume per workout for the overhead press during four periods: normal (pre-CABG) training, immediate post-CABG recovery, virtual coaching, and resumption of his normal regimen. CABG indicates coronary artery bypass grafting; CR, cardiac rehabilitation.

![Figure 1](image-url). The patient's average overhead press volume per workout during (left to right) his normal training regimen (5/3/1, a rotating program of four main lifts that vary in intensity over a 3- to 4-week cycle [reference 5]); his immediate post-CABG recovery period, which included a traditional CR regimen; virtual coaching; and resumption of his normal regimen. CABG indicates coronary artery bypass grafting; CR, cardiac rehabilitation.
virtual CR program in Dallas for patients who are self-motivated and disciplined about reaching their fitness goals.

Acknowledgments

Thanks go to David Allen at NBS Fitness in Cordova, Tennessee, for supporting the patient in his powerlifting training following CABG, and to Jim Wendler, whose encouragement and suggestions guided the patient in his search for an appropriate CR program. Beverly Peters, MA, ELS, a freelance medical editor, assisted with manuscript development and preparation.

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Reverse takotsubo cardiomyopathy with use of male enhancers

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Reverse takotsubo cardiomyopathy is a rare heart failure condition characterized by systolic dysfunction of the basal segments of the left ventricle in the absence of obstructive coronary artery disease. We present a case of a 54-year-old man with an overdose of Extenze (a male enhancer pill containing yohimbine) who was hospitalized with heart failure due to reverse takotsubo cardiomyopathy.

The pathogenesis of reverse takotsubo cardiomyopathy is not well understood, but physical or mental stress is frequently an associated trigger. Less commonly reported, sympathomimetic states have been linked to this disease entity. Reverse takotsubo cardiomyopathy has been reported in cases of hyperadrenergic states secondary to pheochromocytomas, catecholamine-secreting tumors, administration of beta-receptor agonists, such as dobutamine, and consumption of caffeine and energy drinks. In this report, we describe a case of reverse takotsubo cardiomyopathy relating to an overdose of Extenze, a male enhancer pill containing yohimbine.

CASE PRESENTATION

A 54-year-old man was admitted to the intensive care unit after ingesting multiple pills of Tylenol and Extenze, a product that contains yohimbine. He complained of abdominal discomfort and mild dyspnea. He was anxious and had a heart rate of 110 beats/minute. The electrocardiogram showed sinus tachycardia, right bundle branch block, and ST segment depression in lead V3 (Figure 1). A radiograph showed pulmonary congestion (Figure 2). His initial troponin I level was 0.94 ng/L; 7 hours later, it was 13 ng/L. Three hours after admission, he became disoriented, hypotensive, and hypoxic and was intubated for respiratory distress due to heart failure. An echocardiogram showed left ventricular systolic dysfunction with basal hypokinesia but normal mid/distal anterior, inferior, and apical contraction (Figure 3). Coronary angiography was normal without any anatomical or functional abnormalities such as coronary spasm, myocardial bridging, or coronary artery disease (Figure 4). Since the patient had an echocardiogram showing reverse takotsubo cardiomyopathy with severely depressed LV systolic function on the same day prior to cardiac catheterization, no ventriculogram was performed. The patient was treated with vasopressors, diuretics, and invasive ventilatory support. After 72 hours, the patient was extubated and transferred to a regular floor. He recovered fully and was discharged after 1 week of hospitalization. Unfortunately, the patient did not follow up in the cardiology clinic; thus, no follow-up echocardiogram was performed.

DISCUSSION

Takotsubo cardiomyopathy is an increasingly reported syndrome characterized by transient systolic dysfunction of the apical and or mid segments of the left ventricle without the presence of coronary artery disease (1, 2). In contrast, reverse takotsubo cardiomyopathy is a condition with transient systolic dysfunction of the basal segments of the left ventricle. Although transient, reverse, or inverted takotsubo cardiomyopathy was recognized as a different clinical entity >20 years ago, a definite comprehensive pathophysiologic theory for this condition is still lacking (3). Seemingly, reverse takotsubo, which is more common in young female patients with a mean age of 36 years, is thought to be triggered by physical or emotional stress rather than catecholaminergic states. The presence of adrenoreceptors, which are at their apex in older patients, makes the occurrence of the apical variant of takotsubo cardiomyopathy more common among the older population, in contrast to the younger population, where the abundance of adrenoreceptors is within the base of the heart, which may lead to the reverse variant of takotsubo cardiomyopathy (4). There have been documented reports of reverse takotsubo in association with pheochromocytomas, intravenous administration of beta-receptor agonists (dobutamine) or catecholamines, as well as with the use of energy drinks containing caffeine and 1,3-dimethylamylamine (5).

The pathophysiology behind this condition relies on two primary theories: vascular dysfunction and catecholamine-induced toxicity. Multifocal vasospasm has been demonstrated from the Department of Internal Medicine (Rodriguez-Castro, Porres-Aguilar, Said), Division of Cardiovascular Diseases (Gough, Siddiqui, Mukherjee, Abbas), Texas Tech University Health Sciences Center, El Paso, Texas; and Jinnah Postgraduate Medical Center, Karachi, Pakistan (Saifuddin). Corresponding author: Carlos E. Rodriguez-Castro, MD, Department of Internal Medicine, Texas Tech University Health Science Center, 4800 Alberta Avenue, El Paso, TX 79905 (e-mail: ce.rodriguez@ttuhsc.edu).
in some patients undergoing angiography (6). Molecular studies have revealed that high doses of epinephrine are directly toxic to the cells, causing a rise in adenosine 3',5'-cyclic monophosphate and calcium levels that then trigger the formation of free oxygen radicals, the initiation of expression of stress response genes, and induction of apoptosis (7).

The yohimbine contained in the male enhancement formula Extenze is a competitive antagonist that is selective for alpha-2 receptors located in the central nervous system, where it acts to increase blood pressure and heart rate. It has been well acknowledged that with relatively low doses it can produce side effects such as tachycardia, chest pain, hypertension, lacrimation, tremors, and diaphoresis (8, 9). In addition, yohimbine-containing products have been implicated in cases of hypertension emergencies, severe Raynaud’s phenomenon, angina pectoris, refractory priapism, and even death (10–14). Currently, the association of reverse takotsubo cardiomyopathy and yohimbine is not known. Nonetheless, we think that, given the mechanism of action of yohimbine as a sympathomimetic drug acting on

Figure 1. Supraventricular tachycardia with incomplete right bundle branch block and nonspecific ST wave abnormalities.

Figure 2. Chest x-ray showing pulmonary vascular congestion.

Figure 3. An apical four-chamber view showing severe hypokinesis of the basal/mid inferoseptal segment and anterolateral segment of the left ventricle. The apical segment of the left ventricle has normal contractility.
Figure 4. Anteroposterior cranial views of the (a) right coronary artery and (b) left coronary arteries show no evidence of any significant coronary artery disease.

the alpha-2 adrenergic receptors, overdose potentially influenced the development of reverse takotsubo cardiomyopathy similar to cases related to pheochromocytomas and administration of dobutamine.


4. Ramaraj R, Movahed MR. Reverse or inverted takotsubo cardiomyopathy (reverse left ventricular apical ballooning syndrome) presents at a younger age compared with the mid or apical variant and is always associated with triggering stress. *Congest Heart Fail* 2010;16(6):284–286.


Consequence of patient substitution of nattokinase for warfarin after aortic valve replacement with a mechanical prosthesis

Maqsood M. Elahi, PhD, Charles H. Choi, BS, Subbareddy Konda, MD, and Jay G. Shake, MD

This report describes a patient's self-substitution of nattokinase for the vitamin K antagonist warfarin after aortic valve replacement with a mechanical prosthesis. Nattokinase is an enzyme derived from a popular fermented soybean preparation in Japan (natto), which has fibrinolytic properties and is gaining popularity in nontraditional health journals and nonmedical health websites as an over-the-counter thrombolytic. After nearly a year of use of nattokinase without warfarin, the patient developed thrombus on the mechanical valve and underwent successful repeat valve replacement. We believe this is the first documented case of nattokinase being used as a substitute for warfarin after valve replacement, and we strongly discourage its use for this purpose.

Oral anticoagulation with vitamin K antagonists such as warfarin has been the usual standard of care following mechanical cardiac valve replacement. The fear of increased bleeding risk while taking warfarin has prompted some patients to self-adjust their dosing of anticoagulation or to stop therapy completely. Another subset of patients has sought nontraditional medicines to decrease or replace conventional anticoagulation regimens. We describe a patient's self-substitution of nattokinase for warfarin following replacement of the aortic valve with a mechanical prosthesis.

CASE REPORT

A 53-year-old man was admitted to our hospital with dyspnea and mild chest pain. Three years earlier, his stenotic bicuspid aortic valve was replaced with a 25 mm St. Jude mechanical prosthesis. His perioperative course was uneventful, and he returned to work at his busy chiropractic practice. His extracurricular hobbies included strenuous physical activities such as distance running. Approximately 12 months prior to his current presentation, he discontinued his warfarin and began to supplement his diet with 100 mg of nattokinase per day, a dose recommended by an alternative health journal for thrombolysis. The patient first noticed a change in his health about 6 weeks prior to seeking medical attention when he started to get more dyspneic when running. The dyspnea was reproducible when walking 2 blocks and further progressed to dyspnea at rest.

On examination, he did not appear in distress. His lungs were clear to auscultation, and precordial exam revealed a soft, mechanical S2, a 2/6-crescendo/decrescendo systolic murmur and an early diastolic murmur. Two-dimensional transthoracic echocardiogram disclosed at least moderate aortic regurgitation. Transesophageal echocardiogram suggested mechanical disc restriction with both aortic insufficiency and stenosis. Fluoroscopic evaluation of the mechanical prosthesis showed severe restriction of disc mobility. At reoperation, extensive fibrin and thrombus accumulation was present on both the aortic and ventricular sides of both discs. The clotted valve was removed and replaced with a 23 mm Carbomedics Top Hat valve. His postoperative course was uncomplicated. Prior to surgery the patient had agreed to continue using warfarin alone as his oral anticoagulant.

DISCUSSION

Natto is a traditional Japanese food derived from boiling or steaming soybeans and fermenting them with the bacteria Bacillus subtilis. It became a part of the Japanese culture late in the Edo period (1600–1868), particularly in the eastern Kanto region of Japan. During this time, the soybeans were packed in straw and buried underground for a week or more, coming into contact with the naturally occurring bacillus found in the straw. This combination resulted in soybean fermentation.

Natto is available in Japan but is difficult to find in most other countries. In 1987, Sumi et al found that natto contains a potent fibrinolytic enzyme that they coined nattokinase (1), and an oral form is now available to consumers worldwide as a supplement without a physician's prescription. This 275 amino acid has similar sequences to other natural endogenous enzymes. Sumi et al claimed that it closely resembles plasmin and strongly hydrolyzes fibrin. It is also suggested that nattokinase has been the most potent fibrinolytic enzyme among 200 foods investigated for oral fibrinolytic therapy (2). Subsequently, there has been some preliminary evidence of thrombolysis in rats...
and evidence of complete dissolution of arterial thrombi within 5 hours of oral administration of nattokinase in dogs (5). However, the authors of this case report have found limited data on the anticoagulation properties of natto and nattokinase in human subjects (6–8). Thrombin activity has been found to be increased following thrombolysis, which in turn may have paradoxically increased our patient’s risk of valve thrombosis (9, 10). Further studies of nattokinase, recently conducted by Yongjun et al, have given promising insight into the development of mutant strains with improved catalytic efficiency by shuffling DNA from homologous genes of Bacillus species (11). No viable alternatives to warfarin have been found for mechanical heart valves. As a matter of fact, the direct thrombin inhibitor dabigatran was found to be unacceptable and the trial stopped early in favor of warfarin.

A 65-year-old woman with a history of high blood pressure, diabetes mellitus, hyperlipidemia, chronic kidney disease, and stroke went to a walk-in clinic complaining of intermittent neck, left shoulder, and arm pain for several days. After being diagnosed with pneumonia and started on antibiotics, the patient went home. The pain became worse and constant 2 days later, and several hours thereafter her family found her disoriented and diaphoretic. An electrocardiogram on hospital admission showed atrial fibrillation, complete atrioventricular block, and a regular junctional escape rhythm at a rate of 37 beats/min (Figure). QRS, ST, and T changes indicated acute inferoposterolateral myocardial infarction, and the QT interval was long (604 msec; QTc 562).

A survey of 11 studies of the culprit lesion sites in acute inferior myocardial infarction found right coronary artery to left circumflex coronary artery ratios that ranged from 2.2:1 to 7.0:1 with a mean of 4:1 (1). Furthermore, the artery to the AV node is a branch of the right 90% of the time and of the left circumflex only 10% of the time. Thus, there are good reasons for suspecting the right coronary artery as the culprit. Two findings, however, are common in left circumflex occlusions, but uncommon in right occlusions: ST depression in both leads V1 and V2 and ST depression ≥0.1 mV (1 mm) in lead aVR (1).

Coronary arteriography, the ultimate clinical arbiter, demonstrated atherothrombotic occlusion in the middle portion of a dominant left circumflex coronary artery. This was treated with a bare metal stent, and a temporary transvenous electronic ventricular pacemaker increased the rate to 90 beats/min.

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60 beats/min. Serum troponin I peaked at 75 ng/mL; reference, <0.04 ng/mL. Unfortunately, although atrioventricular block decreased to second and then first degree over 2 days, the patient remained poorly responsive for 6 days, suffered transient kidney failure requiring hemodialysis, and had acute respiratory distress syndrome requiring endotracheal ventilation for 12 days. The prolonged intubation caused dysphagia necessitating total parenteral nutrition via a percutaneous indwelling central catheter. Thrombocytopenia, seemingly induced by eptifibatide, abated after the drug was stopped. After 4 weeks of hospitalization, the patient was well enough to be transferred to an inpatient rehabilitation facility.

The electrocardiographic lesson is that because a dominant left circumflex coronary artery supplies not only the usual distribution of the left circumflex, but also most of the usual distribution of the right, occlusion of a dominant circumflex usually causes a large infarct that has electrocardiographic features of both circumflex and right occlusions. The more important lesson is that failure to recognize an impending myocardial infarction often results in a clinical catastrophe.


Reader comments

Dear Dr. Guileyardo:

With great interest, I read your “conversation with the editor” in the October 2014 issue of Baylor University Medical Center Proceedings. I was very impressed by your story, which describes your lively life and dedicated spirit. The article not only reflects the profile of yourself (i.e., versatility) and your family members (i.e., wrong birthday of your father), but also highlights your remarkable contribution to autopsy pathology. It is because of your effort that more autopsy cases are done at Baylor than at any other hospital in Dallas. Nowadays, it has become more and more difficult to get autopsies performed all around the world. Some hospital pathologists prefer histopathology to autopsy. Your outstanding academic achievement should receive awards. We want to read more of your scientific articles.

—Jun Zhang, MD, MS
Former FDA Pathologist
Volunteer at Baylor University Medical Center at Dallas
Anterior spinal cord syndrome of unknown etiology

Merrine Klakeel, DO, Justin Thompson, MD, Rajashree Srinivasan, MD, and Frank McDonald, MD

A spinal cord injury encompasses a physical insult to the spinal cord. In the case of anterior spinal cord syndrome, the insult is a vascular lesion at the anterior spinal artery. We present the cases of two 13-year-old boys with anterior spinal cord syndrome, along with a review of the anatomy and vasculature of the spinal cord and an explanation of how a lesion in the cord corresponds to anterior spinal cord syndrome.

Anterior spinal cord syndrome (ACS) is a lesion affecting the anterior two-thirds of the spinal cord with loss of motor control below the lesion with intact crude sensation (1, 2). A true ACS results from a vascular lesion at the anterior spinal artery (ASA) resulting in ischemic injury to the respective area of the spinal cord. Patients present with complete motor defects below the lesion, along with sensory defects affecting pain and temperature sensation. The intensity of the sensory deficits depends on the level of involvement in the spinal cord. Herein we present the cases of ACS in two 13-year-old boys.

CASE 1

At the end of a class period, a 13-year-old boy was unable to get up from his chair. He was taken to the community hospital and found to have bilateral lower-extremity paralysis, without any signs or symptoms of infection. Computed tomography of the head and laboratory results were within normal limits, and he was transferred to a tertiary care pediatric hospital. Examination demonstrated absent deep tendon reflexes and 0/5 muscle strength in his bilateral lower extremities with a sensory level of T8. He had intact proprioception and vibration, with absent pain and temperature sensation. Diagnostic studies, including hematological workups and blood and spinal fluid cultures, were all negative except for elevated Factor VIII, Protein S, and Protein C, which was attributed to an acute inflammatory reaction. Magnetic resonance imaging (MRI) of the spine showed increased T2 signal intensity in the anterior aspect of the spinal cord from approximately the T5 to T6 level through the mid-T8 level (Figure 1). The patient was treated with a tapering schedule of high-dose corticosteroids. Upon stabilization, he was transferred to a pediatric specialty hospital for further rehabilitation and training.

On admission, he had 0/5 muscle strength and absent deep tendon reflexes in his lower extremities. His sensation to light touch and pinprick was altered below T5 with an absence of sensation around the perianal region. On the American Spinal Injury Association Impairment Scale (AIS), he was diagnosed as T5 grade C.

Over the course of his rehabilitation stay, the patient regained full control of his bladder function along with some lower-extremity muscle strength and was ambulating with moderate to maximum assistance with a walker. His sensation to light touch and pinprick remained abnormal with inconsistent sensation to...
oids with no return of function and then was admitted to a pediatric specialty hospital for rehabilitation therapy. During his inpatient rehabilitation stay, he continued to lose sensation to light touch. The follow-up MRI of the spine was consistent with myelomalacia (Figure 3), prompting transfer back to acute care for further management. He was treated with five sessions of plasmapheresis with no improvement of symptoms and with negative workup. The patient then returned to a pediatric specialty hospital for completion of therapy, at which point he was diagnosed as T11 AIS A. He failed to make any improvements in his motor or sensory function for his remaining rehabilitation stay.

The patient and his family received education about his new diagnosis and any associated complications. The family was trained in management of neuropathic pain and neurogenic skin, bowel, and bladder. He was discharged home at the maximum assist level for all activities of daily living. He received appropriate adaptive equipment and had outpatient follow-up scheduled.

**DISCUSSION**

The spinal cord is an extension of the brain that extends down to L1–L2. It is composed of motor neurons, interneurons, and axons traveling the whole length of the spinal cord. Fasciculus gracilis and fasciculus cuneatus, located in the posterior aspect of the cord, carry sensory information regarding light touch and vibration. The spinothalamic and spinocerebellar tract located in the anterolateral aspect of the spinal cord carry information regarding pain, temperature, and proprioception from the extremities to the brain. The corticospinal and corticobulbar tract located on the anteromedial portion of

**CASE 2**

A 13-year-old healthy boy heard a “pop” in his lower back while doing a “burpee” in his physical education class. He immediately felt pain in his back with tingling and shaking in his legs. While walking to the nurse's office after the class, the patient fell and was unable to get up. He experienced loss of sensation below his waist, an inability to move his legs, and excruciating back pain. Examination in the emergency room revealed paraplegia with intact sensation and strength in both his arms and showed signs of bladder retention. Acute hematological and viral workups were negative. MRI of the spine was suggestive of an ischemic or demyelinating process with no imaging findings of arterial venous malformation or dural arteriovenous fistula on diffusion-weighted imaging (Figure 2). The patient was treated with 5 days of intravenous corticosteroids with no return of function and then was admitted to a pediatric specialty hospital for rehabilitation therapy. During his inpatient rehabilitation stay, he continued to lose sensation to light touch. The follow-up MRI of the spine was consistent with myelomalacia (Figure 3), prompting transfer back to acute care for further management. He was treated with five sessions of plasmapheresis with no improvement of symptoms and with negative workup. The patient then returned to a pediatric specialty hospital for completion of therapy, at which point he was diagnosed as T11 AIS A. He failed to make any improvements in his motor or sensory function for his remaining rehabilitation stay.

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Figure 2. MRI in case 2. (a) An axial image shows an increased T2 signal and edema in the cord at T8. (b) A sagittal image shows increased signal running caudally from T6 to T11.
the spinal cord carry motor information from the brain to the extremities (3).

Blood supply to the spinal cord is provided by one ASA and two posterior spinal arteries, all three of which originate from the vertebral arteries. The posterior spinal arteries occasionally originate from the posterior inferior cerebellar artery. The spinal arteries are supplemented by medullary arteries from the vertebral artery in the cervical region and from intercostal arteries in the thoracic and lumbar region. The artery of Adamkiewicz is a major artery that feeds the spinal arteries in the lower half of the spinal cord and joins the anterior spinal artery at T5. The ASA provides blood supply to the anterior two-thirds of the spinal cord, while the two posterior spinal arteries provide blood supply to the posterior one-third of the spinal cord (3, 4).

ACS results from a loss of blood supply to the anterior two-thirds of the spinal cord, due to a thrombotic or embolic cause affecting the ASA (5, 6). Most of the reported cases are secondary to postoperative complications in adults, such as the repair of an abdominal aortic aneurysm (5), and the patient presents with a complete loss of motor function below the level of injury with altered or no loss in sensation (4).

Depending on the level of injury, the patient is at risk for autonomic dysreflexia, sexual dysfunction, neuropathic pain, gait impairment, and neurogenic bowel, bladder, and skin. The corticospinal and corticobulbar tracts are supplied by the ASA and are affected in ACS. The spinothalamic and spinocerebellar tract can be referred to as the watershed area because of dual vascular supply and location (1, 5). The sensation is altered depending on the level of involvement at the watershed area. In ACS, sensation to light touch is intact since the blood supply to fasciculus gracilis and cuneatus is from the posterior spinal artery.

Successful long-term management of spinal cord injury after the initial hospital stay is dependent upon effective and comprehensive rehabilitation of the patients prior to discharge home. Patients require intensive physical therapy, occupational therapy, and psychological support under the supervision of a health care professional trained in caring for patients with spinal cord injuries. Patients and families should be educated on their new diagnosis and associated complications. Patients need to be evaluated for medical equipment to help with mobility and activities of daily living depending on their level of injury. Social work assistance helps address any challenges concerning patient and family that impact discharge goals. Patients and families need to be trained in caring for and assisting with patient needs. A home visit by a trained therapist will be beneficial in identifying the home modifications needed based on the patient's level of injury. The recommended home modifications should ideally be completed prior to discharge. Furthermore, the patient and family should be provided information about local support groups for community integration. Finally, patients will require long-term physiatric care for the management of spasticity, neuropathic pain, mobility impairment, and neurogenic skin, bowel, and bladder.

Our patients were initially evaluated for transverse myelitis and were eventually diagnosed with ACS due to a lack of serological and imaging studies. We propose considering a spinal cord angiogram or magnetic resonance angiography of the spinal cord in patients presenting with motor and sensory symptoms to evaluate for a true ischemic insult.

