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The radial scar of the breast diagnosed at core needle biopsy

Cory Morgan, MD, Zeeshan A. Shah, MD, Raynal Hamilton, MD, Jean Wang, MD, Joseph Spigel, MD, William DeLeon, MD, Patricia DeLeon, DO, Tyler Leete, MD, and J. Mark Fulmer, MD

The radial scar (RS) or complex sclerosing lesion (CSL) of the breast represents a management dilemma on diagnosis at breast core needle biopsy because of the risk of associated malignancy identified only upon surgical excision. To determine our experience, we retrospectively reviewed core needle biopsies performed at the Darlene G. Cass Breast Imaging Center from 2006 to 2011, identifying 67 patients with RS or CSL, and correlated histology at excisional biopsy with core biopsy results. Of the 67 cases, 6 (9%) were associated with malignancy at surgical excision. The average size of the RS or CSL was 1.42 cm. In conclusion, RS or CSL diagnosed at core needle biopsy still warrants surgical excision because of the significant percentage (9%) of cases with associated malignancy.

Despite being considered benign lesions, radial scars (RS) and complex sclerosing lesions (CSL) of the breast often demonstrate suspicious imaging features that prompt imaging-guided core needle biopsy. Percutaneous diagnosis of an RS without atypical features can present a management dilemma since a significant percentage of these lesions are known to be associated with malignancy (1–11). At our institution, we routinely advise surgical excision of these lesions in order to exclude a more aggressive atypical or malignant component that was not sampled at the time of needle biopsy.

This report reviews the cases of RS or CSL diagnosed at the Darlene G. Cass Women’s Imaging Center by percutaneous imaging-guided core needle biopsy or surgical excision to determine the frequency of associated malignancy.

MATERIALS AND METHODS

The histologic findings of 67 patients diagnosed with either RS or CSL were retrospectively analyzed, beginning with 2006, when the breast center began using a computerized database for pathology results from core needle biopsies. All biopsies were obtained and all lesions diagnosed at our center. The frequency of associated in situ or invasive malignancy was calculated. We included lesions diagnosed by percutaneous core needle biopsy, including both 9 g vacuum-assisted stereotactic biopsies and 11 g sonographic biopsies. Before biopsy, all lesions were suspicious (at least BI-RADS category 4 or greater). Lesions were identified mammographically and/or sonographically and were nonspecific, including masses, microcalcifications, and mammographic asymmetries. The histologic findings were not retrospectively confirmed by a pathologist, and the original histologic diagnosis for each case was accepted.

RESULTS

Six of the 67 lesions (9%) were associated with malignant features. Of the six malignant lesions, two were low-grade ductal carcinoma in situ (DCIS), two were intermediate-grade DCIS, one was an invasive ductal lesion with fragmented architecture that prevented definitive grading, and the final one was a low-grade metaplastic (adenosquamous) carcinoma. The six patients ranged in age from 35 to 69 years. The average size of the identified RS or CSL was 1.42 cm.

DISCUSSION

RS of the breast is a benign lesion with mammographic and sonographic features that can mimic carcinoma. It is the imaging manifestation of an idiopathic scarring process that is unrelated to trauma or surgery (12). If the lesion is >1.0 cm, it is described as CSL. The characteristic stellate histologic appearance of an RS is the result of ducts and lobules radiating outward from a central fibroelastic core (13). This histologic arrangement contributes to the classic radiographic appearance of an RS, described as spiculated masses often having a radiolucent core. If present, these findings may suggest the diagnosis of RS, but they are not adequately specific to allow exclusion of malignancy (12). In fact, RS have been shown to present with a variety of mammographic characteristics and should therefore be considered a prebiopsy diagnostic possibility for almost all mammographic lesions (3, 14).

Furthermore, Linda et al (15) showed that mammographic and sonographic features of a lesion diagnosed as RS are not predictive of the absence or presence of associated malignancy. Historically, RS were most often discovered as incidental microscopic findings, but the common use of screening...
mammography has led to increased imaging detection of these lesions (16). Multiple reports in the literature show an association of RS with surrounding malignancy in anywhere from 3% to 40% of cases (1–11). Furthermore, common associated findings of hyperplastic conditions such as atypia, adenosis, and papillomatosis have prompted the suggestion that RS represents an early stage in the development of invasive carcinoma (17). However, recent articles from Sanders et al (18) and Berg et al (19) conclude that there is no increased breast cancer risk in patients with RS/CSL relative to those with proliferative diseases of the breast with or without atypia. The varying results of these studies reflect the ongoing debate regarding management of these lesions.

At our facility, we routinely recommend surgical excision of any lesion with histologic components of RS or CSL. The results of this review support such a recommendation. The frequency with which malignant features are identified in association with RS or CSL warrants thorough histologic evaluation of the area containing these lesions. Some investigators have suggested that surgery can be confidently avoided if core-needle biopsy is performed with a vacuum-assisted device, more than 12 samples are obtained, no associated atypical hyperplasia is identified, and radiologic-pathologic concordancy is confirmed (3, 11). However, Linda et al (15) reported an underestimation of malignancy using a vacuum-assisted device. Lopez-Medina et al (1) showed that carcinoma was invariably located at the periphery of sclerosing lesions and that the volumetric proportion of malignancy within RS ranged from 3.7% to 16.2%. These findings suggest that malignant foci can easily be missed by the biopsy needle, despite an extensive sampling technique (20).

Several authors have concluded that malignancy in RS or CSL is very rare in patients under the age of 50 (21–24). Although the overall number of patients included in this review is small, it is worth noting that 2 of our 6 patients with malignant features were under 50 years of age (ages 35 and 43). The average size (1.42 cm) of lesions with associated malignancy in our study is consistent with the conclusion by Sloane et al that carcinoma is more common in lesions ≥0.6 cm (22).

Findings of DCIS arising in RS/CSL are most commonly low or intermediate grade while invasive cancers are usually grade 1 or 2, and staging of these patients is historically prognostically favorable (15, 25–27). Metaplastic carcinoma was grade 1 or 2, and staging of these patients is historically prognostically favorable (15, 25–27). Metaplastic carcinoma was identified in one of the patients we reviewed and has been reported in multiple previous cases (28).

In conclusion, there is a noteworthy association of malignancy with lesions diagnosed as RS or CSL at this facility. The frequency of this association along with the lack of predictive imaging characteristics warrants the recommendation that all RS or CSL be surgically excised, even if malignant components are not identified at core needle biopsy.


Acknowledgment of reviewers for BUMC Proceedings, volumes 20–24

Our thanks to those who reviewed and critiqued manuscripts submitted to Baylor University Medical Center Proceedings for publication in volumes 20 through 24. 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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Ground-level falls are the leading cause of nonfatal hospitalized injuries in the US. We hypothesized that risk-adjusted mortality would not vary between levels of trauma center verification if regional triage functioned appropriately. Data were collected from our regional trauma registry for the years 2001 through 2009. A multilevel mixed-effects logistic regression model was developed to compare risk-adjusted mortality rates by trauma center level and by year. GLF patients numbered 8202 over 9 years with 2.1% mortality. Mean age was 74.5 years and mean probability of death was 0.021 (95% confidence interval [CI], 0.020–0.021). The level I center–treated patients had the highest probability of death (0.033) compared to levels II and III/IV patients (0.023 and 0.018, respectively; P < 0.001), with the highest mortality (6.0%, 3.1%, and 1.1% for levels I, II, and III/IV; P < 0.001). The adjusted odds ratio of mortality was lowest at the level I center (0.71; 95% CI, 0.56–0.91), while no difference existed between level II (1.17; 95% CI, 0.90–1.51) and level III/IV centers (1.22; 95% CI, 0.90–1.66). The 95% CIs for risk-adjusted mortality by year overlapped the 1.0 reference line for each year from 2002 to 2009. In conclusion, regional risk-adjusted mortality for GLF has varied little since 2002. More study is warranted to understand the lower risk-adjusted GLF mortality at the level I center for this growing patient population.

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A standard measurement of the quality of care among trauma systems is hospital mortality, since this is the most accessible and obvious endpoint. Proper triage enhances trauma system effectiveness and positively influences patient survival. As such, if a trauma system is properly functioning, patients with the highest probability of death based on anatomic injury should be referred to a level I or II center.

We sought to characterize the cumulative experience of our region's trauma system in caring for one of the growing segments of the trauma patient population—those injured in ground-level falls (GLFs). Specifically, we sought to evaluate the referral practice whereby those patients with higher predicted mortality should be admitted to level I and II trauma centers where resources are available to provide definitive care for critically injured patients. Conversely, those patients with lower predicted mortality should comprise the group of patients admitted to level III and IV trauma centers. We hypothesized that if the triage and referral patterns in our trauma system were functioning appropriately, the risk-adjusted mortality should not vary significantly between level I, II, and III/IV centers within our region.