Vertebral artery dissection after a chiropractor neck manipulation

Jeremy Jones, MD, Catherine Jones, MD, and Kenneth Nugent, MD

The differential diagnosis for ischemic central nervous system infarcts in young patients includes paradoxical emboli through cardiac shunts, vasculitis, and vascular trauma. We report a young woman who developed headache, vomiting, diplopia, dizziness, and ataxia following neck manipulation by her chiropractor. A computed tomography scan of the head revealed an infarct in the inferior half of the left cerebellar hemisphere and compression of the fourth ventricle causing moderate acute obstructive hydrocephalus. Magnetic resonance angiography revealed severe narrowing and low flow in the intracranial segment of the left distal vertebral artery. The patient was treated with mannitol and a ventriculostomy and had an excellent functional recovery. This report illustrates the potential hazards associated with neck trauma, including chiropractic manipulation. The vertebral arteries are at risk for aneurysm formation and/or dissection, which can cause acute stroke.

Young patients may develop central nervous system infarcts following cardioembolic events, paradoxical emboli through intracardiac shunts, vasculitis, and vascular trauma in the neck. We describe a patient who developed posterior circulation symptoms following chiropractic manipulation of her neck. This case illustrates the hazards associated with neck manipulation and the potential for good outcomes in these patients if they develop a stroke syndrome.

CASE DESCRIPTION

A 38-year-old female schoolteacher with no significant past medical history presented with headache, nausea, vomiting, blurred vision, diplopia, dizziness, and ataxia for 2 to 3 weeks. These symptoms started after a visit to her chiropractor and neck manipulation. Her symptoms were further exacerbated by hanging decorations from the ceiling at work. Her level of consciousness gradually decreased over the same time period. She was not taking any medications on admission and denied allergies and use of tobacco, alcohol, or illicit drugs. She was married and had two children. On examination, she was drowsy but aroused with sternal rubs. Her temperature was 97.6°F; heart rate, 71 beats per minute; blood pressure, 144/92 mm Hg; and respiratory rate, 18 breaths per minute. She was disoriented and followed simple commands poorly. She demonstrated nystagmus to the left. She moved all extremities but had left-sided weakness (3/5) with hyperreflexia. Cardiac, respiratory, and abdominal examinations were within normal limits. Her white blood cell count was 13 k/µL; hemoglobin, 13.7 g/dL; and platelets, 286 k/µL. Renal and liver function tests, electrolytes, and coagulation times were within normal limits.

A computed tomography (CT) scan of her head performed on admission showed a non–contrast-enhancing process involving the inferior half of the left cerebellar hemisphere (Figure 1a). There was extensive mass effect with displacement, distortion, and compression of the fourth ventricle causing moderate acute obstructive hydrocephalus and displacement of the cerebellar vermis to the right. There was mild cerebellar tonsillar herniation. No hemorrhage was present. Magnetic resonance imaging (MRI) on day 2 showed an acute left cerebellar infarct involving the posterior inferior cerebellar artery and the anterior inferior cerebellar artery territories with hydrocephalus and pneumoventricle (Figure 1b, 1c, 1d). Magnetic resonance angiography (MRA) performed on day 3 showed severe narrowing and low flow in the intracranial segment of the left distal vertebral artery near the basilar artery (Figure 1e). The right vertebral artery, basilar artery, bilateral anterior cerebral arteries, middle cerebral arteries, and posterior cerebral arteries were not narrowed.

On admission, a ventriculostomy was performed with shunt placement. The patient received mannitol for 7 days and gradually became more alert and responsive. The ventriculostomy catheter was removed on day 9. A follow-up CT of her head on day 10 showed a small amount of air in the ventricles but no intracranial hemorrhage, mass effect, or midline shift. At discharge on day 12, her limb strength and sensation were near normal. She continued to have some residual left-sided facial weakness and impaired sensation. She was discharged on aspirin only. The patient did not return to a follow-up appointment.

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DISCUSSION

Vertebral artery aneurysms and dissections are known complications of spinal manipulation procedures (1, 2). An estimated 1 in 20,000 spinal manipulations results in a vertebral artery aneurysm/dissection and ischemic infarct, but the exact incidence of this complication is unknown (3). These events occur in both men and women at an average age of 40 years and are more common in patients with connective tissue diseases (2), such as Marfan syndrome or Ehlers-Danlos syndrome. They are most commonly reported following neck trauma or manipulation, such as motor vehicle accidents, chiropractic maneuvers, sports, yoga, coughing, falls, and ceiling painting. Presently, no screening modality is available for the identification of patients at risk for cerebrovascular events following spinal manipulation (4). Patients with increased risk of stroke due to atherosclerotic vascular disease, such as those with hypertension or diabetes mellitus, do not appear to have an increased risk for stroke after spinal manipulation (4). Also, attempts to assess vertebral artery patency prior to manipulation have not been successful in identifying patients at increased risk (4). The risk for stroke following neck trauma/manipulation appears to be inherently dependent on the manipulation technique and the rotational forces applied to the neck (2).

In adults with manipulation-related vertebral artery aneurysm/dissections and associated ischemic infarcts, coexistent subarachnoid hemorrhage occurs in about 60% of cases. The proximal portion of the vertebral artery (V1) in the neck is the most common location of atherosclerotic occlusive disease (5). In contrast, atherosclerosis rarely causes occlusions in the distal portions (V2 and V3). These divisions are more commonly
associated with dissections as the artery winds around upper cervical vertebrae (1). Stenosis or dissections of the V4 segment are also common after dural penetration.

The most common symptom is dizziness, which is usually accompanied by vertigo, loss of balance, diplopia, nystagmus, oscillopsia, weakness in both legs, hemiparesis, gait ataxia, and numbness (3, 6). Up to 92% of patients will present with a complaint of head and/or neck pain (2, 3). The sudden onset of new headache is present in about 25% of cases and may present in association with other neurologic symptoms (2). There is no relation between the timing or number of spinal manipulations and the presentation of associated symptoms. Cerebrovascular events have been reported to occur in patients after one or several cervical spinal manipulations, including patients with no prior history of spinal manipulation (2). In a review by Haldeman et al of 64 patients with cerebrovascular events after spinal manipulation, the timing of presentation ranged from 2 days to 1 month, but 63% of patients developed symptoms immediately following the manipulation (2, 4).

The diagnosis of vertebral artery dissection is usually established by MRI, MRA, or CT angiography (6). One study showed that traumatic dissections were more likely to be diagnosed by CTA and spontaneous dissections were more likely to be diagnosed by MRA. However, this difference may reflect the frequency of CT use in the evaluation of trauma patients (7).

There is currently no consensus on the proper management for vertebral artery dissections. Generally, patients are initially treated with heparin, followed by warfarin or antiplatelet therapy alone (aspirin or aspirin and clopidogrel) (6, 8). A study by Arauz et al compared treatment with oral anticoagulation versus aspirin alone and found that the incidence of recurrent ischemic stroke in patients with a vertebral artery dissection is low and likely independent of the type of antithrombotic treatment (9). However, how early the diagnosis is made and the severity of the sequelae may determine the best mode of therapy. More conservative therapy is generally used for delayed diagnoses. If intracranial hemorrhage or persistent emboli are present, endovascular treatment with vertebral artery occlusion or stenting may be necessary. The method of endovascular management is based on the characteristics of the dissection or aneurysm, but double stent-assisted coiling is generally the first choice for aneurysms (10).

Outcomes following vertebral artery dissection are variable, ranging from no residual deficits to death. In general, clinical outcomes for symptomatic intracranial unruptured vertebro-basilar artery dissections are favorable in all patients without ischemic symptoms and in most patients with ischemic symptoms (11). In a retrospective analysis by Saeed et al evaluating the prognosis in 26 patients after vertebral artery dissection, 40% had no residual symptoms, 40% had minimal residual symptoms, and 10% had permanent disabling deficits. The remaining 10% died in the acute stage of the illness (3). Older age and basilar artery involvement are independent predictors for a poor outcome (11). Bilateral dissection and subarachnoid hemorrhage occurring with dissection have also been identified as important factors associated with poor outcomes, including disabling deficits and death (3).

Use of an ultrasonic bone curette (Sonopet) in orbital and oculoplastic surgery

Ivan Vrcek, MD, Victoria Starks, MD, Ronald Mancini, MD, and Grant Gilliland, MD

The use of the Sonopet Omni, an ultrasonic bone curette, has been discussed for ear, nose, and throat, neurosurgical, and maxillofacial procedures. Its use in oculoplastic and orbital surgery has not been extensively described. The Sonopet has a number of advantages that impart particular utility when operating in the orbit. We present three illustrative cases highlighting the unique advantages of the Sonopet: 1) the ability to spare critical soft tissues; 2) the facility to sculpt and restore the complex contour of the orbit; 3) the capability to biopsy infiltrative lesions that may not be as amenable to manipulation with conventional drills; and 4) a small footprint ideal for small operative fields such as the orbit.

The use of the Sonopet Omni Ultrasonic Surgical System (Stryker, Kalamazoo, MI) in oculoplastic surgery has received little attention. The Sonopet’s use in orbital decompression (1), and more recently in dacycystorhinostomy (2), has been documented; its application in orbital tumor excision has not been described. The Sonopet has a number of advantages: 1) it is less traumatic to soft tissues than conventional drills; 2) it allows for sculpting of bone into smooth or contoured shapes; 3) less force is required, allowing more controlled removal of bone, particularly bone that is infiltrated or abnormal; and 4) its relatively small footprint allows access to small operative fields. In this case series, we describe its use, advantages, and disadvantages with a focus on three orbital tumor cases.

The Sonopet unit used here comprised a power supply, foot switch, handpiece, and surgical tip. The footswitch has two pedals: the first engaging vibration with simultaneous irrigation and aspiration, and the second initiating irrigation alone. Several handpieces are currently available. The handpiece used for these cases weighs 110 g, is 140 mm long, and is 20 mm in diameter (Figures 1a, 1b). The longitudinal vibration amplitude varies from 120 to 365 um, at a frequency of 25 kHz. The 20°C irrigation fluid emerges through a sheath near the tip of the handpiece and has an adjustable rate between 3 and 40 mL/min. Aspiration occurs at the tip of the handpiece with a maximum aspiration pressure of 500 mm Hg. Eight surgical tips are currently available. The tip used here is in a Spetzler Claw shape designed for bone fragmentation and removal (Figure 1c).

CASE 1

A 51-year-old woman with a history of multiple intracranial meningiomas presented to our practice with left-sided proptosis, exposure keratopathy with pain, and limited extraocular

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motility. Magnetic resonance imaging revealed a left orbital apex meningioma with proptosis. The patient was taken to the operating room where a bicoronal flap and anterior craniotomy was created to expose the orbital roof. An en bloc excision of the orbital roof was accomplished, followed by subperiosteal dissection of the superior orbit. The periorbita was opened and the mass was identified in the orbital apex.

The oculomotor nerve was noted to be coursing over the mass and was firmly adherent to it. Using the Sonopet, the oculomotor nerve was dissected free from the mass while emulsifying the surrounding firm tumor. The oculomotor nerve was carefully retracted and dissected as the mass was gradually emulsified by the torsional emulsification of the Sonopet.

CASE 2

A 50-year-old woman with no significant past medical or surgical history presented with right-sided orbital pain, proptosis, diplopia, and blurred vision. A computed tomography (CT) scan demonstrated a right orbital mass consistent with fibrous dysplasia impinging on the lateral rectus muscle and the orbital contents (Figure 2a). The patient was taken to the operating suite, where a lateral canthotomy and cantholysis was used to expose the lateral orbital wall. A sagittal saw was used to remove a portion of the lateral orbital wall, and subperiosteal dissection was performed to identify the lesion. Intraoperative navigation was used to identify the extent of the mass, and the Sonopet was used to remove the mass as it extended into the orbital apex, care being taken to identify and preserve the orbital contents. Additional aspects of the mass were exposed and excised along the greater wing of the sphenoid.

The lesion was reduced using the Sonopet to restore the normal contour of the lateral orbital wall (Figure 2b). This was accomplished by gradually sculpting the lateral orbital wall by emulsifying minute layers of bone in a painting fashion, as one might imagine buffing a floor. Small circular movements were used to emulsify the lateral orbital wall to restore the concave shape, allowing for appropriate decompression of the orbital contents.

CASE 3

A 51-year-old woman presented with progressive left-sided enophthalmos and retrobulbar pain. CT scan revealed a left orbit mass with a lobulated consistency as well as left globe retraction (Figure 3). The decision was made to proceed with biopsy given concerning features such as globe retraction and the appearance on CT scan. The patient was taken to the operating room where a Krönlein orbitotomy was performed with dissection into the lateral orbit. The lateral rim was removed with a sagittal saw. Intraoperative CT-guided navigation was used to localize the mass, which appeared to infiltrate the bone in the lateral and superior orbit, producing a mottled effect.

The Sonopet was used to biopsy the mass by retracting the mass from the lateral orbital wall and gradually passing the Sonopet between the mass and the infiltrated bone. The Sonopet's
unique ability to emulsify bone but not the softer mass was critical in separating the mass from the bone to enable a biopsy. Moreover, the Sonopet’s small footprint and relative tissue specificity enabled a biopsy that did not necessitate removal of a large portion of the lateral orbital wall, thus maintaining the volume and shape of the orbit.

**DISCUSSION**

The Sonopet’s primary mechanism of action is torsional oscillation of a metal bone rasp at 25 kHz. This frequency is ideal, as the microenvironment created cuts only mineralized tissue, while soft tissues are cut at frequencies ≥34 kHz (3). This mechanism, as compared to traditional drills, results in less soft tissue damage and less torque-induced bone fragment displacement in our experience. These features are particularly important when one considers the proximity of critical and fragile tissues in small anatomic spaces such as the orbital apex and lacrimal system. The ability to easily sculpt bone into a contoured shape is particularly advantageous in orbital surgery. Additionally, simultaneous irrigation and aspiration is applied to the surgical field, allowing one-handed use and obviating the need for separate irrigation and aspiration. Moreover, bone removal can be accomplished with minimal manual pressure.

The three orbital tumor cases described, summarized in Table 1, highlight these advantages of the Sonopet. In the first case, it was critical to remove the meningioma without damaging the adherent oculomotor nerve. The unique ability of the Sonopet to preserve soft tissues was critical here. In the second, not only was the Sonopet used in the orbital apex where vital soft tissue structures are in close proximity, but the lateral orbit and greater wing of the sphenoid were reshaped to both decompress the orbit and to restore the normal contour of the lateral orbit. Sculpting the concave lateral orbit by removing minute layers of bone would be quite difficult with a tool such as a sagittal saw. In the third case, the Sonopet was used to carefully dissect and biopsy a mass that was infiltrating the bony lateral orbit while minimizing any change in shape or volume of the orbit. Again, the ability of the Sonopet to emulsify bone while preserving softer tissues allowed the dissection of the mass from the bone it was infiltrating. Moreover, the Sonopet allowed for this dissection while preserving the majority of the lateral wall, thus maintaining the contour and volume of the orbit.

The Sonopet is less suited for large bony resections when compared with traditional instruments, as it removes a comparatively small amount of bone per amount of time. For example, in the second and third cases, a saw, rather than the Sonopet, was used to remove the lateral orbital rim. Additionally, the cost of the unit is significant, which may limit its availability to large centers or institutions where the unit can be shared among surgical subspecialists.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case 1: Orbital apex meningioma</th>
<th>Case 2: Greater sphenoid wing fibrous dysplasia</th>
<th>Case 3: Infiltrative mass</th>
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<tbody>
<tr>
<td>Critical tissue spared by Sonopet</td>
<td>Oculomotor nerve</td>
<td>Lateral rectus</td>
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</tr>
<tr>
<td>Additional operative time</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Preoperative exophthalmos</td>
<td>Present</td>
<td>Present</td>
<td>Enophthalmos present</td>
</tr>
<tr>
<td>Postoperative exophthalmos</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Preoperative keratopathy</td>
<td>Present</td>
<td>Present</td>
<td>None</td>
</tr>
<tr>
<td>Postoperative keratopathy</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

A new investigational cardiac pacemaker as small as a vitamin

Cardiologists on the medical staff at Baylor Jack and Jane Hamilton Heart and Vascular Hospital (BHH) have implanted investigational cardiac pacemakers the size of a multivitamin. The first implantable pacemakers, developed in the late-1950s, were nearer the size of a transistor radio. Robert C. Kowal, MD, PhD, principal investigator for this trial at BHH, indicated that the Medtronic Micra™ Transcatheter Pacing System (TPS) “could be a game-changer because of its size and the technology housed inside of it.” BHH is one of 50 institutions around the globe participating in the trial, sponsored by Medtronic. One-tenth the size of a conventional pacemaker, the Micra TPS is delivered directly into the heart through a catheter inserted in the femoral vein. Once positioned, the pacemaker is securely attached to the heart wall and can be repositioned or retrieved if needed. “This miniaturized technology is designed to provide patients with the advanced pacing technology of traditional pacemakers via a minimally invasive approach. In the past, we made a surgical incision in the chest and created a ‘pocket’ under the skin where we placed the pacemaker,” explained Dr. Kowal. “This one is placed inside the heart via catheter.” This eliminates a potential source of complications and any visible sign of the device, he said.

“We are proud that BHH was selected among an elite group of institutions to take part in this clinical trial. If positive, the results of the trial could potentially benefit the more than 1 million people globally who receive pacemakers each year,” said Nancy Vish, PhD, RN, FACHE, president and chief nursing officer of BHH.

Baylor Hamilton Heart and Vascular Hospital expands into Tarrant County

BHH opened a second location in Fort Worth on September 29, 2014, to provide outpatient cardiac services at Baylor All Saints Medical Center at Fort Worth. BHH clinical staff will operate and oversee the interventional cardiac services, electrophysiology services, and noninvasive cardiology services on the sixth floor of Baylor All Saints.

“One of the benefits of being a hospital in a system like Baylor Scott & White Health is the ability to share medical expertise among the hospitals,” commented David Klein, MD, president, Baylor All Saints Medical Center at Fort Worth. “With this new relationship, our patients will have greater access to cardiology research studies and clinical trials along with increased opportunities for collaboration between cardiologists on the two campuses. The goal is always to provide quality care to our patients.”

Baylor Research Institute immunology researchers obtaining promising results with multiple sclerosis vaccine

Thanks to new insights related to dendritic cell vaccines, researchers are investigating a potential vaccine for multiple sclerosis (MS) treatment and prevention at the Baylor Institute for Immunology Research (BIIR), a division of Baylor Research Institute. If future research supports early findings, the study could mark an important first in that it attacks MS early while preserving the immune system. Led by principal investigator SangKon Oh, PhD, with support from Gerard Zurawski, PhD, and Ted Phillips, MD, PhD, the laboratory research was launched 3 years ago, with early promising findings now surfacing.

The study’s inspiration came from previous research related to dendritic cells for cancer and infectious diseases. During those investigations, scientists identified a special property of those cells that could influence the behavior of the immune system and play a role in treating autoimmune diseases such as MS. “We discovered that DC-ASGPR, one of the receptors expressed on human dendritic cells, has novel functions to promote antigen-specific regulatory T cells that can efficiently suppress inflammatory responses,” Dr. Oh said. “This prompted us to test our discovery in autoimmune diseases where antigens are known.”

While the researchers have tempered their enthusiasm, early indicators hint at extraordinary potential for these new MS vaccines. Those results have been so positive, Dr. Oh said, that they are hopeful this study can enter a phase I clinical trial in the next 3 years. Additionally, the researchers will apply these findings to future studies about dendritic cell vaccines, including a planned research effort for type 1 diabetes.

New use for an old drug could impact cirrhosis patients

A common drug used to clean a person’s bowels before a colonoscopy could become the future standard of care for patients with acute hepatic encephalopathy (HE), a mental disorientation problem that affects up to half of cirrhosis patients. The finding comes from new research, known as the “HELP Clinical Trial,” that appeared in JAMA Internal Medicine on September 22, 2014.

Led by Robert Rahimi, MD, of Baylor University Medical Center at Dallas (BUMC), the study compared the current HE treatment, lactulose, with polyethylene glycol 3350-electrolyte solution (PEG), otherwise known as GoLYTELY®, an oral medicine used to clean out the intestines before a colonoscopy. In the small-scale trial, 50 HE-afflicted participants were divided into two groups of 25, with one group receiving lactulose (standard therapy) and the other group receiving the PEG solution (new therapy). About 91% of the PEG patients rapidly improved compared with 52% of the lactulose patients. No adverse side effects were reported. Additionally, patients who received the PEG solution had a shorter hospital stay than the lactulose participants. “On average, [the hospital stay for acute HE] can be about 5 days overall, depending on the underlying precipitant,” Dr. Rahimi said. “In patients who took the PEG solution, HE resolved one day quicker. So there’s an overall potential for decreased length of stay, which could result in cost savings.”

Dr. Rahimi’s team plans to launch future research on the topic that would involve several facilities across the country, Baylor included. As those clinical trials take place, investigators could learn new insights to not only treat acute HE, but in some cases prevent it. “Because lactulose is the standard of care for outpatient as well, this new research might lead to different medicines that can be used from an outpatient standpoint, which could help prevent patients from even getting hospitalized in the first place,” he said. “That’s the hope.”

Innovative care concept set to expand services offered on the Baylor Medical Center at Garland campus

The services offered on the Baylor Medical Center at Garland campus expanded when Select Medical opened the doors of a new long-term acute care hospital on Baylor Garland’s third floor in the fall of 2014. This hospital, which treats medically complex and critically ill patients,
wholly owned by Select Medical and operated as a hospital-within-a-hospital. It consists of 40 patient rooms, including a six-room intensive care unit for the most critically ill patients.

The concept reflects a new model of care for hospitals in a rapidly changing health care landscape. It allows hospitals to better serve communities by collaborating with other health care providers to provide access to a wider range of patient care services. And it’s a concept Baylor Garland plans to further in January 2015 when Timberlawn Mental Health System, a Universal Health Services (UHS) facility, opens its own hospital-within-a-hospital psychiatric facility on Baylor Garland’s campus.

“Working with established, highly respected providers like Select Medical and UHS to give members of our community access to a wider range of specialized health services is critical to our mission and to effectively meeting the future health care needs of the people we serve,” said Tom Trenary, president of Baylor Garland.

Although both Select Medical and UHS will wholly own and operate their respective facilities on the Baylor Garland campus, many of the physicians providing care will be members of Baylor Scott & White Quality Alliance, a clinically integrated accountable care organization, consisting of physicians, hospitals, postacute care facilities, and other care providers who work together toward improving quality and access to care while simultaneously reducing costs for the patients and communities served by Baylor Scott & White Health facilities. Incorporating BSWQA members into the care environment adds to the novelty of the hospital-within-a-hospital strategy and will help promote consistent, quality care practices across a patient’s stay on the Baylor Garland campus.

**100th auto islet cell transplant performed at Baylor Dallas**

In November 2014, BUMC performed its 100th auto islet cell transplant. Considered the preeminent center in the southwestern United States, the Pancreatic Islet Cell Transplant Program is a joint project of BUMC, Baylor All Saints Medical Center at Fort Worth, and Baylor Research Institute.

Since its inception in 2005, the pancreatic islet cell transplant program has made remarkable progress both in the clinical and basic research arenas. Some noteworthy achievements have included becoming the first center in Texas to gain permission from the US Food and Drug Administration to process pancreatic islet cells for transplantation; becoming the first hospital in the Southwest to perform islet cell transplantation from its own lab for type 1 diabetes patients and chronic pancreatitis patients; and being awarded a patent for a potential strategy to improve the outcomes of islet cell transplantation.
Baylor Irving ED expansion anticipates community’s growing needs

The bustling community hospital that serves the Irving, Coppell, and Grand Prairie communities is also the second busiest emergency department (ED) in the Baylor Scott & White Health North Texas division. The Baylor Medical Center at Irving ED, which was designed to accommodate 50,000 patient visits each year, handled 69,914 visits in fiscal year 2013. The much-anticipated renovation and expansion will nearly double the size of the ED, increasing the bed capacity from 33 to 50 beds. The final phase of the expansion is expected to be complete in March 2015.

Baylor Institute for Rehabilitation named a partner in multiple sclerosis care

Baylor Institute for Rehabilitation (BIR) has been named a Partner in Rehabilitative Multiple Sclerosis Care by the National Multiple Sclerosis Society, becoming the first such partner in the country’s South Central region and one of only 26 in the US. Partners in MS Care is a national program that recognizes and supports quality MS care, encouraging strong collaboration between MS clinics and the society to create optimal care and support for people living with MS.

“BIR is dedicated to providing quality care for individuals with MS,” said Dr. Katherine Meredith, neuropsychologist and program director for BIR’s Multiple Sclerosis Center of Rehabilitation and Treatment (MS-CoRT). “Becoming a Partner in Care is an exciting opportunity to build on the quality care we currently provide and work toward further increasing availability of resources for individuals with MS and their caregivers.”

The MS-CoRT program was created to coordinate the range of medical and rehabilitation needs for individuals with MS in one setting. The goal is to minimize the complexities of managing appointments and help improve the quality and consistency of care. The range of services includes physical therapy, women’s and men’s health, occupational therapy, speech language pathology, neuropsychology, health psychology, psychiatry, and an option for in-home care. The clinic also provides an educational series for patients with MS and their caregivers, covering topics such as the basics of MS and managing daily activities with MS.

Baylor Institute for Rehabilitation opens its 49th outpatient clinic in Oak Cliff’s Kessler Park neighborhood

Oak Cliff residents who need physical therapy now have local access to BIR services with the opening of its Kessler Park outpatient clinic. BIR’s 49th North Texas outpatient clinic is located in a remodeled building at 222 E. Colorado Boulevard, at the intersection of Colorado and Zang boulevards. BIR will open two more outpatient clinics this year, pushing the number of locations to more than 50.

PHILANTHROPY NOTES

Celebrating Women raises nearly $2 million to benefit Baylor’s fight against breast cancer

Baylor Health Care System Foundation hosted its 15th annual Celebrating Women luncheon on October 24 at the Hilton Anatole hotel in Dallas. The 2014 luncheon raised more than $2.4 million, including a generous $1 million gift from the Spangenberg Family Foundation, to benefit Baylor Health Care System’s fight against breast cancer.

Since the first Celebrating Women luncheon in 2000, more than $24 million has been raised to support advanced diagnostic equipment, innovative clinical research, and, most importantly, safe, quality, compassionate care for Baylor’s patients and families.

The keynote address was delivered by Amy Robach, Good Morning America co-host and breast cancer survivor, who left few dry eyes after sharing her very personal and very public battle with the devastating disease. She recalled a friend recently complaining about aging and wrinkles. “The first thought that came to my head was ‘God, I hope I have wrinkles. I hope I see my 50s, 60s, and 70s. And now I look at wrinkles as a badge of honor, and it’s just a completely different way of looking at life because I am so grateful. . . . I never knew how beautiful life was until I had cancer.”

Grand Rounds scores hole-in-one for medical education

The 13th annual Baylor Health Care System Foundation Grand Rounds® Golf Tournament was sponsored by Bank of Texas for the sixth consecutive year. The annual fall golf tourney teed off on October 6, 2014, at Northwood Club and raised more than $280,000 to support undergraduate and graduate medical education at Baylor University Medical Center at Dallas. More than 200 leading citizens and 50 sponsors from across the Dallas community came out for the day of golf, including platinum sponsors Duke Realty, General Data Tech, Kaufman Hall, The David B. Miller Family Foundation, Wells Fargo Bank, and Western Extrusions. Gold sponsors this year included JW Homes, Northern Trust, and Perkins & Will.

Since the first tournament, Grand Rounds supporters have contributed several million dollars toward medical education initiatives.

Grand Rounds has taken on an increasingly important role in recent years. The Association of American Medical Colleges has predicted that there will be a shortage of more than 90,000 doctors by 2020. A recognized leader in the training of medical professionals since 1903, Baylor Dallas trains approximately 220 residents and fellows in 30 specialties each year—ranging from internal medicine to vascular surgery to pathology. With donor support, the Foundation plans to fund 23 residents and fellows in fiscal year 2015 at a cost of more than $2.4 million.

Help is a Four-Legged Word™

Baylor Scott & White Health is affiliating with Canine Companions for Independence®, a leader in the training of assistance dogs, to bring a premier service animal training center to Dallas–Fort Worth. Initial construction for the new Canine Companions for Independence at Baylor Scott & White Health–Kinkeade Campus began in November. This facility will be the first Canine Companions training center in Texas and the first in the nation to be connected to a health care system.

The nearly 9-acre Kinkeade Campus will be used to train assistance dogs and will accommodate up to 60 teams per year. It will include dormitory rooms, kennels, indoor and outdoor training areas, and multipurpose common spaces. Assistance dogs are provided to individuals with a broad range of disabilities free of charge; however, the average cost to breed and train each dog is more than $45,000. As a result, Baylor Health Care System Foundation is seeking philanthropic support from the community to cover costs associated the new campus construction, as well as provide ongoing programmatic support.

For information on how you can support these or other initiatives at Baylor, please contact the Foundation at 214.820.3136.
Paul Roscoe Ellis III, MD: a conversation with the editor

Paul Roscoe Ellis III, MD, and William Clifford Roberts, MD

Paul Ellis (Figure 1) was born on August 23, 1952, in Sherman, Texas, but grew up in Dallas. A superb student and athlete in high school, he entered the University of Texas (UT) at Austin, graduating in May 1974 with a bachelor’s degree with honors and a major in psychology. He then entered the Southern Methodist University School of Law in Dallas and graduated in May 1977. Having decided in law school that medicine was his real calling, in 1978 he entered UT Southwestern Medical School and graduated in June 1982. His training including a rotating internship and 4 years as a resident in orthopedic surgery was at the University of South Florida in Tampa. After completion of his orthopedic residency, his family moved to Louisville, Kentucky, where he was a fellow in hand surgery from October 1, 1987, through March 31, 1989. He then returned to Dallas to enter practice with Lankford Hand Surgery Association, specializing in hand and upper-extremity trauma, reconstruction, and microsurgery. He has been there ever since.

For a number of years, Dr. Ellis has been a clinical professor of orthopedic surgery at UT Southwestern Medical School, and the class of 2002 honored him with an “Outstanding Faculty” award for the Department of Orthopedic Surgery. He also received the “Outstanding Teacher of the Year” award at Baylor University Medical Center at Dallas (BUMC). Dr. Ellis has to his credit several publications in peer-reviewed journals and has presented at a number of orthopedic conferences. He and his lovely wife are the parents of three children. He still competes athletically in track among persons in his age group. Dr. Ellis is a very popular physician in the Baylor community, and it’s a pleasure to be in his company.

William Clifford Roberts, MD (hereafter, Roberts): Dr. Ellis, I sincerely appreciate your willingness to have this conversation and am particularly appreciative of your coming to my house to do so. To start, could you discuss your early life, some of your earliest memories, your parents, and your siblings?

Paul Roscoe Ellis III, MD (hereafter, Ellis): My dad, Paul Roscoe Ellis, Jr., was a cardiovascular and thoracic surgeon here in Dallas practicing at BUMC. I was born in Sherman, Texas, by accident. My mother had gone to visit my dad’s parents when she unexpectedly went into labor, and my uncle, Dr. John Ellis, a general surgeon, delivered me at Wilson N. Jones Hospital. I grew up in Dallas. I was the oldest of four siblings—two brothers and one sister (Figure 2)—and we attended Dallas public schools. I recall going to the hospital making rounds with my dad on weekends. When walking through the halls of BUMC, I was often asked if I wanted to be a doctor like my dad, and I responded that I did (Figure 3). I thought being a physician was the answer to everything.

Unfortunately, my dad was killed in a Braniff plane crash on May 3, 1968, at the age of 40. He was attending the Texas Medical Association meeting in Houston and was supposed to return earlier that day, but he presented a paper that won an award and he stuck around to receive the award. The later flight hit a lot of turbulence and crashed, killing 85 on board.

Roberts: How old were you when it happened?
Ellis: I was 15, a sophomore at Hillcrest High School. This was a life-changing event for me. Even though I had a strong...
Influence of physicians in the family (my uncle John Ellis and cousin John Richard Steadman), his death had a negative influence on me at least initially in terms of my motivation to be a physician.

According to some physicians I have talked to at BUMC, my father was on the cusp of doing what might have been the first heart transplant in Texas. He was partners with Ben Mitchell and Maurice Adam. My dad did his fellowship in Houston with Michael E. DeBakey and Denton A. Cooley when they were still together. I went to first and second grade in Houston while he was in training.

I was a good student in high school up until my father’s death, and after that I kind of shut down. I played football and ran track. I didn’t have to study and I still made A’s. When I went to UT in Austin, however, not studying and not attending classes no longer produced A’s. I discovered with organic chemistry to prove that I could do it, and I received an A. So I finished college with a bachelor’s degree in psychology and went out there a lot. We hunted doves. We also had a boat, a 28-foot Chris-Craft, on “Lake Dallas” (now called Lake Lewisville). We spent weekends at Yacht Harbor. My siblings, Patricia Lynn Duvall, John Richard, and David Thomas, were extremely close.

Roberts: What is your mother’s name?

Ellis: Patricia Louise Herzog-Ellis-Budd. My stepdad, C. Burcham Budd, who was a tax lawyer.

Roberts: What was your mother’s name?

Ellis: Patricia Louise Herzog-Ellis-Budd. My stepdad became a good influence on me. He was a great guy. I started thinking that perhaps I was more suited to be a lawyer. After I did poorly in organic chemistry, I decided to switch to pre-law. I repeated organic chemistry to prove that I could do it, and I received an A. So I finished college with a bachelor’s degree in psychology and then went to Southern Methodist University School of Law. I enjoyed law school. I worked hard and did well.

Deep down I still really wanted to be a physician. Around Thanksgiving my second year at law school, I was visiting with two of my friends, Gary Goodfried, now an orthopedic surgeon in Tyler, and Chip Fagadou, an ophthalmologist. Both Chip and Gary told me they knew that I wanted to be a physician and suggested that I should finish law school and go to medical school. They planted the seed. Chip knew Bryan Williams, the dean of students at UT Southwestern, and he set up an interview for me with Dr. Williams. We spoke by phone initially and then he invited me to visit in person. We visited for an hour. I learned that he knew my dad. I think he recognized that I really wanted to be a physician. He encouraged me to finish law school and take the bar exam just in case I didn’t get into medical school. I passed the bar exam, took a week’s vacation, and started reviewing the Stanley Kaplan Review Course for the MCAT. This was right after studying nonstop all summer for the bar exam. I had to go back to college after law school to finish the premed requirements. I had only taken the first semesters of organic chemistry, physics, and some biology courses. I had to take the second semesters of each course and took them at UT Dallas. It was tough.

The first thing I remember about that Kaplan review course was that they gave us a test to break the ice. As I recall, I made <50% on that test. It was most upsetting. I felt so overwhelmed and didn’t think I could do well enough to get into medical school. Despite that initial anxiety, I stuck with it and kept going to all of the review courses, working on all the problems, and ended up doing well on the MCAT. I got accepted to UT Southwestern Medical School the next year. I was very fortunate to be able to make that switch and fulfill my lifetime dream.

Roberts: Did your father get home for dinner? Did you see him much?

Ellis: We siblings didn’t see our father much. My dad was very busy and home for dinner maybe once a week. On the weekends, however, we did a lot together as a family. We had a little farm outside of McKinney and went out there a lot. We hunted doves. We also had a boat, a 28-foot Chris-Craft, on “Lake Dallas” (now called Lake Lewisville). We spent weekends at Yacht Harbor. My siblings, Patricia Lynn Duvall, John Richard, and David Thomas, were extremely close.

Roberts: What position did you play in football?

Ellis: I was a running back and defensive back. I never left the field, playing on the offensive, defensive, kick-off, and kick-return teams.

Roberts: How much did you weigh back then?

Ellis: I weighed 173 pounds and was 70 inches tall.

Roberts: What did you run in track?

Ellis: I ran the 100- and 200-meter dashes and the relays. Ten seconds flat was my best 100-yard dash time.

Roberts: Did you play basketball too?

Ellis: I played through the 10th grade. By then, you had to pick your sport, so it was football and track for me.

Roberts: Were your brothers also good athletes in high school?

Ellis: Yes. Richard was a really good middle linebacker. David was a good athlete too.

Roberts: Did you play collegiate sports?

Ellis: No. That is one of my regrets actually. I still to this day think that I could have been a wide receiver at that level, but I did not pursue it. I decided at the end of high school that I was going to give up football and pursue academics, which I did after my first year or two of college. I did play intramural football.

Roberts: After your father died, what happened in your home? How did your family adjust?

Ellis: Things changed pretty quickly. I remember at the funeral, family and friends came up and told me that I was the
Ellis: They were introduced by friends who knew their situations and thought they would be a good match. Sure enough, they had one date and as far as I know that was it. They were constantly together thereafter.

Roberts: Were there any surprises for you at UT? Were you a happy college student?

Ellis: Yes. The surprise was that in college you have to work, and I was not used to putting much effort into studies. Like any kid going to college, you have to get used to being responsible for doing the day-to-day things like laundry.

Roberts: Did you have a car in college?

Ellis: I had a car from the time I was a sophomore in high school. I was spoiled in that regard. At UT there were no restrictions. In fact, today we take our kids to college and drop them off, but when I went to college, I loaded the car, told my mom I was leaving, and she kissed me goodbye and said to study hard. I drove down to Austin, moved into the dorm, and hardly ever saw my parents during college.

Roberts: Did you have summer jobs?

Ellis: The summer after my sophomore year of high school I worked for a construction company. My job was to clean up the houses they were building in the subdivision outside of Rockwall. They had a huge old Air Force truck that still had the wood panels in the back, and it was hard to drive. I had to drive it to the sites, load the stuff, and empty it at the dump. The summer after my junior year, I got a job through my stepdad with Mayflower Moving Company in their storage warehouse. My job there was to unload the trucks and put the storage in the vaults. The summer after my senior year, I worked on a ranch outside of Sherman. My job there was primarily to build fences. I used a metal hammer device to hammer the post into the ground. I probably built about a mile’s worth of fence that summer. It was a great upper-body workout.

Roberts: Why did you major in psychology in college?

Ellis: Probably because nothing else really interested me. At the time I thought psychology was a good choice since I was unsure whether I wanted to be a physician or a lawyer. It fell between real science and social sciences. I enjoyed psychology. The courses were fun. I thought it worthwhile to understand how the human mind works and how personality develops.

Roberts: Did your stepfather have a good bit of influence in your initial decision to go to law school?

Ellis: Yes, he did. We talked about his tax law practice. He came across as a thoughtful, fair, highly educated man. I liked the way he conducted his life. He didn’t push me to become a lawyer.

Roberts: Did you ever go to his office as you did with your biological father?

Ellis: I had been to his downtown office a few times. After I decided to go into law, I clerked for his law firm for about 6 months after my second year of law school.

Roberts: After you entered law school, how did you do? Toward your second year you mentioned that you were thinking of switching to medicine.

Ellis: I enjoyed law school. I did reasonably well. I was in the top quarter of my class. There are differences between

Figure 4. Diane, Patsy Budd, Donna, and Burch Budd.
law school and medical school. In law school you had certain assignments to prepare for the next day. You knew that you would likely be called on in class, so that was your motivation to read the assignments. If you had 30 pages of case material, you could summarize what was in that, things that you needed to remember, on one page. In medical school, in contrast, if you read 30 pages of pathology you could condense that down to maybe 25 pages. That’s all. Law was generalities, remembering the basic facts, focusing on the issues. The points of law are usually based on logic. I enjoyed that. It was relatively easy for me. In medicine, you had to memorize formulas and build on them. I thought I could be happy as an attorney but deep down I still wanted to be a physician. When I made that decision to go to medical school, I was opening myself up to a huge disappointment if I was not able to make it happen.

Roberts: What do your brothers do?

Ellis: Richard is a store owner in Durango, Colorado. He is a great outdoorsman. He was probably the best athlete in the family. He is a very bright guy. He went to UT Austin. Any time he decided he wanted to try something, he pursued it until he became the best. He was a great fisherman. He would go out on Town Lake on a surfboard and come back with a 10-pound bass. He would hear that a storm was coming into Galveston and run down to the coast to catch these giant waves. He got a dog and trained him to retrieve ducks and birds. Everything he did was outdoor oriented—hunting, fishing. There is a picture of him in The Daily Texan, riding his sidewalk surfboard down the ramps of Memorial Stadium while in college. He found things to do and perfected them. It paid off for him. He ended up being the manager of a sporting goods store in Durango: Gardenswartz Sports. As a manager of the store he did extremely well. Everyone recognized that he knew what he was talking about. He ended up buying that store. It did very well so he opened up a second store.

David works for the 3M Company in marketing and lives in Austin. He has been successful. He has three beautiful daughters and is very happy with his family situation.

Roberts: What does your sister do?

Ellis: Tricia is a registered nurse in Durango, Colorado. She has four great sons and loves being a grandmom.

Roberts: What about your twin half sisters?

Ellis: They are both married, and each has three children. Diane and her husband, Fred, are raising their family in Coppell. Donna and her husband, Kell, are raising their crew in Austin. We are all still a very close family.

Roberts: Were there any surprises for you in medical school?

Ellis: The biggest challenge for me was biochemistry. By the time I was in medical school I was a really good student. I had no problem arriving at the library at 8:00 AM and staying until midnight. Of our class of 200 students, about 20 already had their master’s degree in biochemistry. In contrast, I had had two semesters of organic chemistry. It was an eye-opener for me to master those formulas, amino acids, and Krebs cycle with nothing but a psychology and law degree.

Roberts: But you enjoyed medical school?

Ellis: Yes. I loved physiology, anatomy, pathology. Those courses seemed to pertain and they thrilled me.

Roberts: Were there any teachers—in grammar school, junior high, high school, or college—who really had a major impact on you?

Ellis: Probably the one who first comes to mind is Coach Bill Robbins, my science teacher and coach at Dealey Elementary School. He was required to teach science. I think he had no desire to be in a classroom because his real love was basketball, football, and track. He was a very demanding coach and regimented disciplinarian. We all knew that if you did things the way he required you to, then he was a great guy and would support you and be your friend. If you didn’t abide by the rules, you paid the price. For Coach Robbins, if you didn’t do what you were expected to do, then you had to “sit on the wall.” He had a bench in the gym where the rule breakers had to sit and watch everyone else play. Coach Robbins was my coach from fourth through seventh grade for football, basketball, and track. He also had a summer camp at his farm outside of McKinney, and he would have the football players come. We lived in tents, and his mother and his wife were great cooks and fixed the meals. We had two-a-day football training, which wasn’t heard of back then. It probably was not legal then or now!

Roberts: What about in college or medical school?

Figure 5. The entire Budd/Ellis family: Randall, Sally, Richard, Diane, Donna, Tricia, Paul, and David.
Ellis: The individuals I remember in medical school weren't personal relationships, but several had long-lasting effects on me. In medicine it was Don Seldin. I worried about getting called on in his class. The other one is Bruce Fallis, the professor of pathology. He wrote the pathology text that we used at Southwestern. I don't know if it was actually published. We received mimeographed copies. He was the pathology instructor for second-year medical students. Dr. Bryan Williams, the assistant dean of students, clearly had a significant impact on my life because he was instrumental in my getting into medical school. I would see him periodically on campus, and he would always make a point to stop and ask how things were going.

Roberts: You took a rotating internship. Why did you decide to do that?

Ellis: That came with the territory. That was part of my orthopedic residency. I thought I wanted to do orthopedics, so the third year of medical school I went to visit my cousin, Richard Steadman, who at that time was at Lake Tahoe. Richard, an orthopedic surgeon, did sports medicine and was the chief physician for the U.S. Olympic Ski Team. He operated on professional athletes. I visited him for about 2 weeks. After watching him and spending time with him, I came away having decided I wanted to be an orthopedist. I also enjoyed working with athletes and considered myself one as well. It combined my interest in sports with surgery, so it was a perfect combination. I did some orthopedic rotations during my third year, and in my fourth year I did a month at UT Houston in orthopedics and at Parkland Hospital here in Dallas.

Richard Steadman knew of the program in Tampa, Florida. He was friends with Phil Spiegel, chairman of the orthopedic department at the University of South Florida in Tampa. A course on a technique for internal fixation was being taught at UT Southwestern Medical School when I was in my third year. Dr. Spiegel and my cousin Richard were both faculty members. So Dr. Steadman introduced me to Dr. Spiegel and a couple of the orthopedic residents from Tampa. I was very impressed with Dr. Spiegel and the residents. When I was interviewing for orthopedics, I decided to rank his program highly. I ended up matching with the University of South Florida at Tampa. Their program included a rotating internship. It was a great experience because it included 3 months of orthopedics, 3 months of general surgery, 3 months of internal medicine, and 6 weeks each of emergency department (ED), pulmonary (intensive care unit), pediatrics, and rheumatology.

Roberts: How did you like living in Florida?

Ellis: We enjoyed it. My first son, Paul "Ryan" Ellis, was born on November 12 during my fourth year of medical school. It was sad to have to leave Dallas to go to Tampa, Florida, where we knew no one. We were leaving all my family here with an 8-month-old newborn. That was hard. We enjoyed Tampa, but looking back, I was on call every third night and was extremely busy and had very little time to spend with my family. I realized early on that I did not want to live in Florida permanently. I missed the change of seasons. It was 88° our first Christmas Day. During my second year of residency we had our twins, Rebecca Lauren and Kyle Andrew (Figure 6). That was really hard on my wife, Trish, because with no family there she had to do it on her own. I was gone most of the time. She dealt with a 2-year-old before she had the twins.