Additionally, we evaluated the adjusted mortality of our region’s trauma system. Trauma systems exist to provide optimal acute care for injured patients of all ages. Hoyt and Coimbra suggested that many severely injured patients are never taken to trauma centers, and only 15% of trauma patients actually require the additional services offered by level I and II centers (1). Effective trauma systems must therefore be inclusive and function cohesively to provide the most appropriate care to patients. This is ensured by the leadership of surgeons in the community.

A clear classification of hospital roles based upon trauma response and capabilities was established by the American College of Surgeons Committee on Trauma in 1976. These tiers of care range from level I/II, providing comprehensive care, to levels III, IV and V, providing stabilization and transport to higher-level facilities (2). Further refinement in the definition of trauma systems led to the concept of inclusive versus exclusive systems. Inclusive trauma systems comprise all acute care facilities in a geographical region regardless of their level of verification or expertise. Exclusive systems rely on a few high-level centers to care for the most severely injured patients (3). Utter et al showed that although both types of systems similarly triage patients, severely injured patients treated within inclusive systems experience better survival rates (4). Tinkoff et al recently published a report of the inclusive statewide trauma system in Delaware. Their findings of decreasing mortality of the most critically injured patients over 10 years compared favorably to a cohort of injury severity–matched patients from the National Trauma Data Bank, thus reinforcing the benefits of inclusive trauma systems (5).

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trauma system over time as a means to identify any significant temporal variation in patient mortality. The overarching goal of this study was to demonstrate areas for quality improvement as well as the strengths of our regional trauma system.

MATERIALS AND METHODS

Data from the Regional Trauma Registry for Trauma Service Area G (TSA-G) were analyzed. TSA-G comprises 19 counties encompassing 13,609 square miles of northeastern Texas. The population served is currently estimated to be over 850,000 (8). The coordinated plan for trauma care in TSA-G encompasses emergency medical services, trauma centers designated at all four levels of American College of Surgeons (ACS) verification, acute rehabilitation hospitals, and skilled nursing facilities. The hospitals in this region include one ACS level I, two level II, six level III, and 11 level IV trauma centers providing immediate and definitive trauma care to TSA-G patients.

The data presented in this report were accumulated over 9 years (2001–2009). Individual medical records were reviewed by each center’s trauma program manager and submitted to the registrar for TSA-G. Patients were analyzed according to the ACS level of verification of the facility where inpatient admission occurred. For example, patients initially evaluated at a level III or IV facility and transferred to a level I or II center for definitive care were analyzed in this report as level I or II patients. Patients who were not transferred but were admitted to the level III or IV facility were analyzed accordingly.

Patients were identified by external cause of injury codes 880.1, 884.2, 884.3, 884.4, 884.6, 885.9, 888.0, and 888.1. We excluded patients <14 years of age because there were no designated pediatric trauma centers in TSA-G, and regional protocols required transfer of these patients, once stabilized, to a pediatric trauma center outside of TSA-G. We analyzed data including demographics, comorbidities, acute physiology, injuries, lengths of stay in the intensive care unit and hospital, survival, disposition, and ACS trauma center level of admission. Diagnoses for the acute injuries and comorbid conditions were codified according to the lexicon of the International Classification of Diseases, 9th Edition, Clinical Modification (ICD-9). The comorbidities were enumerated and a comorbidity score was assigned using the algorithm outlined by Elixhauser et al (6). The ICD-9 codes for injury and poisoning (800-999) were also used to categorize injuries into anatomic regions using the Barell Injury Diagnosis Matrix (7). Enumeration of comorbidities for the Elixhauser score and categorization of injuries into the Barell Injury Diagnosis Matrix were performed using the ICDPIC module for Stata developed by Clark et al (8).

The relative incidence of GLF admissions as a proportion of total trauma admissions was estimated and presented with 95% confidence intervals (CIs) per year for the years 2001 to 2008. This time interval was chosen because GLF admissions were not consistently reported as trauma admissions by all centers prior to 2001. Additionally, the data for 2009 did not include all 12 months and were also excluded from this analysis. The difference between the relative incidence of GLF in 2001 and that in 2008 was estimated using a two-sample test of proportion.

Patients were grouped and comparisons were made by the ACS level of admission and by year of admission. The chi-square test was used to evaluate differences between groups for binary variables. The rank-sum test and the Kruskal-Wallis equality-of-populations rank test were used to measure the differences for continuous variables among two and three groups, respectively. The probability of death was estimated using the Trauma Mortality Prediction Model (9).

A multiple variable logistic regression model was developed with death as the outcome of interest. The ability of the logistic regression model to discriminate fatalities from survivors was evaluated using the area under the receiver operating characteristic curve. The Hosmer-Lemeshow statistic was used to measure the goodness of fit of the model to the dataset.

As a means to compare risk-adjusted mortality rates by ACS level of hospital admission and year of admission, a multilevel mixed-effects logistic regression model was employed. Differences between groups were considered significant if the $P$ values were ≤0.05.

RESULTS

During the study period, 8202 patients ≥14 years of age were admitted for GLFs. In 2001 GLF represented 13.3% (95% CI, 12.4%–14.2%) of trauma admissions in TSA-G. This increased over the period of this study to 21.4% (95% CI, 20.3%–22.5%) ($P < 0.001$) (Figure 1). The characteristics of the cohort are...
described in Table 1. The various types of GLF are categorized by their E code. Four of the E code groups had significant univariate associations with death. These E codes were accidental fall from wheelchair (884.3), accidental fall from bed (884.4), slipping, tripping, or stumbling (885.9), and falls resulting in striking against another object (888.1). These mechanisms of GLF were associated with mortality rates of 4.51%, 4.44%, 1.86%, and 4.71%, respectively ($P < 0.05$ for each). The overall mortality rate from GLFs in our region was 2.1% over 9 years.

The characteristics of the cohort were compared according to the trauma center designation level of the facility where the patients were admitted and treated (Table 2). The patients treated at the ACS level I center were younger, had more comorbid conditions, and more often presented with metabolic acidosis. Both the probability of death and the unadjusted mortality rate were highest for the level I center and lowest for the level III/IV centers. However, once the mortality rates were risk adjusted for physiologic derangement on presentation, patient comorbid disease burden, age, gender, brain injury, and totality of physical injury, the adjusted odds ratio for death was lowest for the level I center. It is noteworthy that the 95% CI of the level I center overlapped that of the other trauma center levels. Additionally, the 95% CIs of the level II centers overlapped considerably with those of the level III/IV centers (Table 2). Thus, although the mean adjusted odds ratios for mortality differed among the levels of trauma center verification, the overlap of the 95% CIs demonstrated only modest variation in adjusted odds of mortality among trauma center verification levels in TSA-G.

A multivariate logistic model was constructed to explore the associations of several covariates with mortality (Table 3). The strongest independent predictors of death were hypotension (odds ratio, 8.91; $P < 0.001$) and metabolic acidosis on arrival (odds ratio, 4.51; $P = 0.002$).
Among the comorbid conditions, cancer increased the odds of death nearly fourfold (odds ratio, 3.83; \( P = 0.003 \)). This model adequately discriminated fatalities from survivors (area under the receiver operating characteristic curve = 0.85). Calibration to the dataset was also acceptable (Hosmer-Lemeshow chi-square statistic = 4.98; \( P = 0.89 \)).

The mean adjusted mortality rate with 95% CIs was plotted for the years 2001 through 2009 (Figure 2). With the exception of the year 2001, the 95% CIs of the adjusted odds ratios for mortality from GLF crossed the 1.0 level, indicating the adjusted odds ratio for mortality remained consistent over time.

DISCUSSION

GLFs are an increasing public health concern with significant economic and social consequences. It is estimated that >30% of older adults fall yearly, with >1 out of 5 incidents requiring acute care, costing more than $20 billion a year in the US (10–12). Unintentional falls are currently the number one cause of injury-related death in persons aged 65 and above (16,650 in 2006), and the leading cause of nonfatal injuries treated in US emergency departments in all age groups with the exception of persons aged 15 to 24 years. Even in this group, falls are a close second (13). Additionally, unintentional falls are estimated to contribute to 8 million emergency department visits annually. Given the sweeping demographic changes occurring in the US, it is reasonable to assume that the incidence and impact of GLFs will increase.

GLFs have appropriately drawn the attention of academic and institutional research, most of which has focused on developing strategic fall risk assessment and prevention strategies. These efforts, manifest by scoring systems such as the Morse Fall Scale or recommendations by authorities such as the ACS Subcommittee on Injury Prevention and Control, are being sporadically adopted, but with mixed results (12, 14, 15). Much less has been published regarding the treatment and outcome side of this complex medical and social issue, which highlights the need for the development of evidence-based strategies in the multidisciplinary management of GLF patients (16). A better understanding of injury patterns, predictors of morbidity and mortality, and considerations for special subgroups would clearly benefit clinicians in the triage, assessment, treatment, and disposition of these patients. While measuring the efficacy of our trauma system, our data also contribute to the identification of these factors and point to the significance of factors not yet identified.