Roberts: When did you get married?

Ellis: We were married between law school and medical school, December 17, 1977. I had graduated from law school in May. I proposed to Trish (Patricia Ann) on her birthday, August 31, 1977. Her family happened to be in town. Her dad thought I was crazy to go to medical school after just graduating from law school.

Roberts: What was her maiden name?

Ellis: Power.

Roberts: What was it about her that attracted you to her?

Ellis: We met in Austin. She was on a date at one of my intramural football games. My initial attraction was that she was beautiful, and beyond that I discovered that she was also a beautiful person, loving, kind, and giving. I fell in love with her probably at first sight and then did it all over again when I got to know her (Figure 7).

Roberts: What are your children doing now?

Ellis: Ryan is a "recovering" corporate attorney. He went to UT for undergrad and then UT Law School and was with Gardere Wynne and Sewell here in Dallas for 6 years. When he was approached to become a partner, he looked at his life and those of the partners and decided that law was not what he
She is a third-grade teacher at Providence Elementary in Dallas. Kyle married Allison Hilliard 2 years ago. They live in Dallas. It's been a great experience for Kyle because initially they were in-house attorney. He has been with them for almost 3 years, and joined Matador Resources, an oil and gas company, as an attorney one year. He decided that wasn't his passion, and moved to Dallas. He went to UT Law School. He did very well and after graduation was with Baker Botts law firm for a year. He found it was a lot less expensive for him to stay in Texas, so he decided he wasn't ready after only 6 months of exposure, he realized that he was probably more inclined to be a hand surgeon. Both Belsoe and Greene told me they recognized that it was a better fit for me.

In the meantime, my cousin Richard was disappointed that I wasn't going back to Texas. My sister was married and living in Dallas. It was home. But deep down I really wanted to come back to Dallas. All my family was still here. My mom was well along in raising my twin half-sisters, age 12 at the time. My brothers both lived in Dallas, and my sister was married and living in Dallas. It was home.

Kyle went to the University of Virginia (UVA) and was accepted at UVA Law School. He had the choice of UT Austin or UVA and talked to the dean of UVA about it. The dean advised him that if he really wanted to move back to Texas, it would probably make more sense for him to go to UT Law School. He was on board with that because it was a lot less expensive for him to stay in Texas. He went to UT Law School. He did very well and after graduation was with Baker Botts law firm for a year, decided that that wasn't his passion, and moved to Dallas and joined Matador Resources, an oil and gas company, as an in-house attorney. He has been with them for almost 3 years. It's been a great experience for Kyle because initially they were a private company and he was involved in taking them public. Kyle married Allison Hilliard 2 years ago. They live in Dallas. She is a third-grade teacher at Providence Elementary in Dallas.

Ellis: My orthopedic surgery residency included 6 months of hand surgery. Initially, I thought I wanted to be an orthopedic sports specialist, and in fact the original plan was that I would finish my training and do a fellowship in sports medicine. During my residency one of the first rotations I did was hand surgery. I worked with some really outstanding hand surgeons in Tampa, Robert Belsoe and Tom Greene, and they really influenced me. I discovered that I was better with the small hammers and the finer instruments than I was with the bigger hammers. To do a total knee, you are using a big hammer almost like a sledgehammer, but you are using really small tools to operate on a broken finger. I was better at the more precise, finer-detailed operations and grew to really enjoy microsurgery. With my 6 months of exposure, I realized that I was probably more inclined to be a hand surgeon. Both Belsoe and Greene told me that they recognized that it was a better fit for me.

In the meantime, my cousin Richard was disappointed that I was thinking I might not want to do sports. He suggested my doing 6 months with him after the 6-month hand rotation. But a full-year fellowship in hand surgery is required to be eligible for the Hand Society. Ultimately, I ended up doing an 18-month fellowship in Louisville, Kentucky, with Harold Kleinert as the recipient of the Christine Kleinert Fellowship. There were eight hand surgeons in the group. They were one of the first groups to do reimplantation of amputated fingers and hands. My mentor in Tampa, Robert Belsoe, had also trained with Kleinert.

Ellis: Where is Trish from?

Ellis: Trish was born in Harlingen, Texas, and lived there through the third grade. Her dad was with Freedom Newspapers.
Because of that, they moved around a bit. She was in Pampa, Texas, from fourth through 10th grades. The summer after her sophomore year they moved to Brownsville, Texas. It was a hard move because they had made some great friends in Pampa. They moved back down to Brownsville, and Trish graduated from there. She went to UT Austin. We met there.

**Roberts:** *So how did you get back to Texas?*

**Ellis:** Trish was happy to return to Dallas. It was a matter of where to work. I knew Dr. Lee Lankford, my now deceased senior partner. He had been a hand surgeon in Dallas for probably 30 years. He had operated on my brother David when he had a football injury—a broken finger—as a junior or senior in high school. I called and talked with Dr. Lankford. He said the group was interested in hiring a new partner. He was considering retiring in the not too distant future. We flew down and met with Drs. Lankford, David Zehr, and Arnold DiBella. We had dinner with them, and we were very excited about the opportunity to join their group. I also met with Jim Montgomery, from an orthopedic group of 10 to 12, and they did not have a hand surgeon. I also was offered a position with them. I felt that it would be to my benefit to join a hand group where I still had mentors and others to bounce advice off of rather than join a group where they might expect me to know everything. I clearly made the right choice. I accepted the Lankford offer.

After I signed on, Dr. Lankford indicated that he intended to retire in 3 months.

**Roberts:** *When did you join Lankford Hand Surgery?*

**Ellis:** On April 1, 1989. We were a little cramped with only three offices on our wing of the floor. The plan was for Dr. Lankford to retire pretty soon so our office manager bought another desk and they slid my desk in caddy corner to Dr. Lankford’s in the same office. We were cozy. It turned out to be an awesome educational experience for me—an unbelievable opportunity to tap into one of the brightest minds with the most knowledge of hand surgery in North Texas. The first 6 weeks I spent just going around with him, taking ED calls and getting my own patients. I went to the office to see patients with Dr. Lankford and scrubbed with him for 6 weeks. I remember a case would come in and I would look at the x-ray, not sure if this required surgery or not, and I would show the x-ray to Dr. Lankford. Instead of his looking at the x-ray and giving me a simple answer, he gave me a dissertation on whatever it was. He would give me its treatment history and what other operations were performed previously. In addition, orthopedic surgeries were handled by the ED on-call physician. I do not get those emergencies unless the patient happens to be a former patient of mine and specifically requests me. That situation still happens periodically. Our young hand surgeons who are building their practice want the ED calls. That’s how a hand surgeon builds a practice. After 25 years in practice, I get referrals from patients I operated on 20+ years ago.

**Roberts:** *What is your present age?*

**Ellis:** I turned 62 on August 23, 2014.

**Roberts:** *Who handles the emergency calls now?*

**Ellis:** The three of us share “on call” with two other physicians, Hugh Frederick and Tom Diliberti. In addition, other physicians handle the call for the ED at BUMC. Consequently, open injuries, including gunshot wounds, are handled by the ED on-call physician. I do not get those emergencies unless the patient happens to be a former patient of mine and specifically requests me. That situation still happens periodically. Our young hand surgeons who are building their practice want the ED calls. That’s how a hand surgeon builds a practice. After 25 years in practice, I get referrals from patients I operated on 20+ years ago.

**Roberts:** *What are the most common operations you do?*

**Ellis:** By far the most common procedure I do and have done is carpal tunnel release. It’s the most common procedure done by orthopedic surgeons in the country. A nerve is pinched in the hand, and that causes numbness and tingling. These people wake up at night and their hand is asleep. They shake their hand to get relief. If it gets bad enough to require surgery, a relatively minor outpatient procedure can be done whereby the pressure is taken off the nerve. The operation is usually curative; the numbness disappears. A second common condition encountered is the catching and locking of their “trigger finger” due to inflammation of the tendons. We can treat this problem with corticosteroid injections, and if the injections do not work, there is a minor procedure that works very well. The third most common condition encountered is arthritis, particularly in the base of the thumb. We reconstruct the joints. The fourth is Dupuytren’s contracture.

I do most of these operations probably because I took over Dr. Lankford’s practice and also because of my experience at the Veterans Affairs (VA) Hospital. I was chief of the hand service at...
the VA from 1993 to 2007. During that time I worked with the orthopedic residents helping them do those cases, and we did an incredible number of Dupuytren’s cases. At one time I thought it was the only case we did there. In 2002, the orthopedic residents at the VA Hospital gave me a plaque that said “Paul Ellis, Deacon of Dupuytren’s.” The plaque now hangs on my office wall. Dupuytren’s is a contracture, an inherited disease wherein the tissue in the palm starts to form knots that progress to cords and cause the fingers to contract (flex) down into the palm. The condition is a real problem if the fingers get pulled down far enough that the patients can’t get their hands into their pocket or poke themselves in the eye. It’s a rewarding but challenging operation. We do a host of other little things: ganglions, lumps.

Roberts: How much time do you take off a year? How do you work that out?

Ellis: I take off quite a bit. We don’t have a policy wherein we are restricted to a certain number of weeks off. We just have to make sure to have coverage for the days we are on call. Since I don’t have to take ED call anymore, it’s usually not a problem. Dr. Frederick is on call on Monday, Dr. DiBella on Tuesday, I’m on call every Wednesday, Dr. Zehr is on Thursday, and the rotator who gets the weekend is on call Friday through Sunday. Dr. Diliberti rotates through the week.

We spend a lot of time in Colorado. I developed a passion for Colorado beginning the summer after fourth grade when I went to Ute Trail Boy’s Camp, owned by Hop Hopkins, a Dallasite who took kids from Dallas to experience it. I went for four summers in a row. We camped, hiked, fished, and climbed 14,000-foot mountains, and I loved it. After spending time there, I couldn’t wait for my kids to be old enough to enjoy the environment also. We would go to Lake City to camp at Big Blue Campground about 15 miles off the highway where a stream runs through this gorgeous valley with a series of beaver ponds. Far as I’m concerned, it is paradise. I can’t spend enough time there. My son, Ryan the Renegade Lawyer, is living there now.

Roberts: How many miles is your cabin from Dallas?

Ellis: Unfortunately, it’s 820 miles, and it usually takes about 14 hours driving. But we get up early and try to leave by 6:00 AM and arrive about 8:00 PM.

Roberts: How often do you get your whole family there?

Ellis: In July 2014, we were all there for 9 days (Figure 8). All of us except Ryan, who is living there, drove up together in our Suburban, plus two Siberian huskies, which were shedding clumps of white fur.

Roberts: How many days in general do you take off?

Ellis: At least 3 weeks. I take off a week for the 4th of July, then a week in August, and then the third weekend of September, which coincides with the fall colors and a wine and music festival (Figure 9). I also take time off to go to the meetings of the Hand Society and the American Academy of Orthopedic Surgery. I take off approximately 5 weeks a year.

Roberts: Do you have hobbies here in Dallas?

Ellis: My current hobby is running and competing in the Senior Games, which I’ve been doing for 10 years. One is eligible for the Senior Games when turning 50. Although all types of sporting activities are offered, I focus only on track. A friend of mine, Ken Raggio, who grew up in Dallas (Highland Park) and went to UT Law School, recruited me my senior year at UT to join his track team and compete in the Texas Relays (Figure 10). There were four members for the 440-yard relay team. We won our division. When I came back to Dallas, Ken started warning me that as soon as I turned 50 he wanted me to start competing in the Senior Games. So I started running.

Whenever I ran the 100-meter I would pull a hamstring. I’ve had more pulled muscles than anybody! Two years ago, it became evident that I just was not able to sprint without injury.

Figure 8. Allison, Kyle, Ryan, Becca, Trish, and Paul, Lake City, Colorado, July 4, 2014.

The trout fishing there is great. We also see elk and moose.

Roberts: What about bears?

Ellis: I’ve never seen a bear there, but they are around. You have to be “bear aware” and make sure that your food is locked up securely. After two or three trips to Lake City, my wife and daughter restricted our camping out to no more than 2 nights. After that, they needed a hotel with a shower. We would rent a cabin at Lakeview resort, which is outside of Lake City on Lake San Cristobal, the second largest natural lake in the state. Twelve years ago, we bought a little two-bedroom, one-bath rustic cabin built in 1942 called “Hunter’s Haven.”

The next summer after the purchase, the whole family was there—five adults—with one bathroom. That wasn’t going to cut it. The next year we remodeled it. We have converted it into a small house, with three bedrooms and two baths. As far as I’m concerned, it is paradise. I can’t spend enough time there. My son, Ryan the Renegade Lawyer, is living there now.
When Becca moved back to Dallas, she decided she would help me train because she was a track star during high school. I switched to the 400 meter. Becca and I go to St. Mark’s track. She pushes me to run longer distances than I want to. At the State Senior Games in San Antonio in April 2014, I won my age group for the 400 meter with a time of 71 seconds, and I came in second in my age group in the 200 meter, with a time of 32.4 seconds. My goal is to get under 70 seconds for the 400. Because I won my age group, I qualified for the National Senior Games, which are held every other year. It will be in Minneapolis in July 2015.

Now I’m looking for another race to run in. I ran in Luke’s Locker Allcomers Meet, which is an open track meet. The guy who won my age group at Nationals last year in the 400 ran it in 53 seconds. I have to cut 20 seconds off my time! There’s no way I can be competitive in that division. Some of those runners competed in the Olympics or were Southwest Conference champs who are in their 60s and are still awesome athletes. To make the finals in the 400, I’d probably have to get down to 65 seconds. I think I’m capable of it, but whether it will happen or not I don’t know.

**Roberts**: How much time do you spend a week in training?

**Ellis**: I try to run at least 4 days a week. Sometimes as it gets closer to the event, I run 5 or 6 times a week. The problem at my age is that one needs more time to recover. Maybe my frequent muscle injuries are because I am pushing myself too hard. I still have the mindset of a 40-year-old.

**Roberts**: What’s your height?

**Ellis**: I’m about 5 feet 9½ inches now.

**Roberts**: How much do you weigh?

**Ellis**: About 168 pounds.

**Roberts**: You’ve been that weight for years?

**Ellis**: I weighed about 173 in high school, and the most I’ve ever weighed is 178. The lightest I’ve been is 165.

**Roberts**: What about nonsporting activities? Do you read a good bit? What are your evenings like at home?

**Ellis**: After getting home, I usually go to the track and run. We have dinner around 7:30 or 8:00. Then I dig into my briefcase. There is almost inevitably something I have to do for work. Review a case, read in preparation for an upcoming case, do billings. I also review a significant number of legal cases. (I have two legal cases to review this weekend.) This past week was stressful because I had a conference with an attorney on Tuesday preparing for a deposition on Thursday. Even though I have read all the material, I like to review it again. I had another meeting with the lawyer at 3:30 on Thursday, and the deposition started at 4:00 and wasn’t over until 8:00 PM.

**Roberts**: How many legal cases are you involved with a year?

**Ellis**: Until around 5 years ago, only one or two cases a year. Recently, for whatever reason, I have about six this year.

**Roberts**: Has your law degree helped you in your professional career and in your life work?

**Ellis**: Understanding the law and how the legal system works has helped me adapt my practice in such a way that I am more protected. I realize the importance of doing things with a great deal of care and caution. I try to choose my words carefully and make sure consents are signed. The legal background has helped me communicate with my patients better. The law is about recognizing issues and then communicating about them. It’s given me additional income in that lawyers call me as an expert to review cases. My partners have no interest in reviewing legal cases. I’m more inclined to help because I understand the
situation and can communicate with lawyers and perhaps not be intimidated by them. Also, I recognize that we practicing physicians have a duty to be involved, because if we don’t the lawyers hire physicians who are “hired guns” and not necessarily practicing physicians. Understanding the adversarial system has helped me in being willing to participate.

Roberts: What do you do on the weekends?
Ellis: We have a place at Lake Lewisville. We have a ski/fishing boat and we fish, mostly for black bass or sand bass. When the kids were still in high school, we spent a lot of time out at the lake waterskiing and fishing. Since the offspring are gone, I’m back into running and spending time around the house and less time at the lake.

Roberts: What’s your house like?
Ellis: We have a nice house in Preston Hollow. We lived in Highland Park for 18 years and sold the house after the kids graduated from high school. We moved back to Preston Hollow where I grew up. The original thought was we should downsize since the kids are gone. We found a house but it definitely is not a “downsize.” As long as family and friends keep coming, we will keep it. It’s great for entertaining.

Roberts: How far is it from BUMC?
Ellis: About 12 miles and about 20 minutes.

Roberts: Is your family religious?
Ellis: My kids are devout Christians and were raised at Highland Park United Methodist. I was raised in the Presbyterian faith and went to Preston Hollow Presbyterian Church, and Trish and I were married there. Trish was raised Catholic but soon after she went to college she decided that she was better suited to be a Methodist or Presbyterian.

Roberts: What about alcohol? Do you have wine?
Ellis: I do. I really enjoy wine. At our house we have a refrigerated wine room. My brother-in-law who is an attorney in Cincinnati is a fine wine connoisseur. About 10 years ago he introduced me to Joseph Phelps Insignia, and it is the best wine I’ve ever tasted. Unfortunately, it’s also the most expensive wine I’ve ever tasted. It’s a red blend. Subsequently, I’ve been to the Joseph Phelps winery in Napa. I have a glass of wine three or four nights a week. Becca and I wind down by discussing the day’s events over a glass of wine.

Roberts: Becca is in the advertising business. What did she run in track in high school?
Ellis: She ran all three relays: the 400 meter, 800 meter, and the mile relay. She is only 5 feet 2 inches tall but is incredibly fast for her size. As a ninth grader, she was on the varsity team at Highland Park and ran all three relays. They won regionals. They beat Lancaster, which has always had an incredible track team. They came in second in the mile relay. They had two seniors and two ninth graders. Becca as a ninth grader went to Austin for the state championship in the mile relay. The next year she started running cross-country, and she was team captain her senior year and they won state that year.

Roberts: You’ve won several teaching awards while at BUMC. You must be quite proud of that achievement.
Ellis: The award I’m most proud of receiving is the Outstanding Faculty Award for the Orthopedic Department in 2002, chosen by the Southwestern orthopedic residents. It was quite an honor and was presented at a banquet. They got me to attend by involving Trish in getting me there. It was a total surprise. Another award, a plaque, was given to me by the ancillary surgical technicians (ASTs), these individuals at BUMC who bring the patients to the operating room for surgery and serve in the operating room holding retractors and cutting sutures, etc. They scrub with us every day, so you get to know them as friends as well as coworkers. Through the years I’ve had many different ASTs. Many were premed students working part-time jobs. They presented me with an award for being their mentor and teacher. That was quite an honor to be given that award.

Roberts: Are you going to work forever?
Ellis: Good question. My partners and I have been discussing our exit strategy from practice. Dr. Zehr recently turned 65, Dr. DiBella is 64, and I’m 62. We have all given it a lot of thought. I have friends that are retiring from their various businesses. I do not really want to retire. I enjoy what I do and see no need for retirement. All three of us feel the same way. None of us sees retirement as a way out from something we don’t want to do. In fact, a lot of my friends who have retired have expressed regret for doing so. We have decided to continue our practice but slow down to give us more time to travel and spend time with family. We will keep working until it’s no longer practical or we no longer enjoy it. As long as we are making enough to make it worth the time and effort, and as long as it’s fun, we are going to keep doing it.

Roberts: You talked about microsurgery, and some of the surgery that you do is very delicate. How long can you stay good at that? The eyes give out after a while.
Ellis: Dr. Zehr is the best replant physician in the world, and he is 65. I’ve seen no evidence that he is losing any of those skills. I have not been doing as much microsurgery in the past few years as I did earlier. I have not noticed a loss of hand stability or precision to date. I have seen older hand surgeons lose some precision, but so far I haven’t witnessed it.

Roberts: How many hand surgeons are there in the USA?
Ellis: The last number I saw for the Hand Society was about 3000. There are hand surgeons who aren’t members of the society, so the number might actually be about 5000.

Roberts: How many hand surgeons are in Dallas?
Ellis: Twenty. There are surgeons who dabble in hand surgery now and then, but true hand surgeons do not consider those to be hand surgeons. Before Dr. Lankford did his fellowship in hand surgery, he was a general orthopedic surgeon for about 30 years. He recognized the need for special training in hand surgery and stopped his practice and did a 1-year fellowship. To call yourself a “hand surgeon” you need to finish your orthopedic training and do a year fellowship in hand surgery. You can become a hand surgeon by way of general surgery, plastic surgery, or orthopedics. In terms of fellowship-trained hand surgeons, there are probably 20 in the immediate Dallas area.

Roberts: Is there anything you would like to discuss that we haven’t hit on?
Ellis: One thing that deserves mentioning is that there aren’t many people who have had the opportunity to walk
through a building where they work and pass a picture of their dad on the way to the office. On the first-floor lobby here at BUMC there is a picture that says “Baylor: The Place To Go” and in the bottom left-hand corner is a picture of my dad, which says “Dr. Paul Ellis performs first open heart surgery” (Figure 11). It’s quite touching for me to see that picture of my dad. When I first came to Baylor, it was not uncommon to see a physician looking at me and trying to figure out who I was. Then the eyes would search out my name on my coat and put the two together. Those encounters are much less common now than earlier.

Roberts: Your mother is still alive?

Ellis: She lives in an assisted living community here in Dallas.

Roberts: And your stepfather?

Ellis: He died in 2002. There is one other story that I should tell. As a hand surgeon, I see patients with ganglions, which are very common. I always tell patients their choices: option 1 is to watch it because you could get lucky and it will go away; option 2 is to numb it and pop it with a needle and aspirate it, but it will probably come back; and option 3 is to excise it. They used to call this “the Bible lesion” because you would take the family Bible and put the hand down on the table and whack it with the Bible and it would often go away. In fact, when I was in the fourth grade, a lady came to our house, my dad gathered the kids, sat the lady at the kitchen table, and with a big book he hit the big knot on the back of her wrist. She screamed and sure enough the bump was gone. I’ve always wondered what happened to that lady with the knot. About 15 years ago, while seeing a patient with carpal tunnel with numbness and tingling, she said: “Oh, by the way, honey, I knew you when you were a little boy.” I said, “Really?” She said, “I came over to your house one day with a ganglion on my wrist and your dad smashed it with a book!” I couldn’t believe it and told her that I have been telling my patients that story for years. I asked her what happened. She said, “He smashed it with the book and it was gone for about a month. Then it came back and I went to see him at his office and he smashed it again. It stayed gone for another month or two and came back again. I went over to St. Paul and had a hand surgeon remove it.” She sticks out her hand and shows me the scar. That’s kind of a Paul Harvey—“the rest of the story.”