Mortality is a multifactorial result that incorporates the variable contributions of injury, acute physiology, and the patients’ physiological functional status or burden of comorbid disease. Preexisting medical conditions and older age are
both well-established risk factors of mortality among trauma victims. Each becomes difficult to study independently given that the elderly are more likely to suffer from chronic medical conditions (17). Multiple studies have implicated four disease processes that increase mortality in trauma patients: cirrhosis, cardiovascular disease, respiratory disease, and diabetes. Even after controlling for age, the effect of these diseases on mortality is significant (18, 19). We demonstrated that several comorbidities are associated with mortality in the present study. Malignancy, renal disorders, and cardiac disorders (arrhythmia, valve dysfunction, and congestive failure) were each independent predictors of death among GLF trauma patients in our region.

Two other reports demonstrated the relationship between comorbid conditions and mortality in patients hospitalized with injuries from GLFs. Using data from the Scottish Trauma Audit Group, Kennedy et al found that the mortality rate increased as the number of comorbid conditions increased in patients admitted following low-impact falls (20). Similarly, Hannan et al concluded that "pre-existing conditions . . . are significantly related (inversely) to survival of patients with trauma from low falls." Hannan also advocated that comorbidity and age be included in the physiologic and anatomic injury models currently used to predict survival in these patients (21).

It is important to note that hypotension and metabolic acidosis on presentation to the emergency department carried the greatest odds of death in our cohort. Importantly, the strong associations with these characteristics and death are not unique to GLF patients and have been well described. The model we developed for mortality prediction included variables for age, gender, acute physiology, severity of anatomic injury, and comorbidity. The ultimate purpose of developing such a model was to arrive at a risk-adjusted odds ratio for death for each level of trauma center designation in our region, thus enabling a comparative assessment of the performance of the three levels of trauma centers in our system. Additionally, these data can be observed over time to detect temporal variation in the overall adjusted odds ratios of mortality for our region.

An effective trauma system includes proper triage of patients to a trauma center based not only on the level of injury severity but also on host factors such as age and comorbidities. Such host factors can greatly influence survival and should be integral components in the initial patient assessment. Identifying patient characteristics that adversely affect outcome should ideally prompt transport to a higher trauma center level. We observed that patients in TSA-G with the highest predicted mortality, whether based on anatomic injury severity alone or on the multivariate model we developed, were admitted and treated at the level I and II centers. We also observed that the crude mortality rate was highest at the level I center and lowest among the level III/IV centers, which seems intuitively congruent. However, after risk adjustment, the lowest odds ratios for death occurred in the level I center.

We believe that there should be only minimal differences among outcomes of level I and level II trauma centers serving a common region given the similar capabilities of levels I and II. Culica et al reviewed discharge data from the Texas Health Care Information Council to assess the outcomes of care among the regionalized trauma systems in Texas. Similar to the present study, they observed small variations in survival when the level I and II trauma centers across the state were compared (22). The difference we observed in adjusted odds ratio for mortality between the level I center and the other trauma center levels may reflect variations in triage, transfer, referral patterns, or clinical practice.

Similarities have been observed between outcomes when case mix adjustment was applied in other studies. MacKenzie et al compared mortality rates between level I trauma centers and non-trauma centers using data from 19 states as part of the National Study on the Costs and Outcomes of Trauma. They found that the unadjusted mortality rate was higher among patients treated in trauma centers compared to non-trauma centers. After adjustment for case mix, however, the risk of death within 1 year of injury was significantly lower for patients receiving care at a trauma center (23). Khuri et al also found that risk adjustment had a significant impact on the rank ordering of Veterans Affairs hospitals after implementing a system for the prospective collection and comparative reporting of postoperative mortality rates after major noncardiac operations (24). O’Connor et al sought to improve the mortality rates associated with coronary artery bypass graft surgery in Northern New England. Adjusted mortality rates were used to compare the efficacy of a coordinated intervention among the 23 cardiothoracic surgeons practicing in Maine, New Hampshire, and Vermont.

Risk-adjusted outcomes have become a popular tool for comparing the quality of care between hospitals as part of the so-called quality report cards. Perhaps the best use of risk-adjusted
outcomes, however, may be the identification of opportunities for improvement, such as the refinement of our patterns of referral to higher levels of care for groups of patients at higher-than-average risk for death. As this is our first regionwide comparative assessment endeavor, additional refinement over time of our data acquisition and modeling may yield other significant covariates not included in the present model. Nonetheless, the present study provides a useful benchmark for our region’s performance in triaging and treating patients injured in GLFs.

When our region is considered in total, the overall mortality rate from GLF was 2.1%. This rate compares favorably to other reports focusing on this mechanism of injury. Kennedy et al reported a 2.8% rate in patients with a mean age of 61.6 years (20). Other authors have published GLF mortality rates ranging from 4.2% to as high as 8.9% among adult trauma patients (25, 26). Bergeron et al reported a 13.4% mortality rate among patients admitted to a regional trauma center in Quebec, Canada (26). Our cohort and the Canadian study group had similar median injury severity scores of 9. These figures reflect unadjusted mortality data, though at present, no omnibus metric exists to enable meaningful case mix–adjusted comparative assessment of outcomes between entire regional trauma systems.

In 2006 the ACS embarked on the Trauma Quality Improvement Program (TQIP). A key component of TQIP will be the comparative assessment of observed-to-expected mortality rates based on risk adjustment for institutional case mix (27). A pilot study by Hemmila et al assessed the feasibility of utilizing the infrastructure of the National Trauma Data Bank to provide risk-adjusted benchmarking of trauma centers. They observed differences in the observed-to-expected mortality ratios across similarly verified trauma centers (28). It is possible that efforts such as our study may be supplanted in the future by TQIP as a means of comparing trauma center performance across our region.

In our study, the adjusted odds of mortality remained fairly consistent from year to year. With the exception of 2001, the yearly adjusted odds of mortality did not vary significantly, as the 95% CIs spanned the 1.0 reference line. The variation in unadjusted mortality rates for the years 2002 to 2009 ranged from 1.2% in 2004 to 2.7% in 2002, indicating that the observed mortality was decreased by more than half over 2 years. Yet in the context of the risk adjustment regression model, we can see that the difference in mortality between these outlier years was less dramatic. This is valuable to us because appraisal of our performance from year to year based only on mortality incidence could lead to unfounded concern when unadjusted mortality is trending up, as in 2002. Similarly, when unadjusted mortality incidence is trending down, as in 2004, the lack of appropriate risk adjustment may allow for the misinterpretation that our outcomes had improved.

The most significant limitations of these data are that they were collected over 9 years and from 20 hospitals. As such, it is likely that some variation in data collection and management practices may have occurred between centers and over time. Nonetheless, this analysis provides a basis for future comparison, both in terms of methodology and outcomes. A second limitation to this study is the potential confounding effect attributable to interfacility transfer of GLF patients within our region. No attempt was made to determine correlations between outcome and transfer patterns. The effect of interfacility transfer, if significant, may potentially contribute to the observed difference in adjusted odds ratios for mortality between the level I and level II centers. However, we advocate that patients who require definitive management of injuries be treated in facilities equipped to accommodate the need at hand. Given that there are one level I and two level II trauma centers in TSA-G, appropriate interfacility transfer is an important component of trauma care in our region.

From these observations, we can conclude that the risk-adjusted hospital mortality for patients hospitalized for injuries sustained from GLF in TSA-G has remained consistent since the year 2003. Additionally, these patients are triaged across our region to appropriate levels of care, as demonstrated by the modest variation in adjusted odds ratios for mortality between levels of trauma center verification. More study is warranted to better define the nature of the lower adjusted odds ratio for mortality observed in the level I center compared to the other centers in the region. Understanding the relative contributions of case mix, referral patterns, and clinical practices may allow for an overall improvement in outcomes in our region for this growing population of trauma patients.


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**Notice of duplicate publication**

It was recently pointed out to us that our article, “Anesthesia for the 21st century” by Theodore H. Stanley (2000;13:7–10) is essentially the same as an article that was previously published: “Anaesthesia in the future” in *Journal of Veterinary Anaesthesia* (1994;21:106–109). Dr. Stanley gave this presentation at our medical center, and we invited him to submit a manuscript. *Proceedings* apologizes for this inadvertent duplicate publication.
Fondaparinux-associated heparin-induced thrombocytopenia

Micah Burch, MD, and Barry Cooper, MD

Heparin-induced thrombocytopenia (HIT) is an immune-mediated clinical syndrome of thrombocytopenia and thrombosis occurring after exposure to heparin. HIT most commonly occurs after exposure to unfractionated heparin but has also been reported with low-molecular-weight heparin. To date, there have been very few reports of HIT with the pentasaccharide fondaparinux, and some have proposed fondaparinux as a treatment for HIT. This article presents two cases of HIT associated with fondaparinux use.

Heparin-induced thrombocytopenia (HIT) is a prothrombotic condition associated with characteristic platelet-activating antibodies occurring after exposure to heparin (1). These IgG subclass antibodies recognize complexes of heparin and platelet factor 4 (PF4) and result in a clinical syndrome of thrombocytopenia and thrombosis, typically occurring 5 to 10 days after exposure to heparin. The syndrome is most commonly associated with the use of unfractionated heparin (UFH), with a much lower incidence reported with low-molecular-weight heparin (LMWH) (2, 3).

Fondaparinux (Arixtra) is a synthetic sulfated pentasaccharide that inhibits factor Xa indirectly by binding to antithrombin III. In postoperative orthopedic patients, it has been shown to be effective in the prevention of deep-venous thrombosis (DVT) (4), as well as the treatment of acute DVT and pulmonary embolus (5, 6). Antibodies to PF4/heparin develop in postoperative orthopedic patients receiving fondaparinux at a rate similar to those receiving enoxaparin, but none reacted with PF4/fondaparinux (3). Fondaparinux is likely unable to react with PF4 to generate tertiary immune complexes to provide platelet activation. The risk of HIT is thought to be negligible with this medication, as it has even been proposed as a useful alternate anticoagulant in HIT (7, 8). There have been, however, a few case reports of HIT associated with fondaparinux use (9, 10). We describe two cases of HIT associated with fondaparinux that occurred in the postoperative setting after knee replacement.

CASE 1

A 47-year-old man with osteoarthritis underwent left total knee replacement at Baylor University Medical Center. He had no history of previous heparin exposure, and no heparin was given preoperatively or intraoperatively. His preoperative platelet count was 269 × 10^9/L. Beginning on postoperative day 1, he received prophylactic fondaparinux 2.5 mg subcutaneously daily and was discharged home on day 3 to complete fondaparinux for a total of 9 days.

On the 10th postoperative day, he presented to the emergency department with decreased appetite, abdominal distention, left knee pain, and a temperature of 103°F. His final dose of fondaparinux was given the day prior to admission. At admission, his platelet count was 99 × 10^9/L, and he was initially believed to have sepsis secondary to postoperative joint infection. With antibiotics, his platelet count slowly increased to 147 × 10^9/L over the first 6 hospital days, and he received no heparin or LMWH during this time. An abdominal ultrasound on hospital day 7 to evaluate persistent abdominal pain and distention revealed an occlusive thrombus of his inferior vena cava. Magnetic resonance imaging of the abdomen also revealed bilateral adrenal hemorrhage. An UFH drip was subsequently started, and his platelet count fell precipitously from 140 × 10^9/L to a nadir of 50 × 10^9/L over a 24-hour period. He was also found to have an acute pulmonary embolus and left popliteal vein DVT over this interval (Figure 1).

His anti-PF4/heparin enzyme immunoassay, which was drawn approximately 8 hours after beginning UFH, was positive at an optical density of 2.807 units (normal value, <0.40). This positive result was confirmed with high-dose heparin neutralization studies. Testing for antiphospholipid antibodies as well as other hypercoagulable states was negative. Heparin was stopped, and alternate anticoagulation with lepirudin was initiated. His platelet count normalized over the next week. Warfarin was eventually started, and the patient was discharged home in good condition.

CASE 2

A 63-year-old man with osteoarthritis underwent a right total knee replacement at Baylor University Medical Center. No
heparin was given preoperatively or intraoperatively. His preoperative platelet count was $376 \times 10^9/L$. Fondaparinux at 2.5 mg subcutaneously daily was started on postoperative day 1, and he was discharged on day 5 to continue the anticoagulant.

He was readmitted on postoperative day 7, while still taking fondaparinux, with nausea, vomiting, and abdominal pain. His platelet count was $240 \times 10^9/L$ upon admission. A computed tomography (CT) scan of his abdomen and pelvis only showed findings of duodenal enteritis. He was placed on enoxaparin $40 \text{ mg subcutaneously daily}$ at admission. His abdominal symptoms slowly improved; however, on hospital day 4, he developed acute right lower extremity pain and paralysis with physical exam findings consistent with acute right lower extremity ischemia. A UFH drip was started at this time and given for approximately 5 hours. A CT angiogram of the aorta confirmed complete occlusion of the right distal common iliac artery, as well as splenic and left renal infarcts. He underwent right common iliac embolectomy the same day. His platelet count, which had decreased to $117 \times 10^9/L$ the day prior to the thrombotic event, had decreased to $38 \times 10^9/L$ at the time of surgery (Figure 2).

Given his acute arterial thrombosis and decline in platelets, a strong clinical suspicion for HIT was maintained. His anti-PF4/heparin enzyme immunoassay was positive at an optical density of 3.081 units (normal value, <0.40), and this result was confirmed with high-dose heparin neutralization. All heparin was discontinued and alternate anticoagulation with argatroban was initiated. Over the next 2 weeks, his platelet count rose to normal levels. Warfarin was eventually started, and the patient was discharged home in good condition.

DISCUSSION

These cases demonstrate HIT associated with fondaparinux in two patients undergoing knee replacement. In each case, there was no documented use of heparin preoperatively or intraoperatively, without documentation of incidental exposure to UFH with arterial lines, central venous lines, or cell saver devices. Both patients initially had uneventful postoperative courses following knee replacement; however, both were readmitted to the hospital after discharge. In each case, acute thrombosis was documented with a rapid decline in platelet count, which improved with direct thrombin inhibitor therapy.

Fondaparinux has been shown to be associated with the formation of anti-PF4/heparin antibodies in postoperative orthopedic patients (3). These antibodies cannot be distinguished from those generated from LMWH. Other studies have shown that these anti-PF4/heparin antibodies fail to react against PF4 in the presence of fondaparinux, making a clinical syndrome of HIT associated with fondaparinux unlikely (11). However, a few other cases of HIT associated with fondaparinux have been reported. Warkentin et al reported a case similar to ours of a young woman developing fondaparinux-associated HIT after bilateral knee replacement. She developed bilateral adrenal hemorrhage with DVT on postoperative day 7, with her platelet count decreasing to $39 \times 10^9/L$ (9).

Our cases bolster the observation that, on rare occasions, fondaparinux is associated with HIT. Each case had highly characteristic clinical findings for HIT, including bilateral adrenal hemorrhagic necrosis and inferior vena cava thrombosis in case 1 and acute lower extremity artery occlusion in case 2. Also, both patients demonstrated a drastic decline in platelet count after UFH or enoxaparin was initiated. Each case also demonstrated strongly positive assays for anti-PF4/heparin antibodies and normalization of platelet counts with direct thrombin inhibitor therapy.

These cases highlight two separate potential mechanisms for fondaparinux-induced HIT. The first case likely represents a more rare case of classic HIT related to fondaparinux. Thrombocytopenia and thrombosis developed during a 10-day course of fondaparinux treatment prior to hospitalization and any exposure to heparin. In the second case, however, the patient did receive three daily prophylactic doses of enoxaparin after admission, with platelet counts only decreasing after enoxaparin administration. It seems plausible that anti-PF4/heparin antibodies generated through previous exposure to fondaparinux resulted in a clinical syndrome of HIT. The rapidity of thrombocytopenia with thrombosis suggests an anamnestic response.
to preformed anti-PF4/heparin antibodies upon exposure to enoxaparin.

Finally, cases of “spontaneous HIT” have been reported, in which acute infectious/inflammatory events seem to generate platelet-activating anti-PF4/heparin antibodies (12, 13). Given the case reports associated with knee arthroplasty, it is unclear if the perioperative environment of inflammation resulting from this type of surgery might further potentiate generation of anti-PF4/heparin antibodies in conjunction with fondaparinux. These two cases highlight the complex nature of the pathophysiology of an important clinical syndrome, which seems to be associated with fondaparinux on rare occasions.

Abdominal apoplexy: two unusual cases of hemoperitoneum

Lori N. Harbour, MD, Meghan S. Koch, DO, Thomas H. Louis, MD, James M. Fulmer, MD, and Joseph M. Guileyardo, MD

Abdominal apoplexy, or idiopathic spontaneous intraperitoneal hemorrhage (ISIH), is rare and often fatal. This condition results from a variety of disorders affecting the arterial and venous abdominal vasculature, and nonspecific symptoms usually include abdominal pain, nausea, vomiting, and hemodynamic instability (1). Immediate exploratory laparotomy is the treatment of choice (2), and rapid surgical intervention remains central to a successful outcome. However, accurate preoperative and intraoperative diagnosis remains difficult. Although rare in occurrence, ISIH constitutes a true emergency and should be considered in any patient with atypical abdominal pain and hemodynamic instability (3, 4).