Roberts: That’s great. Thanks for sharing.
STEVEN MARSHALL FROST, MD: a conversation with the editor

Steven Marshall Frost, MD, and William Clifford Roberts, MD

Steven Frost (Figure 1) was born on September 2, 1948, and grew up in Dallas, Texas. He attended public school and then Texas Christian University (TCU) on a football scholarship. After obtaining his bachelor’s degree in biology, he went to the University of Texas (UT) Southwestern Medical School. He also interned and did his residency in urology at that institution, and after training entered the private practice of urology at Baylor University Medical Center at Dallas (BUMC), where he has been ever since.

He built a large practice and became very popular with the BUMC community, served on several of its major committees, and in 1994 was president of the medical staff. In 1995, he was chairman of the executive committee and medical board of BUMC. He has been very active for many years in teaching the urology residents at UT Southwestern who rotated through BUMC and also through Southwestern’s own hospitals, where he has been clinical professor of urology for many years. He has received awards from the urology residents for his outstanding teaching during two different years. He has been one of D magazine’s “Best Doctors in Dallas” for each of the last 13 years and one of Texas Monthly’s “Best Doctors in Texas” for each of the last 10 years. Dr. Frost is a great guy. It is a pleasure to be in his company. He and his lovely wife are the proud parents of two outstanding daughters, and they have been rewarded thus far with one grandchild.

William Clifford Roberts, MD (hereafter, Roberts): Dr. Frost, thank you for coming to my house for this interview. It is August 17, 2014. May I ask you to describe some of your early memories, your growing up, and your parents and siblings?

Steven Marshall Frost, MD (hereafter, Frost): I was born breach at Methodist Hospital here in Dallas, and I spent my earliest years in Oak Cliff. My dad built a house near the corner of Inwood and Mockingbird when I was around 4 years old. The first thing I remember was looking down in a hole in the foundation of that house and wondering how deep it was. I grew up in the Dallas Independent School District and graduated from Hillcrest High School. I went to TCU in Fort Worth and came back to Dallas for medical school at UT Southwestern. I did all of my training at Parkland and Southwestern. After completing my residency, I came to BUMC and have been here ever since. I have one sibling, a sister, Marcia Stebbins Frost.

Roberts: What was her birth date?
Frost: September 25, 1949. She was a schoolteacher until she retired, and she now spends half her time in Houston, Texas, and the other half in Minnesota.

Roberts: What sports did you play?
Frost: I started playing football in the fourth grade. I was an All-City tackle my senior year in high school in 1966 and was one of the two heaviest linemen on the All-City Team at 205 pounds! I received a football scholarship to TCU. One reason I went to TCU is because the coach was the only college head coach who discussed my future education with me during recruitment. He said that if I came to TCU he would make sure I got my premed education.

Roberts: When did you know that you wanted to be a physician?
Frost: I didn’t have any medical people in my family except my paternal great uncle (“Uncle Larry”), a family practitioner in Connecticut, but he did not influence me. I may have met him one time. I got interested in medicine during my high school senior year. During football practice I got kicked in my bicep muscle and developed a huge hematoma. I was taken to Dr. Stony Cotton, an orthopedist who played football and ran track at Baylor University. He took care of me and tried to recruit me (to Baylor) at the same time. He took me to Southern Methodist University (SMU), where they had new ultrasound equipment. He drove me every afternoon to SMU for heat and ultrasound treatment on my hematoma. On Friday afternoon, I went back to his office and he put a soft cast on my arm. While I was there he showed me x-rays of other football players. He also took several football players including me out to dinner. He had a

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rotary-dial phone in his car. That impressed me. I decided that I wanted to go into medicine.

In medical school I debated whether I wanted to be an orthopedist or urologist. I asked Dr. Paul Peters, a urologist at UT Southwestern, after a few of his lectures what he would recommend that I do to look into being a urologist. Pharmaceutical companies used to sponsor a 3-month summer externship. I applied and got it the summer between my junior and senior year in medical school. I served on the urology service at Parkland Hospital with the idea that I would either love it or hate it. I continued to enjoy it. I had one more orthopedic rotation my senior year and when on call I was up all night long. That was another reason I decided to go into urology instead of orthopedics.

Roberts: **What was your father's name?**


Roberts: **Your mother's name?**

Frost: Catherine Cook (November 1924–).

Roberts: **What did your father do?**

Frost: He went to Texas A&M and received a degree in architectural engineering. I can still sing their fight song and alma mater. He was a huge Aggie fan. After his service in the Navy in World War II, he and my grandfather started working together in the real estate business in the Dallas area, in Balch Springs and Pleasant Grove. They built little subdivisions—sold, financed, insured, and maintained the homes. Later on my dad went within a 100-mile radius of Dallas and bought farms and ranches. He would fix them up and sell them as weekend retreats.

Roberts: **Did your mother work outside the home?**

Frost: No.

Roberts: **What was your home like?**

Frost: We were very family oriented. We had dinner every night at home as a family. Dad was gone a lot on the weekends, and Mom would take us to Highland Park Presbyterian Church where she has been the secretary for the 4- and 5-year-olds for 60-some odd years. She first started when I was 4 years old. She still drives at almost 90 years of age. We grew up in that church.

Roberts: **What were some of the conversations around the dinner table at night?**

Frost: My dad and I were involved with athletics, so many conversations revolved around sports, specifically my football practices and games. I remember one time I had gone for my athletic physical and the doctor thought I might have an early hernia. That topic stirred up a huge conversation at the dinner table with all the concerns of its ramifications. There was a lot of discussion about school and grades, but without a lot of pressure on my sister and me to perform academically. Good grades were expected. A's and B's were acceptable, and it was just assumed there wouldn't be any lower grades. It was a pleasant house to grow up in.

Roberts: **You and your parents got along quite well? And your sister?**

Frost: Yes. My sister and I are still close, although she lives in Houston for 6 months and in Minnesota the other 6 months. Both she and her husband are now retired. He is originally from South Dakota and they have a family lake house on a lake in Minnesota and go up there from June through October.

Roberts: **Does she have children?**

Frost: She has two girls.

Roberts: **Did you play sports other than football?**

Frost: I did until the sixth grade. I was at a catechism class at church and got my finger slammed in one of the big church doors. Basically I lost the tip of that finger. They took me to the closest doctor. I remember being held down as he tried to suture the skin back onto my fingertip—without anesthesia—and bandaged my finger up. I had made the starting lineup on the basketball team when I hurt that finger. After that, I played only football. My dad wouldn't let me play baseball during the summer because he wanted to take trips as a family. I was limited to football.

Roberts: **Did your family take vacations?**

Frost: We always went on family vacations. My dad felt that he never needed to leave the state of Texas. Everything one needed was in Texas: piney woods to the east, mountains to the west, beach to the south, and the plains to the north. My father, even though he had been in the Navy, went on an airplane for the first time in his life when he was about 68 years of age.

Roberts: **Where did you go?**

Frost: Every August for 2 weeks we went to Port Aransas. We would stay in a motel. We would catch crabs, fish offshore, and fish off the piers. I'd stay all day on the pier watching people fish. I loved it. The Tarpon Inn, where presidents had caught fish, was there.

Roberts: **What's the biggest tarpon you caught?**

Frost: I have never caught one. I mainly caught kingfish and mackerel. They come in closer to the shore during August.

Roberts: **How big do tarpons get?**

Frost: Seven to eight feet long, over 100 pounds. It is very hard to catch them. Most of the tarpon fishing is in Key West, the Bahamas, and Central Mexico. Back then, the current just brought them in close.

Roberts: **What other places did you visit?**

Frost: My grandfather, father, and I all belonged to Little Sandy Hunting and Fishing Club about 100 miles east of Dallas (Figure 2). We spent a lot of time there, and I still spend a lot of time there. I grew up hunting and fishing with my dad. My dad worked on weekends so he and my granddad would go during the week but, as a family, we typically went on the weekends.

Roberts: **What would you hunt?**

Frost: Deer, ducks, and hogs mainly, and we fished for crappie, bream, and bass.

Roberts: **Did you shoot hogs?**

Frost: I don't shoot hogs. Hogs are considered “pests” because they compete with deer and turkey for food. Some people eat them. A lot of the game wardens say to shoot them because they reproduce like crazy and they take over farms and ranches and compete with game for food.

Roberts: **When you go to Little Sandy, where do you stay?**

Frost: We have a 2-bedroom, 1-bath cottage. There are 84 members in the club (since 1907). Probably about one-fourth of those members use it regularly.
Roberts: What does your wife do when you go there?

Frost: She used to fish with me but not hunt. She’s an animal lover and doesn’t like to look those creatures in the eyes. She will go with me sometimes when I’m fishing and read a book. She mainly takes four dogs for long walks. We just get out in the country and relax. We have some friends down there so it’s a social thing.

Roberts: What about your daughters? Do they enjoy those activities too? What are their names?

Frost: I have two daughters. They love it. Elizabeth Alden, born January 19, 1984 (Figure 3), and Molly Caroline, born April 27, 1985. They’ve grown up going there. When they were young I tried to expose them to everything that I liked to do so they could at least try them all. They both love to fish. Neither has shot any big game (deer), but they have shot some doves and ducks (Figure 4). Boys want to reach their limits, but my girls only want to get one just to prove they did it.

Roberts: As you were growing up, in grammar school, junior high, and high school, were there any teachers or coaches who had a major influence on you?

Frost: That’s a great question. The one teacher I remember from high school who had a major impact on me was my high school English teacher, Tetz Cox. She tweaked my interest in reading. We didn’t read a lot at home. We had hunting and fishing magazines, a few books on hunting or fishing, but not a lot of reading in general. I love to read now. She took a real
interest in me and I soaked it up. I remember going to college and thinking my college English teachers were nothing compared to my high school English teacher. She became the head mistress at Hockaday (private school).

Roberts: She must have complimented you a lot.

Frost: She knew how to criticize without making one feel embarrassed or uncomfortable and still create some new thoughts from the criticism to improve. Also, my line coach at Hillcrest was Ken Kimbrell. I played tight end for a long time. My head coach asked if I wanted to play football in college, and he and the line coach said that if I wanted to play in college I should switch to a tackle position. I agreed.

Roberts: Why did they say that?

Frost: I wasn't quite fast enough to be a tight end in college. Coach Kimbrell worked with me that season. I gained about 30 pounds between my junior and senior years, working out with weights. It was instrumental in talking to college coaches and helped me get a scholarship.

Roberts: How tall were you back then?

Frost: I was six feet tall and weighed 205 pounds and eventually got up to 225 pounds in college. I'm now at 205.

Roberts: As these colleges started recruiting you, what did you think about it? You had already decided you wanted to go to medical school, right?

Frost: Yes. Other than the TCU coach, none talked about my education in college. My first semester at TCU I was in the wrong biology class for premed. No one told me what I needed for premed since I was in with a bunch of football guys signing up for classes. By my second semester I was pointed in the right direction.

Roberts: Do you read fast?

Frost: I'm not sure how you define that. I read fairly quickly.

Roberts: What do you like to read most?

Frost: I used to read mostly nonfiction. A patient suggested the Jack Reacher novels by Lee Child. I've read every one of his novels and so has my wife. Now I read both fiction and nonfiction. I recently read Unbroken, which was fabulous. I read some religious books. I like adventure and The Wall Street Journal.

Roberts: Not many high school athletes play college sports. How did college football hit you? You had to practice a lot and also keep your grades up. How did you manage it?

Frost: It was an interesting experience. I had a lot more fun playing high school football than college football. College sports are a business and grown men are trying to make a living. Their success depends on how their players perform. The head coach made sure I got my premed education. I was a guard at TCU (Figure 5). My offensive line coach didn't like that I had two labs a week, on Tuesdays and Thursdays, and they were not over until 4:00, so I would get to practice for only about 30 minutes on those 2 days. He basically said I would never play because I was not there for practice. He said that I might as well give up football. I told him that I had come to college to get an education and I appreciated his opinion, but I wasn't going to give football up. I then went to the linebacker coach who also was in charge of the specialty teams and I asked him to give me a tryout on those teams. I red-shirted my sophomore
year and then lettered my junior and senior years. I played on the specialty teams—kick-off punt and punt returns.  

Roberts: But you had to go to all the practices?  

Frost: Oh yeah, except for those two lab afternoons. The head coach would check on me and ask how I was doing. It was tough. After a few months I got lined up with a premed advisor and he basically was in my ear all the time about how hard I needed to study and what I needed to do. I did have fun but I had to work hard too.  

Roberts: In college, you obviously had to make the grades to get into Southwestern. Did you sleep much? How did you do it?  

Frost: My routine when we weren't playing football wasn't that tough. During football season after practice, I ate dinner and then went to the library for 2 to 3 hours every night. I had to discipline myself to do it.  

Roberts: What was your major in college?  

Frost: Biology.  

Roberts: What did you do during the summers?  

Frost: Summer jobs were arranged for the football players. My jobs were all manual labor. I had two different construction jobs. The hardest summer job I ever had was working for a cement company, where I had to clean up the cement that sloshed over the sides of the kilns and shovel it into wheelbarrows and trash it. The kilns were made with bricks and occasionally one or more bricks would fly out. When that happened a crew would have to go into the kiln and find and replace the bricks or tighten the loose one. We would wait until the kiln cooled down to about 150 degrees, hydrate ourselves, and jump into the kiln for a maximum of 10 to 15 minutes to fix the bricks. When we came out we'd have to sit around for a couple of hours until we rehydrated and cooled down. Another summer job was at a steel mill. My job was to pick up the excess steel trimmings that were shaved off the steel plates and place them in a big bin for recycling. I worked pretty hard during my summers.  

Roberts: You kept in good shape.  

Frost: I tried to stay in good shape. When I first entered medical school I stopped working out because I had been working out so hard for so long. I found, however, that I needed some sort of exercise as a break from studying. I started running.  

Roberts: When were you at TCU did you join a fraternity?  

Frost: I was a Sigma Alpha Epsilon—SAE. I was the chapter vice president during my senior year.  

Roberts: When did you get married?  

Frost: I've been married to my wife for 32 years. We got married in 1982.  

Roberts: What's your wife's name?  

Frost: Linda Sue Williams. She was born on July 9, 1949.  

Roberts: And you were born when?  

Frost: September 2, 1948.  

Roberts: What were some of Linda's features that attracted you?  

Frost: When I was playing high school football, there used to be a ward called “12 to 20”—a teenager ward—on the sixth floor of BUMC, where Hoblitzelle Hospital is now. A friend of mine had surgery and I was visiting him. While I was walking out of his room, a cute gal was walking down the hall, and it was Linda. She was 17 and I was 18. We looked at each other, said “hi,” and started a conversation. We dated in our late teens. She went to SMU. We had other boyfriends/girlfriends but we would get together during the summers. Then we didn't see each other for a long time. She went to nursing school at Baylor and ended up as the supervisor of the neurointensive care unit. During my sophomore year of medical school I did an externship with Charlie Shuey and Charles Jarrett, pulmonary physicians at BUMC. When walking into her unit with them, I ran into Linda again. It was an awkward moment. I didn't see her again for a while. Then a mutual friend arranged a blind date for both of us. This was in the late 1970s. The blind date was Linda. We've been together ever since. She was a cute gal—a real head turner.  

Roberts: It sounds like she reads a lot too and that you are best friends.  

Frost: She and I trade books all the time. We are reading more fiction than nonfiction now. She is my best friend (Figure 6).  

Roberts: What else do you do together?  

Frost: We've always enjoyed doing things outdoors. We used to play tennis, snow ski (Figure 7), hike, and walk. She's given up the tennis and snow skiing. Now the most we do together is walk with our four dogs.  

Roberts: Where do you live?  

Frost: We live in Preston Hollow.  

Roberts: When did you come to apply to medical school, what did you do?  

Frost: I applied to UT medical schools in Galveston, San Antonio, and Dallas and also to Baylor College of Medicine in Houston. Virtually every premed student at TCU went to Galveston back then. I assumed that I would be going to Galveston too, but I was rejected. I felt like my world had caved in. But fortunately within 2 days of being rejected at Galveston I got an acceptance letter from Southwestern, although I almost didn't get it. A neighbor down the street found it blowing in the street and brought it to our house. The letter hadn’t made it into the mailbox. I had dreams of being a good high school biology teacher for a couple of days before that acceptance letter arrived.
Roberts: When you first went to Southwestern, were there any surprises?

Frost: I’m not sure I was really ready for being around so many smart people. It was intense. A lot of my classes in college were very small. All of a sudden I’m in classes of 125 to 130 hyperintense and nervous students. It was a lot more intense experience than what I was used to. Overall, the atmosphere I encountered was one that had not been discussed with me earlier.

Roberts: As you rotated through the various subspecialties, did you figure out pretty early that you wanted to be a surgeon?

Frost: I figured that I wanted to be a surgeon before I ever got there. I had that surgeon mentality. When I went to Galveston to interview I’d never seen an operation. They took me into one of the amphitheaters where a laparotomy was being performed. They opened the abdomen and laid the bowels out. I knew that I was going to pass out if I didn’t get out of there. I said something to the fellow I was with and he took me into the hallway. Then I’m thinking to myself, “Great, here I want to be a surgeon, see my first surgical case and nearly pass out.” I never had trouble after that. Maybe that’s why Galveston didn’t take me.

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

Frost: Dr. Paul Peters. He got me interested in urology from his enthusiasm. Everyone loved Hal Weatherby, the anatomy teacher.

Roberts: Do you think it was urology that attracted you or Paul Peters?

Frost: A little of both. I knew I wanted to be a surgeon. Urology is such an interesting subspecialty because of its unique and interesting surgical techniques which have evolved from scopes and open surgery to robots and endoscopy procedures. We do our own pathology and radiology. There are a number of patients who have chronic conditions that have to be tended to, but a lot of urologic issues can be treated and resolved. Paul Peters may have had the bigger influence on me.

Roberts: Did he influence George Hurt?

Frost: Probably before Dr. Peters was Dr. Harry Spence. My favorite story about Dr. Spence was that he also got rejected by Galveston. He went to Massachusetts General Hospital! When I was a resident, the most common operation done was open kidney stone surgery. One of the last cases I ever did with Dr. Spence was a kidney full of stones. We made a huge flank incision and tried to remove all the stones seen (radiographs were taken during the surgery). Dr. Spence asked me to take off my glove and put my index finger in each calyx of the kidney. “The most sensitive stone instrument is the tip of your index finger,” he indicated. I did as he said. It was quite an experience. I guess the person who influenced Dr. Hurt was Dr. Foster Fuqua, who hired him. George Hurt was an incredible guy. When I was training I always thought he was unbelievable. When he offered me a job I was honored. He and I shared the same side of the office until he retired.

Roberts: I suspect a lot of readers don’t really know much about a urology practice. What is a usual day like for you? How many cases do you do a week? How much time do you spend in the office versus the operating room?

Frost: It depends on where one is in his or her career. I’m slowing down a bit now. A year or so ago I decided to stop doing big open surgical procedures. I have two young partners who are excellent surgeons, and I let them do the big cancer operations now. Probably half of my practice is in the office and the other half is in the operating room. We do a lot of fairly minor procedures in the office: cystoscopies, vasectomies, and excision of small bladder tumors, for example. Our operations include a broad spectrum, from burning off warts and circumcisions to radical cystoprostatectomy (removing the urinary bladder, prostate gland, and reconstructing the urinary tract). We also deal with infertility issues, urinary tract infections, and kidney stones. Some urologists find it more efficient to operate for an entire day. We’ve become very involved with robotic procedures for prostate gland and small kidney tumors. We still do a few artificial urinary sphincters and penile prostheses. I think in the future one will see more urologists focusing on specific areas instead of doing it all. I am now focusing more on the endourologic procedures and more office-based procedures.

Roberts: What is your age?

Frost: I am 66.

Roberts: Who are your partners?

Frost: When I went to work at BUMC, they were Drs. Elgin Ware, George Hurt, and Mike Goldstein. Now I’m the oldest practicing urologist at BUMC. Bob Schoenvogel, Matt Shuford, Scott Webster, and I are now in the office (Figure 8). In the next couple of years all of the BUMC urologists will be consolidated into one big group. BUMC is planning to build a new office building across Gaston Avenue from the present BUMC, and the plan is that we will move into that building.

Roberts: Does the prostate gland get big in every man eventually?

Frost: One of my favorite sayings to my patients: “In all men and dogs as we get older our prostate glands get bigger and/or tighter.” We formerly thought the size of the prostate gland was the all-important factor. Now we know muscle tone is just as important. That’s why alpha-blockers do such a good job on the prostate. I cannot tell you the exact percentage of men who have prostate trouble as they age. I think some guys slide...
by throughout their life and never have any prostate problems, but lots of men do eventually.

Roberts: Are there many men by age 80 who are not on an alpha-blocker or have a prostate problem?

Frost: Yes. But we see only the men who are having a problem. A lot don’t realize that they have a problem until they have another procedure done or have an anesthetic or pain medicine and then the problem is apparent. We see many patients with postoperative urinary retention, the inability to void after surgery. Some will come back, some don’t.

Roberts: The procedures you do for prostate gland enlargement have changed radically over the years?

Frost: Yes, no, maybe. Basically the techniques have not changed that much. I tell patients to think of their prostate like a thick-rind orange with a channel through the middle. The procedure removes the meat of the orange and leaves the rind behind. How you do that depends on the surgeon’s skill and preference. In the good old days, a lot of open prostatectomy procedures were done. The TURP procedure uses a monopolar electrical current which has been around forever and is now considered the gold standard. The laser technique destroys the periurethral tissue. I’m currently using bipolar as opposed to monopolar technology. I think it’s more hemostatic.

Roberts: How many urologists are in the Dallas metroplex?

Frost: I would have to guess 50 to 60. Years ago all urologists knew one another. We had monthly meetings.

Roberts: Your biggest society is the American Urologic Association?

Frost: Yes.

Roberts: Do you go to those meetings every year?

Frost: I don’t. The American Urologic Association meeting has gotten so big and there is a lot of international attendance, so it’s a three-ring circus. One can get the meeting information online. If I have a little time off I would rather take a vacation with my wife.

Roberts: How much time do you take off a year?

Frost: We have no rigid rule about that. We let everyone in our group do what they want to do. I probably take 4 to 6 weeks off a year. I take more time off now than I did when I was younger. My partners and I take as much time off as we want, but we are a production-based group so if someone isn’t there they aren’t making any money. I can’t ever recall anyone abusing our rule.

Roberts: You are 66. When you were 40, what was on-call like?