CASE 1

A 70-year-old Caucasian woman was transported to Baylor University Medical Center after complaining of nausea and weakness and collapsing at home. She had recently been hospitalized for treatment of a urinary tract infection, acute renal injury, and a flare of gout, and she had been discharged for outpatient therapy. On route to the hospital, she developed cardiac arrest and required cardiopulmonary resuscitation. Upon arrival at the emergency department, a heart beat had been reestablished, but she was severely hypotensive. Her hemoglobin was 7.1 g/dL, representing a decrease of almost 50% compared to her admission less than a week earlier (13.7 g/dL). Her lipase was 519 U/L. A noncontrast computed tomography (CT) scan of the chest, abdomen, and pelvis was interpreted as possible acute hemorrhagic pancreatitis. The superior mesenteric artery and superior mesenteric vein were completely engulfed by “inflammatory stranding.” The integrity of these vessels was in question but could not be adequately evaluated without contrast. There was apparent inflammation involving the distal stomach and duodenum as well (Figures 1 and 2). She was converted to a do-not-resuscitate status, and surgery was not performed. Despite supportive measures, the patient’s status declined, and life support was eventually withdrawn.

At autopsy, there was approximately 700 mL of liquid and clotted blood within the abdominal cavity in addition to extensive retroperitoneal and mesenteric hemorrhage, but an obvious source of hemorrhage was not initially apparent. After fixation, the pancreas, mesentery, regional vasculature, duodenum, and common bile duct structures were again carefully examined and dissected. There was extensive intraparenchymal and peripancreatic hemorrhage; however, inflammatory findings were not present. Surrounding the superior mesenteric artery and smaller...
arterial branches, as well as the superior mesenteric vein and venous branches, there was densely clotted blood. Within areas of diffuse hemorrhage surrounding the gastroduodenal artery and its branches, there was a grossly apparent perivascular space that contained a blood clot circumscribed by surrounding connective tissue planes (Figure 3).

Microscopically, there was extensive hemorrhage surrounding the pancreas; however, there were no changes of pancreatitis involving the parenchyma. Within the media of the gastroduodenal artery, there was a blood-filled, cleft-like disruption, typical of spontaneous arterial dissection (Figure 4). Movat pentachrome staining highlighted the lesion and revealed disruption of the internal elastic lamina with central compression of the vascular lumen by the dissecting blood (Figure 5). There was extensive hemorrhage surrounding the vessel, and there was no histopathologic evidence of a specific vasculitis or vasculopathy. Additional autopsy findings included significant hypertensive cardiovascular disease and severe aortic, coronary artery, and renal artery atherosclerosis.

**CASE 2**
A 55-year-old Caucasian woman presented to Baylor University Medical Center with acute-onset abdominal pain, diarrhea, nausea, vomiting, and dizziness. Her physical examination revealed diffuse abdominal tenderness, and her hemoglobin was 7.5 g/dL. A CT scan of the abdomen revealed a large hemoperitoneum, predominantly in the lesser sac. There were diffuse inflammatory changes about the head of the pancreas and porta hepatis, along with a circumscribed hematoma near the junction of the superior mesenteric vein and the portal vein (Figures 6 and 7). She was taken emergently for exploratory laparotomy, where a large hemoperitoneum was confirmed. The portal vein, mesenteric vein, and surrounding tissues were extremely friable, and vascular ligation was attempted at sites of possible rupture. Postoperatively, the patient required pressors and numerous units of blood; however, supportive measures were ultimately unsuccessful and she died. An autopsy was requested.

At autopsy, 5100 mL of liquid and clotted blood was found within the abdominal cavity, and there was a 4-cm circumscribed thrombus within the central abdominal region. Again,
a definite source of bleeding was not initially apparent. After fixation and careful dissection of the vasculature, the thrombus was found to be located within connective tissues adjacent to the head of the pancreas and external to the superior mesenteric and portal veins (Figure 8). This thrombus was enclosed within a pseudoaneurysm wall composed of friable connective tissue with recently placed surgical sutures for attempted hemostasis. A true vascular aneurysm wall was not identified at autopsy; however, sutures at the superior mesenteric vein–portal vein junction were consistent with a repaired venous disruption. Microscopic sections showed no evidence of intrinsic vasculitis or specific vasculopathy involving the superior mesenteric or portal veins. There was focal intramural and perivascular hemorrhage with some thinning of the portal vein, but a true aneurysm was not identified. Furthermore, there was no evidence of intrinsic pancreatitis or hepatic cirrhosis, and there were no historical or anatomic findings to support recent abdominal trauma or hypertensive cardiovascular disease. There was no atherosclerotic cardiovascular disease.

These findings were interpreted as consistent with spontaneous intraabdominal hemorrhage associated with idiopathic venous rupture and perivascular pseudoaneurysm formation.

DISCUSSION

In general, intraperitoneal or retroperitoneal hemorrhage may be secondary to blunt trauma, aneurysmal rupture (central or visceral), solid organ malignancy (hepatic or renal), or inflammatory erosive processes (pancreatitis or pseudocyst); however, it may be idiopathic as well (2, 3, 5).

Abdominal apoplexy, or the newer term, ISIH, describes a rare finding of nontraumatic intraabdominal bleeding. ISIH was first reported by Barber in 1909, but the term “abdominal apoplexy” was coined by Green and Powers in 1931 as a comparison to its cerebral counterpart (3–5). Traditionally, abdominal apoplexy refers to spontaneous hemorrhage arising from one of the smaller abdominal arteries or veins, after hemorrhage from a grossly apparent aortic aneurysm or aortic dissection is excluded. Additionally, cases of hemorrhage from visceral malignancy and gynecologic lesions such as ectopic pregnancy, as well as abdominal hemorrhage associated with known traumatic injury, are also excluded (6). Thus defined, abdominal apoplexy is exceedingly rare. There is a male predominance (2–3:1), and the majority of cases present in the fifth and sixth decades of life (3, 6).

Abdominal small vessel rupture often occurs at the site of an aneurysm, but up to 30% of cases have no identifiable source (3, 5). Historically, aneurysms have been mycotic, syphilitic, or traumatic in origin but are now more likely related to essential or portal hypertension (2, 3). Fibromuscular dysplasia has also been associated with aneurysm formation. In the absence of portal hypertension, known trauma, or fibromuscular dysplasia, a specific etiology of venous disruption remains elusive. Predictably, arterial aneurysms often occur at secondary or tertiary branch points from the aorta; 60% involve the splenic artery, 22% renal, and 10% to 20% hepatic, with common celiac and mesenteric arteries less common (3). Most cases with no identifiable source are probably related to common vascular diseases including arteriosclerosis and essential hypertension.
The exact mechanism is unknown but likely represents weakness of the tunica media, predisposing to rupture in the face of abrupt increases in pressure. Pathology specimens regularly exhibit disruption of elastic lamellae. Less frequently, spontaneous hemorrhage may be associated with inflammatory and necrotizing processes such as polyarteritis nodosa and rheumatoid arthritis, etc. Venous rupture, on the other hand, is usually associated with portal hypertension due to hepatic cirrhosis.

In addition to the above disorders, rare cases of abdominal apoplexy have been attributed to arterial dissections involving splanchnic vessels such as the gastroduodenal, hepatic, superior mesenteric, gastric, and splenic arteries. Various theories regarding risk factors for arterial dissection include common disorders such as essential hypertension and less common connective tissue disorders such as the Marfan and Ehlers Danlos syndromes.

These two cases demonstrate the continued therapeutic and diagnostic challenges associated with the clinical management of patients with abdominal apoplexy. Angiography was not clinically feasible in either case. The limitations of noncontrast CT prevented exclusion of pancreatitis as well as identification of a specific bleeding source. Furthermore, the source of bleeding was not obvious upon initial autopsy examination, and accurate diagnosis required careful preservation of the specimens with subsequent dissection and microscopic sampling before the source of bleeding was localized. These cases also demonstrate the wide spectrum of arterial and venous abnormalities that can result in spontaneous abdominal hemorrhage, and the case involving venous rupture is especially unusual since this patient did not have cirrhosis or portal hypertension. Although autopsy examination demonstrated the source of bleeding in both cases, a specific underlying cause for development was not apparent.

Both cases also demonstrate our currently imperfect understanding of abdominal apoplexy, and further research is certainly required. Although this disorder has been called idiopathic and spontaneous, it is unlikely that such hemorrhage occurs without an underlying vascular lesion, which may be apparent only at the molecular level.


Proceedings welcomes Dr. Andrew Fenves as associate editor

Dr. Andrew Fenves, an editorial board member since 2004, has assumed the role of associate editor of the journal. Dr. Fenves has been chief of the nephrology division for the past 10 years and is a former program director for the nephrology fellowship at Baylor University Medical Center at Dallas. He has also been the Ralph Tompsett Professor of Medicine at Baylor since 1996. Dr. Fenves has over 70 peer-reviewed publications and 11 book chapters and is currently involved in three ongoing National Institutes of Health–sponsored clinical research trials. In addition to his role at Baylor, Dr. Fenves has been a clinical full professor at the University of Texas Southwestern Medical School since 1996. An interview with Dr. Fenves was published in the July 2004 issue of Proceedings, describing Dr. Fenves’ childhood in communist Budapest, where he was a young chess competitor and the son of a physicist; his family’s immigration to Dallas in 1969; his education at Stanford University, where he majored in mathematics, followed by the University of Texas Southwestern Medical School; his residency and fellowship training at Baylor University Medical Center; and his career as a nephrologist with a strong interest in education and research.
Focal segmental glomerulosclerosis and parvovirus B19

Catalina Sanchez, MD, Andrew Fenves, MD, and John Schwartz, MD

Focal segmental glomerulosclerosis (FSGS) is a glomerular disease with a characteristic pathologic presentation that includes segmental scarring involving some but not all glomeruli. On immunofluorescence, deposits of immunoglobulin (Ig) M and C3 may be found in the areas of segmental scarring. Electron microscopy typically demonstrates diffuse epithelial cell foot process effacement and focal areas of retraction of glomerular basement membrane with collapse of the involved tuft (1). Due to the focal nature of the process, it is sometimes challenging to recognize this lesion in the biopsy specimen. Accordingly, special attention needs to be directed at the corticomedullary regions of the kidney where FSGS is more likely to be found. Otherwise, an errant diagnosis of minimal change disease could be made. Once underlying causes of this particular glomerular presentation are ruled out (such as obesity, sleep apnea, heroin abuse, reflux nephropathy, and HIV), one is left with a diagnosis of primary or idiopathic FSGS. It is important to identify patients who present with nephrotic-range proteinuria and have FSGS because early treatment of these patients may alter the course of the disease and prevent relentless progression to terminal renal failure (2).

The collapsing form of FSGS, which occurs more commonly in African American patients than in Caucasians, carries a particularly poor prognosis with respect to renal survival (3). This variant is morphologically similar to the glomerular lesion often associated with HIV infection. However, the term idiopathic collapsing glomerulopathy is reserved for patients who are HIV negative.

Collapsing glomerulopathy has been associated with non–HIV-related pathologies. These include associations with medications like pamidronate and interferon-alpha and with viral infections like parvovirus B19, cytomegalovirus, and hepatitis C (4, 5). Rarely, multiple myeloma has been associated with this lesion (6, 7). A case of collapsing FSGS in a patient with parvovirus B19 infection is presented with review of the known literature.

CASE PRESENTATION

A 56-year-old African American man with a history of hypertension, hyperlipidemia, and chronic kidney disease, with a baseline serum creatinine of 1.9 mg/dL 4 months earlier, presented to the hospital with worsening fatigue and malaise. Renal laboratory results had deteriorated, with a creatinine of 17 mg/dL and blood urea nitrogen of 94 mg/dL. He denied any recent use of nonsteroidal antiinflammatory drugs or herbal supplements and reported compliance with his medications, which included metoprolol 50 mg twice daily and verapamil (dose unknown). Physical examination was remarkable only for a blood pressure of 170/88 mm Hg and bilateral lower extremity edema. Urinalysis revealed 3+ proteinuria, 1+ blood, and hyaline casts. The spot urine protein/creatinine ratio was 5.2 (normal, <0.2). Renal ultrasound revealed normal-sized kidneys with increased echogenicity. Tests for HIV by enzyme-linked immunosorbent assay and polymerase chain reaction were negative, as were tests for hepatitis B surface antigen and hepatitis C antibody and urine drug screens. Serum protein electrophoresis, urine protein electrophoresis, and urine immunofixation revealed no monoclonal protein. Tests for parvovirus antibodies were positive, with titers of IgM 5.2 and IgG 4.5, indicative of active infection.

A renal biopsy revealed collapsing FSGS glomerulopathy with patchy tubular dilatation (Figure 1). The patient’s clinical course was characterized by nonoliguric renal failure and difficult-to-control hypertension. However, his renal function gradually improved with no specific therapy, with his serum creatinine falling to 4 mg/dL. Subsequent parvovirus IgM and IgG titers fell, indicating a resolution of his viral infection.

DISCUSSION

It is postulated that in collapsing glomerulopathy, unlike other podocytopathies, the podocyte dedifferentiates, and this results in a dysregulated phenotype (8). Diseased podocytes exhibit a loss of differentiation and gain of proliferation. Podocytes have been described to “transdifferentiate” towards a macrophage-like cell (9–13) (Figure 2).

Patients with FSGS usually present with nephrotic-range proteinuria, hypertension, and decreased renal function. The collapsing variant of FSGS was first recognized and described by...
Schwartz and Lewis (14) and was later confirmed by Weiss et al (15), Detwiler et al (16), and Valeri et al (17). These patients are likely to have higher levels of proteinuria, are more commonly African American, and have a poor prognosis with more rapid progression to terminal renal failure.

Parvovirus B19 infection is a common disease, with 50% to 80% of adults having parvoviral-specific IgG. The infection is usually minimally symptomatic, but aplastic anemia can occur in patients with sickle cell disease and other chronic hemolytic disorders. Parvovirus B19 can evolve into a chronic infection in patients who are immunosuppressed. Clinical symptoms of active disease include skin rash and arthralgias.

FSGS has been described as a clinical consequence of parvovirus B19 infection (18–20). Moudgil et al presented a series of 23 patients with collapsing glomerulopathy, and 18% of these cases revealed parvovirus B19 DNA in the renal specimens. In another series, 10 more cases of collapsing FSGS were reported by Tanawattanacharoen et al, where 90% of the cases had DNA evidence of parvovirus B19 in renal tissue (21). It has been speculated that some patients have a predisposition that makes them susceptible to defects in their ability to generate a cellular and humoral immune response to clear this virus. The persistence of viremia increases the infectivity and has a possible impact on a variety of clinical disease presentations.

The collapsing variety of FSGS is rare. African Americans are hyperproducers of transforming growth factor B, a cytokine associated with fibrosis, which could contribute to excessive proliferative and sclerosing in response to a viral insult. In certain individuals, this may initiate a cascade of events in the kidney, which results in collapsing glomerulopathy (16, 18, 22, 23). However, other individuals may have resistance to this viral infection due to lack of the viral receptor (in the erythrocytes and/or kidney tissue), which protects their renal epithelial cells from parvovirus infection. In our patient, there was a temporal relationship between active parvovirus B19 infection and the development of collapsing FSGS, with clinical improvement as the viral infection resolved.

No evidence-based therapy exists for collapsing FSGS. Current therapies are based on empiric experience and have been extrapolated from treatments used for FSGS. Treatments utilized include steroids, cyclophosphamide, and cyclosporine (9). The usual recommended course of steroid therapy is 6 months of daily or alternate daily prednisone. Unfortunately, despite aggressive therapy, remission is uncommon. Various studies have reported full remission rates of 9.6% and partial remission rates of 15.2%. Furthermore, Crenshaw et al, in their retrospective series, did not find a beneficial effect of steroids in African Americans (3, 24). For patients who are intolerant of prednisone, various immunosuppressives have been tried, again with variable success.

Figure 1. Renal biopsy showing collapsing FSGS with microtubular dilatation: (a) trichrome stain; (b) silver stain.

Figure 2. Speculative “best-fit” model for the pattern of parenchymal injury in collapsing glomerulopathy. Reprinted from Albaqumi et al, 2006 (9) with permission from the American Society of Nephrology; permission conveyed through Copyright Clearance Center, Inc.

A recent report presented a patient with cyclosporine-resistant collapsing FSGS who was successfully treated with rituximab and achieved a complete remission. Therefore, this agent may emerge as yet another therapeutic option for patients with refractory collapsing FSGS (25).

Treatment of hypertension is an important aspect of treatment for all patients with renal disease, regardless of etiology, and angiotensin-converting enzyme inhibitors (ACEIs) are considered first-line drugs for this purpose. ACEIs control systemic hypertension and simultaneously reduce intraglomerular pressure and hence decrease proteinuria (3). Prasher et al assessed the efficacy of enalapril in controlling proteinuria in steroid-resistant idiopathic nephrotic syndrome and found that enalapril exerted a long-lasting effect (26). Also, a randomized controlled trial of losartan therapy in 23 normotensive patients with primary FSGS who were refractory to immunosuppressive therapy showed a reduction in proteinuria compared with the control group after 1 year of treatment (27).

In summary, a rare subtype of FSGS called collapsing FSGS is reported. This glomerulopathy, often associated with active...
HIV infection, has a very aggressive course leading to terminal renal failure. In this case a coexistent acute parvovirus B19 infection was identified. The patient’s clinical presentation and renal biopsy findings are indistinguishable from those features in patients with HIV nephropathy. This finding raises the possibility that parvovirus B19 may be the precipitating or causative etiologic agent for this form of FSGS. This possibility is further supported by the patient’s marked clinical improvement as the parvovirus B19 infection resolved.