Frost: Fortunately, at BUMC, when a urologist hits 65, emergency room coverage is waived. I was quick to remind my partners last September that I was 65. I still take Wednesday night call for our group. When I first went into practice I wanted to be on call for the emergency room because that was one way to build a practice. Now, the BUMC emergency room is the referral center for all of North Texas. About 2 weeks ago I was on call and saw two patients with Fournier’s gangrene (necrotizing fasciitis of the genitals, pelvis). These patients are really sick and generally require one to three operations to debride tissue and are in the hospital for at least a week. Wound care services are involved. Patients who are very ill are referred to BUMC’s emergency room for “a higher level of care.” Now at age 66 and thinking about slowing down, I’m taking care of some very sick patients. We are going to add a new partner in July 2015 and hopefully then I’ll be able to give up all on call. That will allow me to continue seeing patients in the office for a few more years.

Roberts: How about weekends? Do you take call on weekends?

Frost: That ended when I turned 65.

Roberts: How did your on-call rotation go when you were younger?

Frost: There are two groups of urologists at BUMC now: our group and the Drs. Fine and Eric Smith group. We all share the same business entity but we are separate practices. With the five physicians, one would be on call for the emergency room every fifth weekend. Those could be busy times. I’ve had as many as 20 patients to see in the hospital. When on call for the emergency room, that same person is also on call all week long for referrals from the emergency room.

Roberts: Do you and your wife travel much now?

Frost: Yes. We have one grandbaby so we go to see her pretty often or they come here. My other daughter lives in Dallas and we see her often. My wife and I enjoy traveling. We try to go somewhere at least once a year. We go to the fishing and hunting club on the weekends. We are part-owners of a condominium near Beaver Creek, Colorado, and try to get there a few days each year. I still enjoy snow skiing at least once a year.

Roberts: One daughter lives in Birmingham? What is the situation with her?

Frost: Her husband is a fourth-year urology resident. She graduated from SMU Law School, got married, and stays at home with her daughter.

Roberts: Does she anticipate working as an attorney sometime in the future?

Frost: I think right now she is concentrating on being a mom and doesn’t have to work. We assume they will be coming back to Dallas since they both grew up here.

Roberts: What about your youngest daughter? Is she married?

Frost: No. She got an MBA from SMU. She is dating someone she met while in school.

Roberts: What is your house like? Do you have a lot of books around? Do you keep the books that you read?

Figure 8. With Scott Webster and Matt Shuford at a Baylor fundraiser.
**Frost:** Yes. My wife tries to haul them off to Half-Price Books, but we have quite a few bookshelves and I have stacks everywhere. I think our house is warm and inviting and we have lots of friends visit us. Whenever the kids are in town they stay at our house. We have four terriers running around all the time, barking and nipping.

**Roberts:** What's your life like now? What time do you get up in the morning? What time do you get home from work, and what time do you go to bed?

**Frost:** I usually wake up between 5:30 and 6:00 AM.

**Roberts:** Do you set an alarm to do that?

**Frost:** No. I go to bed early. I'm frequently in bed between 9:30 and 10:00 PM. I rarely see the 10:00 news. I usually read from 9:00 to 9:45 at night and lights out by 10:00. I still have a fair amount of 7:10 AM surgical cases, particularly on Tuesdays. If I don't have to be at the hospital early, I enjoy walking or riding a stationary bike for 45 minutes. I typically get home by 6:30 PM. I usually see about 30 patients each day in the office. While my younger partners are in the operating room doing cases, I'm holding down the fort in the office.

**Roberts:** When you come home at night do you have a glass of wine or cocktail?

**Frost:** Ever since we've known each other, my wife and I will usually have a drink when I get home and catch up on the day. I enjoy having a glass of wine with dinner. I usually try to get my heart-healthy two drinks in.

**Roberts:** You mentioned that you were very active in the church?

**Frost:** We have a strong Christian faith. We are not active in a particular church right now. We were when the kids were younger. I taught Sunday school and my wife helped with that activity.

**Roberts:** As you have gotten older, have you lost any of your operative skills?

**Frost:** Yes, a bit. Several years ago I realized I couldn't see out of my left eye and I was told I had a posterior capsular cataract and I got a crystal lens put in. So now my left eye is perfect; my right eye is still 66 years old. There has definitely been a change in my vision, but not enough to compromise my ability to do procedures. I do get tired a little easier now than in the past.

**Roberts:** You are active in the Salesmanship Club. How did you get into that club?

**Frost:** First, one has to know lots of individuals in the Salesmanship Club. Then one needs a sponsor. Only 16 are admitted every year. It's a little difficult to get in. I've enjoyed that club a lot (Figure 9). Although it is a social organization, the club does provide community service to over 7000 kids and their families.

**Roberts:** You meet how often?

**Frost:** Every Thursday for lunch. I've been a member for 16 years.

**Roberts:** Are there many medical individuals in that club?

**Frost:** Not many.

**Roberts:** Sounds like you have a good number of friends outside of medicine?

**Frost:** Yes. I probably have more outside of medicine than inside.

**Roberts:** One of your daughters got her juris doctorate and the other one got a master's in business administration. You must be very proud of them.

**Frost:** I certainly am. I get along famously with both of them. We are all real close. I'm blessed to have such a loving family (Figure 10).

**Roberts:** What are your plans for the next 10 years?

**Frost:** I still enjoy practicing medicine. I don't have any plans to retire. I'm hopeful that my son-in-law will be joining us in a couple of years. In our group, you have to be an employee for 2 years before you are considered for a partnership, so that's another 4 years or so. I remember George Hurt saying he wasn't retiring until he was 70½ and had to start taking IRA distributions. As I am getting closer to that age, that sounds like a pretty good idea. Right now I envision another 4 or 5 years practicing, I will reassess my situation after my son-in-law has been here a couple of years.

**Roberts:** Let's say you are 71 and you retire. What are you going to do?

**Frost:** That's the big question. Getting up at 5:30 AM, having a couple of cups of coffee, and reading the paper and being done by 6:30 AM, that's the biggest concern. I love my wife, she's my best friend, but being together all day long I'm not sure is such a great idea. Right now, I don't know. The Lord may send some new interest or calling for me and I'll just wait and see.
Roberts: But your health is good?
Frost: Yes.
Roberts: How do you keep your body weight the same as it was when you were in high school?
Frost: I try to eat right, whatever that is. I do enjoy exercise. I probably walk 10 to 20 miles a week and ride a bike 10 to 20 miles a week. I used to be a marathon runner (Figure 11). I have run 10 marathons and finally had to admit that my right knee and lower back will not let me do that anymore. I don't have any serious issues if I don't run.
Roberts: How many miles would you train a week for a marathon?
Frost: The best marathon I ever ran was in 3 hours 35 minutes. At that time I was probably running 40 to 60 miles a week.
Roberts: Now, 3.5 hours for 26.2 miles averages what pace a mile?
Frost: A 9-minute pace yields a 3:54 marathon. So, I was running close to an 8-minute mile pace. I did this as a resident.
Roberts: Did your wife run with you?
Frost: I used to try and drag her along with me. She just doesn't like running. I did get her to train with me for 6 weeks one time, and then she ran a 5K and came in second in her age group. That was the only time she ran a race.
Roberts: Are your girls natural athletes too?
Frost: My oldest daughter likes exercise. My youngest daughter has run a marathon. She and I ran several half-marathons together. They didn't compete like I did in high school and college, but they enjoy athletics.
Roberts: I understand that BUMC no longer has urology residents?
Frost: We have had urology residents at BUMC for 40+ years and recently UT Southwestern pulled them out, citing that they were getting too busy and needed them at Parkland. The Baylor Scott & White alliance created a competitive situation. I always told the residents two things. First, medicine is a jealous mistress. It will try to take most of your time, and consequently you have to learn to balance your life between taking care of patients and trying to keep a happy family at home. Second, make sure your wife wants to live where you want to work because you are going to spend as much time or even more in private practice than you do as a resident, and if your wife isn't happy where you are living, you are asking for trouble.
Roberts: It must have been quite an honor to be elected president of the medical staff at BUMC?
Frost: That was a surprise, and, again, a great experience. I was relatively young at the time and got to meet many people. I learned so much from all the meetings. Administration of a hospital is not an easy task.
Roberts: You've won several awards from the urology residents?
Frost: That was in the good ol’ days. They would pick their favorite staff person at BUMC, and I was fortunate enough to be selected a couple of times.
Roberts: That must create a very good feeling to be elected by people who watch you work every day.
Frost: Absolutely. I enjoyed working with the residents and allowed them to do as much as I felt they could do competently.
Roberts: When did the program stop?
Frost: July 1, 2014.
Roberts: It has always seemed to me that urologists have fun and are a happy group. Is that a proper assessment?
Frost: Absolutely. One reason I chose urology was because I observed that all the urology residents got along fine. The patients have a fairly well-defined problem that we can either solve or focus on. It’s certainly gratifying to solve. I’m not sure...
why urology attracts pleasant personalities, but for the most part most urologists tend to be easy to get along with and fun. The Lord knows there is enough seriousness going on in medicine so it’s nice to have a break in the intensity.

Roberts: What percentage of your patients are women?
Frost: Probably 50% women and 50% men. The only unique problem for men is testicular or penile or prostatic problems. Otherwise, both sexes have urinary tract infections, cancer, kidney stones, and incontinence. A lot of the urological problems are shared. Now, the urogynecologists have taken a lot of the vaginal prolapse problems from us. But those problems can be difficult, and the urogynecologists have extended training in that area so it doesn’t bother me much.

Roberts: Are there enough urologists in the USA?
Frost: No. There is a shortage, and therefore lots of job opportunities are available. The problem is that most physicians want to live in an urban setting and in the larger cities. With the baby boomers getting older, there are more and more older patients.

Roberts: Do you know what percent of your patients come from outside the Dallas metroplex?
Frost: No. We see lots of patients from East Texas, but also from many different locations.

Roberts: How much contact do you have with nephrologists?
Frost: It depends. We have a lot of contact with them on kidney transplant patients. A lot of patients present in the emergency room with renal failure. We end up working with the nephrologists to evaluate. We see a fair number of patients referred to us for “kidney failure” and we rule out some sort of obstructive uropathy and then refer them to nephrologists. I probably see one patient a day who initially might have seen a nephrologist or need to see one. The general internists might get a nephrology consult and then the nephrologists suggest a urology consult and vice versa.

Roberts: Steve, this has been a pleasure. Thank you.
Frost: Bill, it has been a pleasure discussing my professional life and life in general. Thank you.
Teaching with questions

Lonnie Gentry, MTh

In medical education, questions are constant. Questions are asked of fellows, residents, and students. Questions are asked at conferences, rounds, and morbidity and mortality meetings. Questions drive medical education. However, not all questions promote learning. Some questions actually hinder learning. Knowing the difference, and asking questions that promote learning, are key aspects to being an effective teacher. So what kinds of questions promote learning, and what kinds of questions do not? A good place to begin is to understand the difference between pimping and Socratic questioning.

POMPING

Definitions of pimping typically include the following:

1. Someone higher on the ladder questions someone lower on the ladder in a way that reinforces the hierarchical order. In other words, intimidation is present.
2. The questions have specific, factual answers, so there is a right answer and many wrong answers.
3. The questions have an evaluative purpose: Who knows the answer? Who doesn’t?
4. Failure to give the right answer to the question leaves the learner feeling embarrassed, humiliated, and feeling like a failure (1).

By simply defining pimping we have revealed it to be a poor approach to teaching. Intimidation, embarrassment, and humiliation do not foster adult learning (2). Therefore, to be a good teacher, we should avoid pimping. The better alternative is Socratic questioning.

SOCRATIC QUESTIONING

To define Socratic questioning, reflect on the difference between these two related questions:

1. What are the 14 causes of diastolic murmur?
2. What factors can you think of that would cause a diastolic murmur to develop?

The first is a pimping question, as it wants 14 right answers all at once. No thinking is required here, just a regurgitation of facts. And with 14 right answers required, there is a very good chance of failure, causing the learner to feel humiliated and embarrassed (3).

The second question, on the other hand, is a Socratic question because it asks the learner to think, thereby promoting critical thinking. With each right answer there can be praise. With each wrong answer there can be follow-up questions that reveal to the learner his or her need for additional self-directed learning. When done carefully, this kind of questioning avoids humiliation.

Socratic questions can take many forms, as the Figure illustrates. The figure also illustrates how Socratic questions promote critical thinking, a must for practicing medicine.

To ask questions that promote learning, here are some pointers:

1. Diagnose the learners and teach to their level. New knowledge is best built on prior knowledge in small increments.
2. Avoid asking questions for questions’ sake. Do students really need to know the year the stethoscope was invented?
3. Tell learners your goal in asking questions. Your goal is to teach, not to embarrass.
4. Emphasize important learning points. What are the need-to-know items?
5. Do not attempt to intentionally embarrass or humiliate learners. When you do humiliate a learner, reflect on how you can avoid doing the same thing going forward (1).

Finally, to be a good teacher, keep the words of Cicero before you: “Often, the authority of the teacher gets in the way of those who wish to learn” (3).

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Opposing thoughts and objections:
How would you answer someone who said ____? What might these people say?
How could someone else look at this? Why? Why do you think your way of looking at it is better?

Clarification:
Why do you say that? Can you explain further?

The belief, statement, or diagnosis made by the learner

Implications and consequences:
Are you implying ____? If that's true, then what else must be true? How would we put that into action? What happens when you act on that belief?

Assumptions and evidence:
Is this always the case? Why do you think this assumption holds here? Why do you say that?
Is there reason to doubt the evidence?

As I was recently reminded by our colleague, Dr. John Fordtran, the term “autopsy” literally means “to see for oneself” from the Ancient Greek autos (oneself) and opsis (to view). Many pioneers in internal medicine, such as Sir William Osler, performed autopsies because they were anxious to see for themselves the internal derangements that might explain their patients’ symptoms and death. One of Osler’s mentors, James Bovell, stressed that books were very good, but doctors learned medicine by direct observation. Bovell had marked for him a passage from Latham’s Clinical Medicine: “It is by your own eyes, and your ears, and your own minds and your own hearts that you must observe and learn and profit” (1). In this spirit of direct observation, Osler repeatedly stressed the importance of bedside teaching and, when treatment failed, careful follow-up postmortem study.

William Osler entered the practice of medicine because of a fascination with the natural history of disease and morbid anatomy, but he also clearly believed that medicine was fun (2). Osler performed many autopsies, and while at McGill, he decided to write his thesis on postmortem studies of diseased organs. He pestered another mentor, Palmer Howard, for information and literature, and one day Howard gave him Samuel Wilk’s Lectures on Morbid Anatomy. “From that time on,” Osler recalled, “everything was plain sailing” (1). Osler’s thesis included the inspiring statement,

To investigate the causes of death, to examine carefully the condition of organs, after such changes have gone on in them as to render existence impossible, and to apply such knowledge to the prevention and treatment of disease is one of the highest objects of the physician (1, 2).

In his first monograph Osler also quoted Wilks, “Pathology is the basis of all true instruction in Practical Medicine” (3). By all accounts, Osler quickly became one of McGill’s most popular professors, and it was his special classes in pathology and histology that students found mesmerizing. It was also known that large consultation fees might not entice him out of town to see a patient, but he would always come for an interesting autopsy. Osler thus became a great morbid anatomist, and his ‘clinics’ in the autopsy room were, if anything, more interesting that those by the bedside (3).

Osler also stated, “No more instructive work is possible than carefully demonstrated specimens illustrating disturbance of function and explanatory of the clinical symptoms” (3), and such instruction remains a primary goal of our current morbidity and mortality conferences at Baylor University Medical Center at Dallas. Some have also opined that these clinical-pathologic conferences have brought us all back together in an exciting and collegial atmosphere of learning.

Many believe that the study of morphology was the gateway through which Osler attained those high achievements in clinical teaching and practice (3). Unfortunately, however, current trends in medical education jeopardize the use of anatomic pathology in teaching clinical medicine. Today’s avalanche of molecular discoveries are crowding the medical curriculum to the point that hard choices have to be made, and traditional anatomic pathology is one of the first things to go. Again we turn to the writings of Osler himself, which carry a timely message:

The new pathology, so fascinating and so time-consuming, tends, I fear, to grow away from the old morbid anatomy which was of incalculable advantage to the physician, and it is hard to have the student see enough morbid anatomy which has such an important bearing upon the mental attitude of the growing doctor. It is a subject which one must learn in the medical school, but the time assigned is rarely sufficient to give the student a proper grasp of the subject (4).

Osler’s “new pathology” primarily referred to discoveries in bacteriology, but today’s genomics are also displacing traditional anatomic pathology. Molecular studies, however, cannot replace the teaching value derived from a comparison of anatomic findings and symptoms in order to improve a clinician’s acumen. A patient is not simply an amorphous bag of molecules. In addition, many medical schools have eliminated the traditional course in anatomic pathology in favor of focused case-based studies. One effect is that fewer medical students develop a passion for the science of pathology, and currently there are fewer applicants for pathology residencies. Combined
with the trend away from autopsy pathology by many practicing pathologists, the result is that fewer clinicians currently have an opportunity to see for themselves what caused their patients’ symptoms and death.

As I reviewed Osler’s biographies and speeches for this editorial I found myself, once again, becoming inspired and enthusiastic about the practice of pathology in particular and medicine in general. The timeliness of many of his statements is eerie, particularly regarding medical economics and the philosophy of medical practice, and, sadly, today’s medical students and residents can barely identify Osler (2).

In today’s world of rapidly advancing molecular discoveries, dwindling financial resources, and heated arguments over medical economics, it is easy to lose sight of the higher principles which led most of us to choose medicine as a career in the first place, and more and more physicians are leaving medicine rather than face this maelstrom. Some of us, however, are finding guidance and a renewed passion for medicine in the words of Sir William Osler, whose courageous and optimistic message remains relevant and continues to instruct and inspire. Osler stated that we should live our lives in “day-tight compartments,” not worrying about past mistakes or future problems, but addressing the work that is directly in front of us. He often quoted Thomas Carlyle, “Your business is not to see what lies dimly at a distance, but to do what lies clearly at hand.”

In my opinion, today’s preoccupation with economic issues threatens to obscure the altruistic goals of medicine: to relieve suffering and to promote healing. Although we must be good stewards of our limited financial assets, Osler cautioned against what he called the “corroding influence of mammon,” and he had the greatest contempt for the doctor who made financial gain the first object of his work. “Our best protections are high standards and high purpose.”

Osler also believed that the hospital would continue to be necessary within every community:

What wonder that many fall by the way and need a shelter in which to recruit or to die, a hospital in which there shall be no harsh comments on conduct, but only, so far as is possible, love and peace and rest. Here, we learn to scan gently our brother man, judging not, asking no questions, but meting out to all alike a hospitality worthy of the House of God (Hotel Dieu), and deeming ourselves honored in being allowed to act as its dispensers.

Of medicine, Osler warned: “The ancients attempted to make it a science and failed, the moderns, to make it a trade and succeeded.” He went on to add,

Engrossed late and soon in professional cares, getting and spending, you may so lay waste your powers that you find, too late, with hearts given away, that there is no place in your habit-stricken souls for those gentler influences which make life worth living.

He further warned: “If your hearts desires are for riches, they may be yours; but you will have bartered away the birthright of a noble heritage and falsified the best traditions of an ancient and Honourable Guild.”

Today, as we struggle to find our way, the writings of Sir William Osler remain a resource for guidance, inspiration, and renewed commitment to our profession. I believe that through his writings a sense of higher purpose, and yes, fun, can still be found in the practice of medicine.

Acknowledgment
The author wishes to thank Beverly Warren for assistance in locating reference 3.

Coffee: grounds for concern?

Allen B. Weisse, MD

Caffeine is the most widely ingested nonregulated substance on earth. A major portion of this drug is consumed as coffee, with an annual production of over 7.8 million metric tons. Over 2.5 billion cups of coffee are consumed worldwide each day. Given its popularity, it is hard to conceive of how Western civilization might begin each workday without this critical liquid allotment.

Despite the prominent role it has assumed in our daily lives, comparatively little about it has been published in the strictly academic press over the past 300 years or more. The most comprehensive compilation of this literature is, undoubtedly, contained in the two-volume collection of von Hünersdorff and Hasenkamp (1). Included within these 1661 pages are over 16,000 references. However, there is no index, making it difficult to use for research. Furthermore, almost all references predate the late 20th century and thereafter. The references themselves are principally works concerning the distribution, planting, preparation, and other aspects of coffee, with few representing physiological studies or what we would now consider adequate population studies.

Often referred to as “the bible” of pharmacology, Goodman and Gilman does not even list coffee among its references and only includes a few remarks about symptoms related to caffeine withdrawal (2). Fortunately, a number of excellent monographs concerning coffee and caffeine have appeared in recent years, and two of these were consulted for this article (3, 4).

As well entrenched as coffee is in our daily lives, it might be difficult for some to imagine the trials and tribulations coffee has endured over the centuries. Significant consumption of coffee spread from the Middle East and Africa to Europe in the latter half of the 17th century. The first coffeehouse in England opened in Oxford in 1637. The first in France opened in 1639. Before this, in large cities such as London, the available drinking water was so vile that those who could would fortify themselves with various kinds of beer or wine each morning. On switching to coffee, such consumers were immediately struck by the improvement in their mental alertness and clarity, as the haze of alcohol was removed from the start of each day, and coffeehouses soon became centers of lively debate and enlightened conjecture. This dichotomy of response between alcohol and coffee is well recognized by all today.

While coffeehouses became centers of lively debate and conjecture for the concerned public, they were soon seen by some monarchs and other autocrats as breeding places of sedition and unrest. One memorable attempt to abolish them was that of Charles the Second of England. In 1675 he issued a decree banning coffeehouses. This attempt to prohibit the consumption of coffee was no more successful than a similar decree by the ruler of Mecca in 1511. The uproar this caused was so intense that the decree was revoked 11 days following the initial pronouncement. Other attempts to restrict or abolish coffee drinking have also been unsuccessful. A notable response in Germany to such sentiments was Johann Sebastian Bach’s Coffee Cantata (1732), in which, under the glaring disapproval of her father, the young heroine’s right to ingest her favorite beverage is championed.

In the United States, another source of opposition was probably related to a puritanical streak that remains with us to this day. It implies that anything that is pleasurable must, ipso facto, be evil. The critic and journalist Alexander Woollcott expressed this in his own inimitable way: All the things I really like to do are illegal, immoral, or fattening. While no one could ever condemn coffee as fattening, some opposed it either on ethical or religious grounds. To this day, coffee—as well as other caffeine-laden drinks—is prohibited by the Church of Jesus Christ of Latter-Day Saints, for example. The specific questions regarding the health effects of coffee have only been addressed relatively recently in historical terms, perhaps only during the last five or six decades. One gathers in reading such reports that concerns arose based on suspicions that, more likely than not, bad things could happen to you if you indulged in coffee drinking.

What bad things might there be? Many of the complaints about coffee relate to the direct effects of caffeine, to which there is a wide variability in sensitivity. For the highly sensitive imbibers, problems such as insomnia, nervousness, restlessness, anxiety, and palpitations related to extrasystoles are common but easily reversed by reducing intake or abstaining. A withdrawal syndrome including such symptoms as headache and irritability has been described (5). Of greater importance is the possibility of an increased risk of spontaneous abortion among pregnant women consuming large amounts of coffee (6).