Ruptured intracranial dermoid cyst

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Rupture of an intracranial dermoid cyst is a rare event with considerable associated morbidity and potential mortality. We present a case of intracranial rupture of a dermoid cystic tumor with consequent dissemination of subarachnoid fat droplets resulting in acute aseptic chemical meningitis. Radiographic findings, operative treatment, and pathologic features are described.

Intracranial dermoid cystic tumors account for <1% of all intracranial masses. Dermoids are nonneoplastic, congenital ectodermal inclusion cysts that contain varying amounts of ectoderm derivatives to include apocrine, sweat, and sebaceous cysts as well as hair follicles, squamous epithelium, and possibly teeth. They are not to be confused with an epidermoid cyst, which contains only squamous epithelium. Teratomas, although similar in some respects, are a separate entity. Teratomas are true neoplasms that contain tissue from all three embryonic germ cell layers (1).

Dermoid cystic tumors arise from the inclusion of ectodermally committed cells at the time of neural tube closure during the third to fifth week of embryogenesis. These lesions are slow growing due to the active production of hair and oils from the internal dermal elements (2). The presentation of dermoid tumors is quite variable. Occasionally they are incidental findings discovered on brain computed tomography (CT) or magnetic resonance imaging (MRI) for otherwise unrelated clinical complaints, or they are discovered during imaging investigation of unexplained headaches, seizures, and rarely olfactory delusions (3, 4). When dermoid cystic tumors rupture and spread their contents into the ventricles and subarachnoid and/or subdural spaces, the most common clinical presentation is that of headache and seizures. Headache may be the consequence of compression of adjacent neural structures, chemical meningitis from cyst content irritation, or perhaps the effects of hydrocephalus if present.

CASE REPORT

A 46-year-old man, without significant past medical history, presented for the evaluation of constant unrelenting headaches of 1 month’s duration. The headaches had a waxing and waning course with sporadic episodes of photophobia. The patient complained of severe right trigeminal nerve-type pain. The patient had no complaints of nausea, vomiting, altered mental status, or seizures. On presentation, vital signs were normal. Laboratory evaluation revealed only a mild leukocytosis. No focal neurologic deficits were identified. An initial CT scan of the brain without contrast material demonstrated a 2.4 cm diameter extra-axial fat-containing mass with scattered intralobional calcific deposits centered near the anterior clinoid process and overlying the superior orbital fissure (Figure 1). Portions of the mass were contained within both the anterior and middle cranial fossae. Scattered fat-containing droplets were disseminated throughout the subarachnoid space. A subsequent MRI scan showed additional imaging features characteristic of a ruptured dermoid cystic tumor (Figure 2).

In the operating room, a craniotomy flap was elevated for exposure. The dura was then opened along the sphenoid ridge...
for visualization of the skull base. Microscopic dissection clearly determined the mass to be extra-axial, growing from the anterior clinoid region superiorly toward the brain. Arachnoid adhesions were released and the sylvian fissure opened proximally, exposing the lesion (Figure 3). A clear fat plane existed between the tumor and the brain parenchyma, and the borders were separated. The mass was too large for en bloc resection. It was incised and found to be amorphous and amenable to suction. Pathology evaluation of the submitted tissue confirmed the diagnosis of a dermoid cystic tumor (Figure 4).

The patient's postoperative course was uneventful. An MRI scan of the brain obtained 4 months after resection showed minimal persistent intraventricular fat droplets without recurrence or discernible complications of the resection. The patient has resumed most normal activities.

DISCUSSION

Intracranial dermoid cystic tumors are rare, benign, slow-growing masses. They are most often found in a sellar or parasellar location as well as the frontonasal region and frequently reside near the skull base. Intracranial dermoids can also be found in the posterior cranial fossa within or in close proximity to the fourth ventricle. These lesions can also be found in the pineal gland fossa, in addition to a number of other less frequent intracranial sites (4–6).

Symptoms typically are ascribed to mass effect created on adjacent intracranial structures. If rupture occurs, aseptic chemical meningitis may ensue with profound irritative effects from the disseminated cholesterol debris. Chemical meningitis is a relatively rare development and is reported in approximately 7% of cases of dermoid tumor rupture (1, 5). Chemical meningitis may elicit transient cerebral ischemia secondary to vasospasm with complicating infarction that may result in the death of the patient. Morbidity may also be related to chemical arachnoiditis (7). Symptom onset typically does not occur at the time of rupture, since the irritative effects of the spilled contents require time to develop, but may be delayed from 3 months to 6.5 years after rupture (3).

Dermoid cystic tumor rupture usually occurs spontaneously; however, cases of rupture secondary to closed head trauma or iatrogenic surgical complications have been reported (5). Supratentorial dermoids often present in the second or third decades of life, while posterior fossa dermoids typically present in the first decade of life as a consequence of mass effect exerted on the fourth ventricle with resulting hydrocephalus (3). Posterior fossa cystic tumors may have visible occipital scalp dimples or sinus tracts. If present, these are usually discovered in infancy. A fistulous sinus tract may lead to recurrent bouts of bacterial meningitis (1).

Imaging features of intracranial dermoid tumors on brain CT scans are virtually pathognomonic. These lesions will have internal density characteristics consistent with fat (negative Hounsfield units) (Figure 1), although density values greater than fat may be encountered depending on the nature of an individual tumor’s

Figure 2. (a) T1-weighted MRI, (b) T1 midline sagittal, and (c) T2-weighted MRI images demonstrate a hyperintense lesion in the middle cranial fossa corresponding to the dermoid tumor (solid arrows). Note scattered foci of hyperintensity throughout the subarachnoid space (broken arrows). The lesion was intimately associated with the left middle cerebral artery, which is apparent on the T2-weighted image (c).

Figure 3. (a) The dermoid tumor (arrow) is seen through the microscope with the proximal sylvian fissure separated. (b) The internal carotid artery (solid arrow) and optic nerve (broken arrow) can be seen after the dermoid tumor has been resected.
contents. The dermoid wall is typically seen and can calcify. Occasionally the wall will at least partially enhance following the administration of CT-iodinated contrast material. On MRI scans, dermoids will be hyperintense (bright) on T1-weighted imaging and heterogeneous on T2-weighted imaging (Figure 2). If the internal fat content is relatively low, the lesion will reveal cerebrospinal fluid–like signal intensity. In such cases, fluid attenuation inversion recovery (FLAIR) is useful, in that the fat will appear hyperintense (bright) on a background of suppressed fluid signal (dark). On MRI, fat constituents create a so-called “chemical shift” artifact due to misregistration of the signal in the frequency-encoded direction. This can be particularly useful in diagnosing these lesions preoperatively. When a dermoid tumor ruptures, fat droplets—appearing hypodense on CT or T1 hyperintense on MRI—may be seen scattered and floating within the nondependent portions of the ventricular system and/or subarachnoid space. This is considered a classic imaging feature of these lesions. In the setting of complicating chemical meningitis, intense pial and ventricular ependymal enhancement may be detected after the administration of MRI gadolinium contrast (1–3).

Although the imaging appearance of dermoid tumors is characteristic, several other intracranial lesions must be considered in the differential diagnosis, such as epidermoids, teratomas, lipomas, craniopharyngiomas, and occasionally arachnoid cysts. A review of all available CT and MRI images often allows the radiologist to offer an accurate preoperative diagnosis.

Surgical care focuses on complete microsurgical resection of the mass and wall. If the tumor has not ruptured preoperatively, great care is made to avoid spilling the contents in the surgical bed. Patients typically do well after operative intervention. Recurrence is rare but is more common if there are retained portions of the tumor wall. Rare reports describe the development of squamous cell carcinoma in retained remnants of a dermoid cystic tumor wall (3, 8).

Bowhunter's syndrome diagnosed with provocative digital subtraction cerebral angiography

William B. Taylor III, MD, Clayton L. Vandergriff, MD, Michael J. Opatowsky, MD, and Kenneth F. Layton, MD

Bowhunter’s syndrome, also known as rotational occlusion of the vertebral artery, involves posterior circulation ischemia resulting from dynamic compromise of the dominant vertebral artery. This case highlights the importance of provocative digital subtraction angiography in making the diagnosis. A 41-year-old man presented for outpatient neurological evaluation for “lightheadedness” of several years’ duration provoked by leftward head rotation. The only abnormality identified on initial magnetic resonance angiography was atresia of the nondominant left vertebral artery. Conventional digital subtraction angiography (DSA) followed by provocative DSA revealed development of a dynamic stenosis of the right vertebral artery involving the extraforaminal segment just superior to the C1 vertebra. Noncontrast computed tomography of the cervical spine confirmed ossification of the posterior right atlanto-occipital membrane leading to a near complete bony arcuate foramen. Following neurosurgical decompression, the patient demonstrated complete resolution of all neurologic symptoms. Bowhunter’s syndrome is a unique clinical entity that must be considered in the evaluation of patients with symptoms of posterior circulation ischemia. Provocative DSA remains the preferred modality for definitive diagnosis.