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The possibility of an increased risk of developing cancer by coffee drinking has been entertained for some years. A high point in this literature was reached in 1981 with an article in the *New England Journal of Medicine* claiming that “a strong association between coffee consumption and pancreatic cancer was evident in both sexes” (7). However, other groups of investigators performing similar studies were unable to confirm these results, and the study is now considered to have been flawed (8).

Let us now consider some of the notable benefits of coffee drinking reported relatively recently (Table). Coffee has been found to lower the risk of developing Parkinson’s disease (9). Rather than increase susceptibility to cancer, coffee has been found to prevent both prostate cancer (10) and liver cancer (11). The risk of developing type 2 diabetes is reduced (12, 13). Coffee has also been found to protect against cirrhosis of the liver (14); decrease the risk of depression among women (15); and decrease total and cause-specific mortality (16).

We continue to discover new things about caffeine itself. In 1989, a report from Boston appeared demonstrating extreme daytime sleepiness rather than acuteny in five heavy coffee drinkers who finally wound up for evaluation in a sleep laboratory (17). The effects of the sleepiness upon their daily routines were often considerable. Although the incidence of extreme daytime sleepiness is not known, the condition seems to be somewhat rare but not insignificant. All individuals returned to a normal sleeping/awake pattern of behavior upon eliminating caffeine from their diet. How can this occur? Normally adenosine has a sedating effect, but caffeine eliminates this effect by blocking the adenosine receptors in the central nervous system. However, in a few patients, coffee triggers an overly robust response with an increase in adenosine and the number of receptors to counteract the caffeine. This accounts for somnolence rather than the usual increase in awareness among these individuals. While this response might prove disabling in some patients, as reported by Regestein, in others this effect might prove tolerable or even desirable when ingesting coffee shortly before retiring.

In reviewing the multitude of effects that coffee has demonstrably elicited, one must conclude that all of these are not due to the effects of caffeine alone. There are many other chemically active substances in coffee, and we are just beginning to recognize what they are and what they do. Within each coffee bean are carbohydrates, proteins, phosphates, volatile and nonvolatile acids, and, of great interest, polyphenols with their antioxidant properties. How do they relate to reducing the risk of such diverse conditions as cancer, cirrhosis, and Parkinson’s disease?

Recently a coffee genome has been generated (18). Perhaps secrets about this incredible plant will be disclosed through this investigatory portal. In the meantime, we can all take comfort in continuing to discuss this and other promising breakthroughs in medical science—perhaps over some cups of steaming hot delicious coffee.

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<td>Lowers risk of Parkinson’s disease</td>
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<td>Decreases risk of depression in women</td>
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The opening words of the first chapter of this book—“Chester, South Carolina, late evening of February 16, 1865”—caught my attention since Chester happens to be my hometown as well as Dr. Babcock’s birthplace. James Woods Babcock (1856–1922) was the son of a Chester physician who served as a Confederate surgeon and tried to raise his two sons as best he could in the impoverished circumstances of the postwar American South.

After completing his mediocre high school education, Babcock went north to Phillips Exeter Academy and, helped by a series of scholarships, spent 4 years at Exeter and 4 years at Harvard College (where he belonged to the famous Class of 1882 crew team), followed by Harvard Medical School and, finally, training as a psychiatrist at McLean Asylum.

In 1891, Babcock returned to South Carolina as superintendent of the woefully underfunded and overcrowded state lunatic asylum in Columbia. He did his best amidst difficult circumstances and tumultuous state politics before ultimately resigning, in 1914, after his staff physicians—backed by stormy Governor Cole L. Blease—tried to dismiss his uncommonly gifted and dedicated assistant physician, Eleanora Saunders, who was probably the first woman in the US to graduate vale dictor of her medical school class.

Babcock during his lifetime was widely known and respected as a leading psychiatrist, asylum superintendent, and public citizen, but his posthumous reputation rests largely on his contribution to the American response to pellagra. He recognized the disease in December 1907, unaware that Dr. George H. Searcy of Alabama had described it earlier that year. Medical students memorize pellagra as “the disease of four D’s”—dermatitis, diarrhea, dementia (or severe depression), and death, caused by niacin deficiency—but the manifestations are extremely protean.

The American epidemic of pellagra, which at its peak around 1914–1915 may have affected 250,000 Americans with 7000 deaths each year, may have been caused by the introduction of the Beall degerminator for corn, which converted what had been a whole grain into a highly-refined carbohydrate for millions of Americans. Controversy about its causation was not put to rest until 1937, when chemists at the University of Wisconsin demonstrated that nicotinic acid and nicotinamide prevented and cured canine black tongue (an animal model for pellagra), which was quickly followed by wide usage of niacin for humans, including use in food fortification.

The conquest of pellagra is usually associated with a single name, that of Joseph Goldberger, MD, of the US Public Health Service. Most popular accounts tell how Goldberger went south in early 1914, quickly concluded that pellagra is caused by dietary deficiency (not infection, as was commonly thought), and proved his case the next year with dietary experiments in two Mississippi orphanages and two wards at the Milledgeville, Georgia, asylum, and preached the gospel of a balanced diet with meat, milk, and vegetables, and, before his death in 1929, identified a cost-effective way to prevent and treat it: brewer’s yeast. Goldberger never told the story this way, and Charles Bryan tells the story as it has not been told before: namely, how a coalition of asylum superintendents, private physicians, local health officials, and a few members of the US Public Health and Marine Hospital Service (as it was then known) established for the first time a broad English-language competence in pellagra, sorted through the competing hypotheses, narrowed the viable alternatives to basically two, and thus set the stage for Goldberger.

James Babcock led the way. In 1908 he went to Italy, accompanied by the controversial politician Governor Benjamin Tillman (who had appointed Babcock, and who became Babcock’s friend and patient), and verified that pellagra in the US was the same disease familiar to the Italians. Later that year he organized on short notice the first conference on pellagra in an English-speaking nation, which took place at the South Carolina State Hospital for the Insane (as it was renamed) in Columbia.

The following year Babcock organized the first of three triennial conferences of the National Association for the Study of Pellagra, of which Babcock was the first president. Babcock and Claude H. Lavinder, MD, of the US Public Health and Marine Hospital Service brought out the first English-language monograph on pellagra. This was followed by three other American treatises on the disease and numerous journal articles. One treatise was written in 1912 by Dr. Stewart R. Roberts, a cardiologist from Atlanta, Georgia, who is the father of Dr. William C. Roberts and grandfather of Dr. Charles S. Roberts. Thus, by the time Goldberger went south, nearly all American doctors

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**Asylum Doctor: James Woods Babcock and the Red Plague of Pellagra, by Charles S. Bryan, MD**

Columbia, SC: The University of South Carolina Press, 2014. 402 + xxvi pages, hardcover, $34.95.

Reviewed by S. Robert Lathan, MD

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**Book Review**
could identify the key features of pellagra and many could recite the competing hypotheses.

The new “vitamine” hypothesis was introduced in the US at the pellagra conference in Columbia in October 1912, having been put forward earlier that year by Casimir Funk, a Polish-born chemist working in London. Bryan demonstrates, for the first time, how a flamboyant, charismatic European named Louis Westerna Sambon influenced the Americans who launched the Thompson-McFadden Pellagra Commission of the New York Post-Graduate Medical School, which backed Sambon’s insect vector-borne infection hypothesis. News of Goldberger’s breakthrough came during the 1915 pellagra conference in Columbia. The cooperation and goodwill that had previously characterized the American pellagra effort evaporated instantly. Those who refused to accept the inconvenient truth that the root cause was southern poverty drew their semblance of scientific legitimacy from the Thompson-McFadden Commission’s elaborate studies in Spartanburg County, South Carolina. Bryan argues that Goldberger’s need to disprove the Thompson-McFadden Commission’s conclusions seriously delayed the demonstration that brewer’s yeast constitutes an effective therapeutic and preventative measure. Thousands probably died as a result.

Bryan recounts how, as a freshman medical student, he heard the eminent medical historian Owsei Temkin state that “great discoveries are seldom the work of one person. There is usually something ‘in the air,’ so to speak.” Bryan relates how Goldberger, who did little or nothing to establish a hero-myth for himself, duly acknowledged those who helped him reach his conclusions.

Bryan’s own biography was recounted during a 1999 “Conversation with the Editor” of BUMC Proceedings in which Dr. William C. Roberts called him “one of the most interesting people” he knew. Bryan has published extensively in infectious disease, medical history, and medical biography, but Asylum Doctor is probably his most ambitious undertaking, requiring as it did 15 years of painstaking research. He presents Babcock as a flawed hero and thus achieves what he describes as “the ultimate purpose of biography”: to depict one’s subject “as an exemplar of character traits worthy of emulation or avoidance.”

**CV OF CHARLES S. BRYAN, MD (BY S. ROBERT LATHAN, MD)**
—Graduated from Dreher High School, Columbia, SC.
—Attended Harvard College and transferred to the Johns Hopkins School of Medicine in 1963 through the 5 Years Program (receiving both a BA and MD in 1967). I first met Charles in 1963 at our social fraternity, the Pithotomy Club, when I was a senior in medical school. Owsei Temkin, medical historian, was in our first year at Hopkins.
—Edited the Journal of the South Carolina Medical Association for 36 years, from 1976 to 2012, and wrote over 300 editorials.
—Is professor of internal medicine emeritus at the University of South Carolina School of Medicine. Now 72 years old, he is retired but working regularly as a consultant with numerous community activities.
—Is a Master of the American College of Physicians and a recipient of the Order of Palmetto, 2013. He was secretary for many years and later president of the American Osler Society. In 1997, he published a book on Osler. The Charles S. Bryan History of Medicine Room at the University of South Carolina School of Medicine was named in his honor in 2003.
—Has written 12 books, and his current book, Asylum Doctor, shows his meticulous research, with over 1000 footnotes. Around a third of the book consists of footnotes, bibliography, and index.
—As a humanitarian, was a principal founder of the care of patients with HIV/AIDS in central South Carolina.

He is a teacher, scholar, medical historian, author, and a compassionate and skilled physician.

The reviewer, S. Robert Lathan, MD, is a retired internist who was affiliated with Piedmont Hospital in Atlanta, Georgia. He is a member of the American Osler Society and other medical history organizations.
LIPID LEVELS IN PATIENTS WITH CORONARY HEART DISEASE

Sachdeva and colleagues (1) from 6 US medical centers described admission lipid levels in 136,905 patients hospitalized with coronary artery disease from 2000 to 2006. The mean lipid levels were as follows: low-density lipoprotein (LDL) cholesterol, 105 ± 40; high-density lipoprotein (HDL) cholesterol, 40 ± 13; and triglycerides, 161 ± 128 mg/dL. LDL cholesterol <70 mg/dL was observed in 18% of the patients, and ideal levels (LDL <70 with HDL ≥60 mg/dL) in only 1% of patients. HDL cholesterol was <40 mg/dL in 55% of the patients. Before admission, 28,944 (21%) of the patients were receiving lipid-lowering medications. Thus, almost half of patients hospitalized with coronary artery disease had admission LDL cholesterol levels <100 mg/dL; more than half had admission HDL levels <40 mg/dL; and <10% had HDL levels >60 mg/dL. To prevent coronary disease, it is likely that the serum LDL cholesterol will need to be <50 mg/dL.

HYDROCODONE

The most prescribed drugs in the USA are painkillers containing addictive opioids, and they are also driving the deadliest drug problem in the USA (2). On average, 46 people a day die from painkiller overdoses, and 1150 enter emergency rooms each day. Deaths from illegal drugs do not even come close to this number. In 2013 alone, physicians wrote about 180 million prescriptions for hydrocodone and oxycodone, nearly one for every adult in the USA. After underplaying the problem for years, the US Food and Drug Administration (FDA) recommended restrictions on access to drugs containing hydrocodone, which is highly addictive. The changes, which limit refills and mandate more frequent visits to physicians to obtain prescriptions, went into effect in October 2014.

Just one day later, the FDA approved Zohydro ER (hydrocodone bitartrate), a new drug that is pure hydrocodone (3). Unlike other hydrocodone drugs, Zohydro contains no acetaminophen, which in high does can cause liver damage. Zohydro comes without the abuse-resistant measures now common in most narcotic painkillers, such as hardened shells which make them difficult to crush. In capsule form, Zohydro can be easily crushed to be snorted or injected. In the Zohydro case, the FDA flouted the recommendation of its own expert panel, which had voted 11-2 against approval. Overriding a panel is not unheard of but is infrequently done. The FDA's safety mission ought to be broad enough to preclude placing an easily abused painkiller on the market amid an abuse epidemic. An unsigned editorial in USA Today (September 30, 2014) opined that the FDA should reconsider Zohydro and should encourage other approaches to curbing painkiller abuse as well. It advised state monitoring systems that can prevent doctor shopping by patients seeking multiple prescriptions.

The FDA commissioner, Dr. Margaret A. Hamburg, emphasized that the FDA reviews drugs using a scientific approach within our legal framework and considers not only those who abuse opioids, but also those who use them responsibly. She continued, “While we appreciate the concerns surrounding our recent approval of Zohydro, it should be recognized that Zohydro is a time-released analgesic that, without the added risk of acetaminophen, fills a need for pain patients who respond best to hydrocodone.” She indicated that the problem of opioid overdose is largely driven by inappropriate prescribing, use, and diversion of these drugs. FDA is part of a broader administration-wide strategy to combat overdose. She concluded: “Opioid abuse in this country can only be brought under control by concerted effort by many prescribers, pharmacists, scientists, public health officials, law enforcement, patients and their families. FDA will continue to do its part to overcome this public health crisis.”

OBESITY AND CANCER

The American Society of Clinical Oncology recently indicated that obesity is now implicated in as many as 1 in 5 cancer deaths—about the same rate as cancers linked to smoking (4). Yet, most people aren’t aware of this link. A poll released in 2013 found that only 7% of Americans realized there was a link between obesity and cancer. Obesity-related cancers have contributed to increased health care spending. The price per patient of cancer treatments has gone up about 35% since 1996, and the number of people with cancer has risen from 9.2 to 16.1 million. Together, price and incidence have pushed cancer spending...
from $38 to $89 billion. In Texas, about 18% of adults smoke, a significant drop from smoking rates 40 years ago. Since 1990, however, the incidence of obesity (body mass index >30 kg/m²) has climbed to more than 30%. The nationwide obesity rate now is 35%. Obesity also appears to cause more aggressive breast cancer in postmenopausal women and prostate cancer in older men than in the nonobese victims of these cancers. Obesity also has been implicated in several other cancers. Texas Oncology, a major cancer treatment group, opined that obesity and lack of exercise are factors in cancer of the colon, uterus, gallbladder, pancreas, thyroid gland, and esophagus. The prevention: lose some pounds.

TEXAS’S OBESITY

In 1990, just 24 years ago, only 1 in 10 Texas adults were obese; by 2013, nearly 1 in 3 were obese (5). American adults today on average weigh 24 more pounds than they did in 1960. In 2010, 1.26 million Texans had heart disease; it is projected that 5.7 million will have heart disease by 2030. The national obesity rate for Latinos is 42.5%. The report estimated that Texas cases of adult-onset diabetes mellitus could rise from about 2 million in 2010 to nearly 3 million by 2030. Cases of obesity-related cancer in the state could climb from approximately 330,000 to just over 800,000 by 2030. Six states had increases in obesity in 2013, and none of the 52 states or territories had a decrease in the frequency of obesity! In Texas, in 2011, 16% of high school students were obese. If all American adults lost 10 pounds, our health would skyrocket.

GERMS IN THE WORKPLACE

Sumanthi Reddy (6) described a study performed by some University of Arizona researchers at an office building with 80 employees. The researchers contaminated a push-plate door at the building’s entrance with a virus called bacteriophage MS-2. (The virus does not infect people yet it is similar in shape, size, and survivability to common cold and stomach flu viruses.) Within 2 hours the virus had contaminated the break room—coffee pot, microwave button, fridge door handle—and then spread to restrooms, individual offices, and cubicles. There the virus had heavily contaminated phones, desks, and computers. By 4 hours they found the virus on more than 50% of the commonly touched surfaces and on the hands of about half of the employees in the offices. Most of the people did not know each other. The studies were funded by Kimberly-Clark, the Irving, Texas, maker of consumer brands including Kleenex and Huggies.

In an intervention, the Arizona researchers then gave about half of the employees hand sanitizer and disinfectant wipes to use. After the intervention, detection of the virus on people’s hands went from about 30% to 10%. The results were similar to an experiment in which the researchers infected a single employee with a droplet containing an artificial virus that did not cause illness. Within 4 hours, half of the commonly touched surfaces and the hands of half of the employees were infected with at least one virus.

Studies indicate that average adults bring their hands to their nose, mouth, or eyes about 16 times an hour! For children aged 2 to 5, the number can be up to 50 times an hour. The researchers calculated that employees would have had a 30% chance of infection if the organism experimented with affected humans. Just because we are exposed to a virus or bacterium does not mean we will get sick. Much depends on the dose or number of virus particles that we are exposed to, whether we have been exposed to the germ before, and our overall susceptibility and health. Many people have devised low-tech methods of avoiding germs. One can use his or her elbow or knuckle in the elevator rather than the fingertips. The use of a paper towel in one’s hand to open the door in any public restroom is helpful.

Different viruses, of course, have different lifespans, and they also are dependent on factors such as temperature and the material where they are harboring. Some viruses are more infectious than others. Our bodies harbor viruses all the time. The average person harbors trillions of bacteria and dozens of virus species. The norovirus, the most common cause of infectious diarrhea, is super infectious, while others may be less infectious or more difficult to catch. Studies conducted at day care centers have found that 30% to 40% of children without symptoms have respiratory viruses on them. Pathogens have survival rates ranging from seconds to months. Most respiratory viruses can survive a minimum of 2 to 4 days. Some viruses die at high temperatures. Microbes survive differently on different materials. Microbes on porous surfaces, such as carpeting and upholstery, have better survival rates on synthetic fibers like polyester than on cotton. Pathogens are readily transferred on stainless steel surfaces although certain metals such as copper tend to have an antimicrobial effect, and germs will not be able to survive on them more than a few hours. Microbes have comparatively good survival on plastic or Formica. Anything with textured grooves or connection points, like a keyboard or a child’s toy, will have a tendency to collect dirt, which can help survival.

While the University of Arizona researchers believe the use of hand sanitizers and disinfecting wipes can sharply reduce the spread of viruses, not all experts agree. Dr. Martin J. Blaser, director of the Human Microbiome Program at New York University’s Langone Medical Center, says he generally does not recommend hand sanitizers and disinfectant wipes because they kill good bacteria, which can help protect against bad bacteria. Exceptions, he says, are in hospitals and during the flu season. Of course, a handshake can transfer from 10 to 20 times the bacteria as a fist bump.

The University of Arizona researchers have also conducted experiments in hotels, schools, and health care facilities. They found that infecting one hotel room with the virus led to the infection of nearby rooms. They speculated that cleaning tools, like mops and towels, spread the germs. The virus also spread to the conference room. Their next study will involve restrooms.

MYTHS ABOUT GERMS ON AIRCRAFTS

Everett Potter described 5 myths about germs on aircraft (7):

1) The most dangerous health hazard in the air is the cabin air itself. No. The real problems lie on the chair upholstery, the tray table, the arm rest, and the toilet handle, where bacteria such as methicillin-resistant Staphylococcus aureus and Escherichia coli have better survival rates on synthetic fi  bers like polyester than on cotton. Pathogens are readily transferred on stainless steel surfaces although certain metals such as copper tend to have an antimicrobial effect, and germs will not be able to survive on them more than a few hours. Microbes have comparatively good survival on plastic or Formica. Anything with textured grooves or connection points, like a keyboard or a child’s toy, will have a tendency to collect dirt, which can help survival.

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*coli* can live for up to a week on airplanes that aren’t properly cleaned. Tray tables have the highest levels of bacteria, and seatbelts and arm rests also are places where bacteria like to survive.

2) *Bagged pillows and blankets are okay to use.* Blankets sealed in plastic are okay, but only for the lower legs. Pillows should be avoided because the pillowcases are not changed.

3) *The aircraft is cleaned between flights.* How often and well an aircraft is “cleaned” is something of a secret. Removing trash and magazines is routine, but most industry watchers say a proper cleaning occurs infrequently. The Federal Aviation Administration does not regulate cleaning, so the frequency and thoroughness of cleaning are left to the airlines. An aircraft is supposed to be completely wiped down every 30 days of service or at 100 flying-hour intervals, but that means an aircraft can be used for dozens of flights between deep cleanings.

4) *Airlines have taken steps to ensure that passengers can’t contract diseases like the Ebola virus in the aircraft.* There have not been any reported cases of the Ebola virus spreading within the confines of an aircraft cabin so far. Ebola, of course, is not an airborne virus but is spread through bodily fluids. Still, passengers should adhere to rigorous hygiene practices.

5) *There is not much we can do to protect ourselves when trapped in an aircraft cabin.* Not true. There are multiple steps that every passenger can take to prevent the spread of bacteria when flying. First, travel with and use an alcohol-based hand sanitizer. Also travel with a pack of disinfectant wipes. Wipe the armrest and the table tray. Stay hydrated. Use a tissue or paper towel to open bathroom doorknobs and touch toilet handles. The most vulnerable area may be the eyes. Keep your hands away from your eyes, as tear ducts are a fast route for germs to the nose and throat.

**SIMPLE STEPS TO LIVE LONGER**

Leslie Barker (8), writing in *The Dallas Morning News*, provided 10 simple steps to add time and quality to our lives:

1) *Flax.* Flax removes plaque, the bacterial film that forms along our gum line. It might even lessen our chances of heart disease, Alzheimer’s disease, and some forms of cancer.

2) *Get a colonoscopy.* Nine out of 10 people whose colon cancer is discovered early will still be alive in 10 years.

3) *Stop eating before you are full.* Being 100 pounds overweight can subtract at least a decade from your life.

4) *Use sunscreen.* In 2014, 3.5 million people in the US will get skin cancer, and 76,000 more will develop melanoma. Only about one-third of adults in the US use sunscreen.

5) *Stop smoking.* If you quit at age 30, you can increase your life by 10 years; at age 40, 9 years; at age 50, 6 years; and at age 60, 3 years.

6) *Get enough sleep.* Not getting enough sleep has been linked to memory problems, hearing problems, anger, high blood pressure, stroke, depression, vehicle accidents, and obesity.

7) *Exercise.* People who exercise 15 minutes a day add 3 years to their life. Every minute we exercise adds 7 minutes to our lives!

8) *Eat produce.* Eating 5 or more servings per day reduces our risk of stroke by about 25%. Seventh-day Adventists who typically follow a vegetarian diet outlive those who do not by 3 to 7 years.

9) *Cultivate healthy relationships.* People with friends and people in healthy relationships tend to live longer.

10) *Be grateful.* Be positive and complimentary. Those actions may not lengthen life, but they make it more enjoyable.

**HOW LONG IS ENOUGH?**

Ezekiel J. Emanuel, who helped write the Affordable Care Act and who is a brother to Chicago’s mayor, says that 75 years is enough (9). That is how long he wants to live. He indicated that by the time he reaches 75, he will have lived a complete life:

I will have loved and been loved. My children will be grown and in the midst of their own rich lives. I will have seen my grandchildren born and beginning their lives. I will have pursued my life’s projects and made whatever contributions, important or not, I am going to make. And, hopefully I will not have too many mental and physical limitations.

He is now 18 years short of 75. He will have plenty of time to change his mind. He explained:

I am talking about how long I want to live and the kind and amount of health care I will consent to after 75. Americans seem to be obsessed with exercising, doing mental puzzles, consuming various juice and protein concoctions, sticking to strict diets and popping vitamins and supplements, all in a valiant effort to cheat death and prolong life as long as possible. This has become so persuasive that it now defines a cultural type: what I call the American Immortal. I reject this aspiration. I think this maniac desperation to endlessly extend life is misguided and potentially destructive. For many reasons, 75 is a pretty good age to stop. Americans may live longer than their parents, but they are likely to be more incapacitated. Does that sound very desirable? Not to me. What are those reasons?

Let’s begin with demography. We are growing old, and our older years are not of high quality. Since the mid-19th century Americans have been living longer. In 1900 the life expectancy of an average American at birth was approximately 47 years. Today, a newborn can expect to live about 79 years.

Ezekiel Emanuel indicated that his view has practical implications. He stated that once he has lived to 75, he will not actively end his life but he will not try to prolong it. He indicated that at age 75 and beyond, he will need a good reason to even visit a physician and take any medical tests or treatment, no matter how routine and painless. And that good reason is not “it will prolong your life.” He will stipulate a do-not-resuscitate order and a complete advance directive indicating no ventilators, dialysis, surgery, antibiotics, or any other medication—nothing except palliative care. He went on:

Again, let me be clear: I am not saying that those who want to live as long as possible are unethical or wrong. I am certainly not scorning or dismissing people who want to live on despite their physical and mental limitations. I am not even trying to convince anyone I’m right. Indeed, I often advise people in this
age group on how to get the best medical care available in the United States for their ailments. That is their choice and I want to support them. And I am not abdicating 75 as the official statistic of a complete, good life in order to save resources, ration health care or address public-policy issues arising from the increases in life expectancy. What I am trying to do is delineate my views for a good life and make my friends and others think about how they want to live as they grow older. I want them to think of an alternative to succumbing to that slow constriction of activities and aspirations perceptively imposed by aging.

I hope that I am around in 2032, the year Ezekiel Emanuel reaches age 75, to see whether he still believes his ideas generated 18 years earlier.

TRAFFIC FATALITIES

In 2002, highway deaths totaled 38,491; in 2012, they totaled 30,800 (10). During those 12 years, a number of cars were added to the road, so in proportion to the increased number, the decrease is rather remarkable. Wearing a seatbelt is another way to lengthen survival and increase life's quality.

FOOTBALL INJURIES, CHRONIC TRAUMATIC ENCEPHALOPATHY, AND THE NATIONAL FOOTBALL LEAGUE

Each week, The Dallas Morning News publishes the Dallas Cowboys' injury toll. In 2013, 15 of the 40 team players missed one or more games, and one missed all 16 season games. So far in 2014, 8 players have missed one or more games, including 1 who has missed all 8 so far. And Tony Romo with 2 back operations was recently injured again (as of October 2014).

Steve Almond has published Against Football: One Fan's Reluctant Manifesto (11). Professional football has displaced baseball as America's number 1 fan sport. Almond, who used to be a major National Football League (NFL) fan, has now turned his back on the game. He asks fans to consider their own complicity in ignoring and even encouraging the darker side of the sport. He indicated that “the reason ferocious hits get broadcast over and over, often in slow motion, is because fans love to see them.” The TV people, of course, know the fans' appetite.

Almond reported on the effects of head injuries and on a form of dementia called chronic traumatic encephalopathy (CTE), common in former football players. The NFL has not just been slow to react to these findings; it has employed junk science to muddy the debate. Even more chilling is how little we know about the effects of football on brains that are still developing. Almond cited a Purdue University study that showed that high school football players experience diminished brain function even in the absence of concussions.

A chapter on NFL's business practices could make the most ardent pigskin fan bristle. The NFL has created what amounts to a risk-free business environment where taxpayers get bilked. Almond provided plenty of blood-boiling examples, like the NFL's tax-exempt status—unique among major sports leagues—and the now commonplace arrangement that sees taxpayers fund NFL stadiums while team owners reap the economic rewards. The New Orleans Saints even receive an “inducement payment” of up to $6 million a year just to keep the franchise in the city. That's on top of the $200 million that taxpayers forked over for renovating the Mercedes-Benz Superdome. They will see none of the $50 to $60 million the team received in naming rights from the carmaker. NFL Commissioner Roger Goodall's salary in 2013 was $35 million. Between the recent domestic violence scandals and the stream of medical research revealing that football is more dangerous than previously thought, the sport that Goodall oversees has garnered plenty of negative headlines. But will the bad press ever cause fans to stop enriching America's most popular pastime?

The thought of any large-scale exodus of fans is unlikely. TV ratings are up again this season from already astronomical levels. The continued popularity, as Almond pointed out, is due in part to the way the sports media promote rather than cover the games. “Sports represent one of the few growth sectors for the corporate media,” he observed. “It's far more profitable to cover football as a glorious diversion than as a sobering news story.”

The decline of boxing from one of America's popular sports might have seemed equally impossible. The steady supply of future gridiron warriors is already starting to thin. High school football participation has fallen 2% since 2008, and the drop is more pronounced for younger players. While falling participation might bring about football's decline, Almond dared fans to consider how long they could continue to ignore football's obvious flaws to preserve their weekend ritual. The average age of death of former NFL players is 55 years!

A proposed $765 million settlement of concussion lawsuits against the NFL is presently on the table (12). There are approximately 19,500 retired NFL players, and 6000 (28%) are expected to develop Alzheimer's disease or at least moderate dementia. Dozens more will be diagnosed with amyotrophic lateral sclerosis (Lou Gehrig's disease) or Parkinson's disease during their lives. That is nearly 3 in 10 former players who will develop these debilitating brain conditions earlier than and at least twice as often as the general population. The NFL's calculations show that players <50 years had a 0.8% chance of developing Alzheimer's and dementia, compared with <0.1% for the general population. For players 50 to 54, the rate was 14% compared with <0.1% for the general population. The gap between the players and the general population grows wider with increasing age. The proposed settlement includes $765 million for player awards, $75 million for baseline assessments, $10 million for research, and $5 million for public notice. The settlement would not cover current players.

Some have argued that the NFL's offering is a pittance given its $10 billion in annual revenue. Critics also lament that the settlement plan offers no awards to anyone diagnosed with CTE in the future and that the Alzheimer's and dementia awards are cut by 75% for players who also suffered strokes. The plan would pay up to $5 million for players with amyotrophic lateral sclerosis, $4 million for deaths involving CTE, $3.5 million for Alzheimer's disease, and $3 million for moderate dementia and other neurologic problems. Only men under 45 who spent at least 5 years in the league would get these maximum payouts.
The awards are reduced on a sliding scale if the men played fewer years or were diagnosed later in life. The players’ data, therefore, predicts the average payout in today’s dollars to be $2.1 million for ALS, $1.4 million for death involving CTE, and $190,000 for Alzheimer’s disease or moderate dementia. Only 60% of those eligible for awards are expected to enter the program. My daughter does not allow her 2 boys to play football. It’s understandable.

A NONMEDICAL EBOLA CZAR

Thomas G. Donlan (13), writing in Barron’s, said that “the mere use of the word czar ought to be considered a sign of approaching futility.” He indicated that “the services of at least 149 czars have been appointed in the USA since 1918, including for example AIDS czar, Asian carp czar, bank czar, bioethics czar, bird flu czar, car czar, climate czar, copyright czar, cyber securities czar, democracy czar, drug czar, economic czar, energy czar, food czar, green jobs czar, health czar, homeland security czar, homelessness czar, inflation czar, information czar, intelligence czar, and on through the alphabet to the weatherization czar.” The Ebola czar Ron Klain is the latest in the long dynastic succession, but Donlan indicated that these czars are essentially unable to perform miraculous feats of organizational efficiency. The American czars have responsibility without power.

Donlan indicated that scientists and drug companies have neglected the development, testing, and marketing of vaccines, including the Ebola vaccine, because there is no money for them in doing so. Sixty years ago, Dr. Jonas Salk devised his own trial for his vaccine to protect against polio. Salk simply asked parents to sign consent forms for the kids to participate in a double-blind study in which neither the children nor the parents nor the people administering the injections would know if a hypodermic needle contained a vaccine or a placebo. About 2 million children participated. Today, a drug company would not be allowed to do that in Africa or in the USA. An Ebola vaccine that is 100% effective at preventing the disease in monkeys was developed 10 years ago but never tested in humans according to Donlan. But we commonly hear the drug companies blamed for the supposed lack of a vaccine. Drug companies have resisted spending the enormous sums needed to develop products useful mostly in countries with little ability to pay. As Donlan said, “This produces two choices: either drug companies must be allowed to raise prices on their other drugs to create a surplus for charity work or the government must raise taxes and borrowing to pay for vaccines and orphan drugs.”

Donlan indicated that the real problem could be the enormous expense created by a safety and regulatory system imposed on the world by the FDA and its counterparts in Western Europe and also by a small corps of professional ethicists who have excessive concern for informed consent in drug trials and insufficient concern for scientific progress to aid victims of dreaded diseases.

Donlan concluded as follows: “Given a choice between the regulatory protection of 2014 and the mass vaccine testing of 1954, we’ll take the system that worked to fight disease. And we would like to take the one that doesn’t crown a czar.” Donlan also indicated that “too often we forget that the real czar—of all the Russians—was deposed, imprisoned, and executed. Nicholas II is an inappropriate symbol of power or wisdom, and remains so.”

DRUGSTORE CEASES SELLING CIGARETTES

CVS Caremark stopped selling cigarettes in September 2014 (14). It has 7700 retail locations and is the second largest drugstore chain in the US behind Walgreens. It manages the pharmacy benefits for 65 million Americans and has 900 walk-in medical clinics. Its tobacco sales total about $2 billion a year. Good for CVS!

UNDERAGE ALCOHOLISM

In 2012 the National Institute on Alcohol Abuse and Alcoholism reported that 855,000 people between ages 12 and 17 years struggled with alcohol dependence or abused alcohol (15). And 5.9 million people aged 12 to 20 consider themselves binge drinkers. According to a piece by Stephanie Embree in The Dallas Morning News, 6 times as many young adults die from alcohol abuse than from any other substance. No one knows whether that first drink is the beginning of alcoholism or not.

MARKETING DRUGS

The system is changing (16). When physicians were mainly in private practice, pharmaceutical representatives visited them frequently urging use of drugs manufactured by their company. Today, 42% of physicians practice as salaried employees of hospital systems, up from 24% in 2004. As a result, the pharmaceutical industry is shifting its sales efforts from physicians to the institutions they work for. In 2005, drug companies employed about 102,000 US sales representatives, who mostly pitched to physicians. By mid-2014, their numbers were down to about 63,000. Stepping in are so-called “key-account managers” who build relationships with hospital administrators. The 20 biggest drug companies employ roughly 600 key-account managers, 3 times the number 5 years ago. The trend is in early stages. Sales representatives still account for the bulk of drug sales, but companies are increasingly deploying key-account managers in regions where hospitals have moved more quickly to buy practices.

Eli Lilly & Company, for example, last year scrapped its old sales-rep approach in 6 metropolitan areas including Boston and Salt Lake City in favor of key-account teams. The pharmaceutical companies are asking how they can get health system adoption. Getting a drug on the hospital system’s formulary can mean potentially millions of dollars in sales from thousands of physicians’ prescriptions. Drug companies used to send armies of sales reps to woo individual physicians after introducing new drugs. The reps would sometimes take physicians to sports events or cater lunches for their offices, and they usually left samples. Physicians were often more interested in a drug’s clinical trial results than costs. Reps could generate hundreds of millions of dollars over the few months after a drug’s introduction.
But physicians are losing influence. Hospital systems are growing more powerful as they bulk up by buying physician practices, nursing homes, urgent care centers, and other hospitals. Insurers and the federal health care overhaul are squeezing hospitals and physician payments and shifting reimbursements from how much care is given to how effective it is. To manage costs, hospital systems are taking control of what drugs their physicians can prescribe. Many limit physician contact with sales people. The gatekeepers are committees and administrators. Today’s key-account managers can spend many months trying to persuade administrators to put a drug on the formulary. And big systems have more negotiating power over price than small systems. At health systems, the sales emphasis has shifted to not just how the medicine works but also how it lowers the total cost of managing disease. Formulary committees in the hospital systems decide what drugs to recommend based on evidence of effectiveness, toxicity, and cost. A committee in one hospital recently standardized treatment of certain colorectal cancer patients around the use of the drug Vectibix, which costs about $38,000 for a 16-week course, removing a drug from its list that was found to be similar but cost about 15% more. It says that physicians working in its 21 hospitals follow the cancer drug-prescribing protocols about 80% of the time.

For drug companies, health systems’ expanding control not only can slow new drug acceptance but may also hurt profits by limiting a drug’s peak sales and by driving down prices as systems use their increasing control over what physicians prescribe to press for discounts. For patients, the trend can be a mixed blessing. They are more likely to get drugs that evidence shows will keep them healthy and out of the hospital, but patients may face more restrictions on their choice of drugs. Physicians are finding the trend mixed. Physicians are losing their ability to negotiate with insurers. Some systems bar physicians from meeting drug sales reps during office hours and the systems are drafting formularies that will direct what their physicians can prescribe. The good side from the physician standpoint is that more time is available to spend on patient care. But, it is harder to learn about new drugs.

BOVINES AND METHANE

Cows have long been castigated for their methane-belching, manure-producing ways, one of agriculture’s top contributors to climate change (17). The Environmental Protection Agency has fingered the methane emissions of “enteric fermentation”—the digestive process of animals with multichambered stomachs—as second only to emissions from natural gas and petroleum systems in greenhouse gas emissions. Our president has proposed cutting methane emissions from the US dairy industry by 25% by 2020. The US dairy industry has pledged the same goal. Th ey are finding the trend mixed. Physicians are losing their ability to negotiate with insurers. Some systems bar physicians from meeting drug sales reps during office hours and the systems are drafting formularies that will direct what their physicians can prescribe. The good side from the physician standpoint is that more time is available to spend on patient care. But, it is harder to learn about new drugs.

MEGADROUGHT IN THE WEST

According to bioclimatologist Park Williams, the Western USA has been in a drought during the past 15 years, worse than any other 15-year period since about 1150, or 850 years ago (18). The megadroughts have been called “the great white sharks of climate: powerful, dangerous, and hard to detect before it’s too late. They have happened in the past and they are still out there, lurking in what is possible for the future, even without climate change.”

A megadrought is a threat to civilization and is defined more by its duration than its severity. It is an extreme dry spell that can last for a decade or longer. It has parched the West periodically, including present-day California, long before Europeans settled the region in the 1800s. Most of the USA’s droughts of the past century, even the infamous 1930s Dust Bowl that forced migration of Oklahomans and others from the Plains, were exceeded in severity and duration multiple times by droughts during the preceding 2000 years. The difference now is the Western US is home to >70 million people who were not here for previous megadroughts. The implications are far more daunting. Droughts are cyclical and these long periods of drought have been commonplace in the past, according to a climatologist at the National Drought Migration Center in Lincoln, Nebraska. “We are simply much more vulnerable today than at any time in the past. People just can’t pick up and leave to the degree they did in the past.”

How do scientists know how wet or dry it was centuries ago? Though no weather records exist before the late 1800s, scientists can examine “proxy data” such as tree rings and lake sediment to find out how much or little rain fell hundreds or even thousands of years ago. These rings are wider during wet years and narrower during dry years.

Prolonged droughts, some of which lasted more than a century, brought thriving civilizations to starvation, migration, and finally collapse, wrote Lynn Ingram, a geologist at the University of California Berkeley in her recent book, _The West Without Water_. Decade-long droughts happen once or twice a century in the Western USA. But much worse droughts, ones that last for a century or more, occur every 500 years or so. Has California
reached megadrought status? Not yet: “This one wouldn’t stand out as a megadrought.” But this is the state’s worst consecutive 3 years for precipitation in 119 years of records.

As of August 28, 2014, 100% of the state of California was considered in a drought, according to the US Drought Monitor. More than 58% is in “exceptional” drought, the worst level. Record warmth has fueled the drought, as the state has seen its hottest year since records began in 1895. Because of the dryness, California Governor Jerry Brown declared a statewide emergency in 2014. Since then, reservoir storage levels have continued to drop, and as of late August 2014, they were down to about 59% of the historical average. Regulations restricting outdoor water use were put in place in July 2014 for the entire state. People are not allowed to hose down driveways and sidewalks, nor are they allowed to water lawns and landscapes. There are also reports of wells running dry in California. About 1000 more wildfires than usual have charred the state. The drought is likely to inflict over $2 billion in losses on the agricultural industry. If California suffered something like a multidecade drought, the best-case scenario would be some combination of conservation, technological improvements (such as desalinization plants), multistate economic-based water transfers from agriculture to urban areas, and other things like that to get humans through the drought. In the worst-case scenario, there might be all-out migration and/or ghost towns. We must learn how to use water more efficiently.

What role does climate change play in this or future droughts? Scientists apparently say that they don’t have the tools to tease out how much of this specific drought might be attributed to climate change. As of now, probably very little of the California drought can be attributed to climate change with any certainty. Overall, past droughts have probably been due to subtle changes in water temperatures in the tropical Pacific Ocean. Colder water temperatures tend to produce drier conditions in the West. According to some computer models, California could actually see more, not less, winter rain and snow because of climate change. Overall, rising temperatures would tend to favor more droughts, however. During the 20th century, California’s population increased from 1.5 to almost 40 million, and that increase may well have occurred during an outlier, an unusually wet century. Overall, the 20th century experienced less drought than most of the preceding 4 to 20 centuries, according to a study in Science.

Megadroughts are likely to hit the Southwest USA in this century. Megadroughts, according to an American Geophysical Union conference spokesman in 2014, could possibly be even worse than anything experienced by any humans who have lived in the Western part of the US in the last 1000 years! And we need rain badly here in Texas. If there is not enough water, medicines are hard to swallow.

PERFORMANCE OF HIGH SCHOOL STUDENTS

The highest SAT score available is 800. In math, the 2014 high school students across the nation registered 512 and those in Texas, 495; in reading, the US average was 496 and in Texas, 475; in writing, the US average was 487 and in Texas, 460 (19). Texas education officials have attributed the declining SAT scores in the state to an increase in the number of minority students taking the exams. Minorities generally perform worse than white students on standardized achievement tests, like the SAT and ACT, the nation’s two leading college-entrance exams.

California students outperformed Texans by big margins in 2014: by 15 points in math and 22 in reading. Demographics of the student populations in the two states are similar: California is 53% Hispanic and 26% white, while Texas is 51% Hispanic and 30% white. Additionally, >60% of seniors in both states took the SAT.

The drop in SAT math scores in Texas might rekindle debate over the state’s recent decision to no longer require all high school students to take algebra II. The College Board reported that just over one-third of the 179,036 Texas students who took the SAT met its college and career readiness benchmark, which requires a score of 1550 out of a possible total of 2400. That was well under the national average of 43% who hit the benchmark. Most minority students fell short of the benchmark: only 19% of Hispanic and 14% of black students in Texas met the college readiness standard. Both percentages trailed the national averages for those groups. We can do better in this great state!

ENDANGERED JOBS

According to a piece in The Dallas Morning News, the following are jobs expected to decline in the next few years: mail carrier, farmer, meter reader, newspaper reporter, travel agent, lumberjack, flight attendant, drill-press operator, printing worker, and tax examiner and collector (20). Technology killed the switchboard operator, the lamplighter, and the ice cutter, and it’s now a threat for workers in a variety of other fields. When economics change, it kills opportunities, but it also brings other opportunities.

ADVERBS AND LAWYERS

A piece by Jacob Gershman indicated that no part of speech has had to put up with so much adversity as the adverb (21). It is supposed to be used sparingly, if at all, to modify verbs, adjectives, or other adverbs. Although it is generally believed that the adverb is not the writer’s friend, there is one place where the adverb not only flourishes but wields power—the American legal system. Adverbs in recent years have taken on an increasingly important and often contentious role in courthouses. Their influence has spread with the help of lawmakers churning out new laws packed with them. Words such as “knowingly,” “intentionally,” and “recklessly,” which deal with criminal intent, appear frequently in legal writings. Other adverbs like “substantially” or “indiscriminately” have been pivotal in some federal appeals court rulings. The word “quickly” has gotten some attention. Tax law allows the government to immediately freeze the assets of a suspected tax cheat who “appears to be designing quickly” to hide his or her wealth. A legal anthropology professor at the University of Kentucky College of Law recently stated, “Contrary to the ordinary view that adverbs are superfluous, law generally and criminal law especially, emerges through its adverbs.”
The number of adverb-dense disputes over how to properly construe a criminal statute has surged since the 1980s. A US Supreme Court case in 2009 turned on the modifying reach of the word “knowingly,” tucked into a federal statute defining the crime of aggravated identity theft. In 2013, House Republicans clashed with Justice Department attorneys over a Justice Department lawyer’s use of fuzzy adverbs, like “traditionally,” “typically,” and “ordinarily” in his statements about the Obama administration’s response to an investigation of the Fast and Furious gun-trafficking operation. Even among the most adverbially disinclined, virtually everyone recalls backtracking on promises not to use the adverb. Hemingway used few adverbs. Avoiding adverbs forces one to confront the significance of one’s word choice, opined Justice Anthony Kennedy of our Supreme Court. Maybe those of us in medicine can learn something from the lawyers about our use of adverbs.

9. Emanuel EJ. Why I hope to die at 75: An argument that society and families—and you—will be better off if nature takes its course swiftly and promptly. *The Atlantic*, October 2014.
18. Rice D. California’s 100-year drought: Fierce fires, agricultural losses—severe water shortage a ‘threat to civilization.’ *USA Today*, September 3, 2014.
Acknowledgment of reviewers for BUMC Proceedings, volumes 24–27

Our thanks to those who reviewed and critiqued manuscripts submitted to Baylor University Medical Center Proceedings for publication in volumes 24 through 27. Reviewing scientific papers is an often unrecognized, arduous, and time-consuming task. We are grateful to our editorial board members and to the following additional reviewers for contributing their valuable comments and suggestions.

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