A 41-year-old man presented with “lightheadedness” of several years’ duration. His symptoms were provoked only by leftward rotation of the head. This position reliably resulted in presyncope, which was quickly relieved by returning to a neutral position. Cervicalgia and neurologic deficits were absent. The patient disclosed a medical history significant only for colon cancer. Examination revealed mild left-sided ataxia while performing the heel-to-shin maneuver. The remainder of the exam was unremarkable.

Because of the clinical suspicion for vertebrobasilar insufficiency, an intracranial and extracranial magnetic resonance (MR) angiogram was requested. It disclosed an atretic left vertebral artery, but no other abnormality. A conventional cerebral digital subtraction angiogram (DSA) was subsequently performed followed by provocative DSA. Initial angiographic images obtained in the neutral position revealed no diagnostic abnormality. Specifically, the posterior arterial circulation was patent (Figure 1). The patient was asked to rotate his head leftward, and additional angiographic images were obtained. These revealed dynamic development of a severe stenosis of the right vertebral artery involving the extraforaminal segment just superior to the C1 vertebral body (Figure 2). The immediate cause of the dynamic stenosis was not evident by conventional angiogram. To better evaluate the osseous structures of the cervical spine, a noncontrast computed tomography (CT) exam was performed and confirmed ossification of the posterior right atlanto-occipital membrane resulting in a near complete bony arcuate foramen (Figure 3).

The patient underwent decompression of the right vertebral artery by removal of osteophytic ridging associated with the C1 vertebral body. Ultimately, the patient experienced complete resolution of all neurologic symptoms induced by rotational head movement.

DISCUSSION

Bowhunter’s syndrome is the clinical manifestation of posterior circulation ischemia provoked by dynamic compromise.
of the dominant vertebral artery. The colloquial name refers to the rotational position of the head that a bowhunter assumes when properly aiming his bow. In adults, bowhunter’s syndrome is most commonly caused by rotational compression of the dominant vertebral artery by a hypertrophic osteophyte, typically arising from the uncovertebral joints (1). This results in dynamic impingement upon the vessel lumen, compromising flow to the posterior circulation and provoking typical features of vertebrobasilar insufficiency. Classic examination findings are rotational vertigo with horizontal nystagmus towards the compressed artery (1). The most common inciting factor in bowhunter’s syndrome is cervical spondylosis, although numerous additional causes have been identified, including surgical fixation, chiropractic manipulation, and rheumatoid subluxation (2). Other causes of vertebral artery compression secondary to a fibrous band or a thickened atlantoaxial membrane have also been reported (3).

The vertebrobasilar system is composed of paired vertebral arteries, which may allow for compensation in the instance of unilateral disease. However, one of the vertebral arteries, more commonly the left, is often found to be significantly larger than the contralateral side and provides the majority of inflow to the posterior circulation. Bowhunter’s syndrome is classically described as affecting the dominant vertebral artery, although cases involving the nondominant vessel have been documented (4). The ischemic changes of bowhunter’s syndrome are commonly transient, though permanent deficits, including lateral medullary infarcts (Wallenberg syndrome), have been described (4).

Although ultrasound, CT, or MR angiography may demonstrate disease, for a number of reasons, DSA is the preferred method of diagnosis. DSA provides precise localization of the flow-limiting lesion and confirms that the occlusion occurs during head rotation (1). Treatment for this condition is most often surgical; however, conservative measures such as neck immobilization or a conscious effort not to rotate the head to the affected side may initially be attempted. Surgical treatment most commonly consists of osseous decompression tailored for the patient’s particular cause of rotational compression, and, if cervical subluxation is the cause, fixation has been advocated (5, 6). Recently, there has also been discussion of stent deployment in the contralateral vertebral artery if it has hemodynamically significant severe atherosclerotic stenosis (7).

With medical advances, mortality and morbidity rates associated with myocardial infarction (MI) have declined dramatically (1). Nevertheless, cardiogenic shock is the most common cause of death after an acute MI, followed by left ventricular (LV) rupture (2). A pseudoaneurysm, albeit rare (3), is more likely to rupture than is a true aneurysm and thus is a post-MI complication that warrants urgent surgery (4). It is usually the result of an infarction involving the entire thickness of the myocardium. A localized pericarditis develops, and the resulting adhesions between the visceral and parietal pericardium rupture, with extravasated blood being contained by the adherent pericardium. The aneurysmal wall contains dense fibrous tissue but lacks myocardial fibers and coronary arteries. A true aneurysm, in contrast, consists of focal convex deformities of the heart, has wide communications between the aneurysmal cavity and left ventricle, contains myocardial fibers, and is lined by the former endothelium (3). This area of thin myocardium subsequently moves dyskinetically (5).

Although transthoracic echocardiography (TTE) has been most studied in distinguishing pseudoaneurysms and true aneurysms (5), transesophageal echocardiography (TEE) is considered superior in the evaluation of pseudoaneurysms (6, 7). We report intraoperative management of a case presented for repair of a giant LV pseudoaneurysm and true aneurysm.

**CASE REPORT**

A 47-year-old woman with a body mass index of 35.3 kg/m² and hypertension, type 2 diabetes mellitus, dyslipidemia, hypothyroidism, and coronary artery disease presented with a 2-week history of lower-extremity/abdominal edema, shortness of breath, paroxysmal nocturnal dyspnea, a productive cough, and weakness/fatigue. Two months prior, she was admitted to an outside hospital following an acute MI. Cardiac catheterization at that time showed 100% left anterior descending artery and 90% posterior LV artery occlusion, diffuse circumflex disease, “faint” right to left collaterals from the right coronary artery to the left anterior descending artery, severely reduced LV function with anterior akinesis, and an anteroseptal aneurysm. Additionally, her hospital course was complicated by a cardioembolic cerebrovascular accident. She was eventually discharged home on medical management consisting of a beta-blocker, angiotensin-converting enzyme inhibitor, loop diuretic, and statin.

At the time of presentation to our hospital, her physical examination was positive for elevated jugular vein pressure and distention, a systolic ejection murmur, bilateral crackles and wheezing, 3+ pitting edema up to the knees bilaterally, and multiple skin ulcerations. An electrocardiogram demonstrated normal sinus rhythm, low-voltage QRS with poor R wave progression, residual anterior ST elevation, and Q waves in leads I...
and aVL. Chest x-ray showed a left pleural effusion. Laboratory evaluation was significant for a brain natriuretic peptide level of 6249 pg/mL and troponin T level of 0.02 μL. Her serum cholesterol was 99 mg/dL and triglycerides, 103 mg/dL. Subsequent cardiac catheterization revealed a cardiac index of 1.3 L/min/m², consistent with cardiogenic shock. Her arterial blood pressures were in the 80s to 90s mm Hg systolic and 60s mm Hg diastolic. Initiation of dobutamine increased her blood pressure to the 100s mm Hg systolic and 70s mm Hg diastolic.

Impressions from TTE were severe LV dysfunction, extensive distortion of the LV apex presumably related to an extensive aneurysm filled with thrombus, and diastolic inward movement of the thrombus in the aneurysm. A mass was seen anterior to the heart overlying the right ventricle (RV) and was determined to likely represent thrombus or possible contained myocardial rupture next to an aneurysm. Finally, there was compression of the RV free wall from the mass/thrombus. Referral for magnetic resonance imaging (MRI) was recommended.

Cardiac MRI showed RV compression by a large clot, severely depressed (14%) LV function, moderately depressed (38%) RV with obliteration of the RV cavity, and a large thrombus contained within the pericardium compressing the RV from the mid RV to the apex. In addition, there was pericardial enhancement outside the posterior portion of the RV that was consistent with a pseudoaneurysm.

An intraaortic balloon pump was placed immediately prior to presenting to the operating room for a planned Dors procedure (8), which is an LV patch plasty, and a coronary artery bypass graft. After successful induction of anesthesia, a TEE was performed. The estimated ejection fraction was 20% to 25%, and severe tricuspid, mild pulmonary, and mitral regurgitation and mild aortic insufficiency were noted. A large pseudoaneurysm was visualized compressing the RV and LV (Figure 2). The identification was made based largely upon the lack of myocardial continuity within the aneurysmal wall.

A midline sternotomy was performed with careful entry into the pericardium. After cannulation of the aorta, right atrium, and superior vena cava, the pseudoaneurysm was entered with immediate initiation of cardiopulmonary bypass (CPB). The pseudoaneurysm was described as being the size of a grapefruit, measuring approximately 10 to 15 cm in diameter. The pseudoaneurysm was thought to be old and not acute. After debridement of the pseudoaneurysm, a true aneurysm measuring approximately 5 x 8 cm in diameter was visualized.

The surgeons decided to keep the heart warm and beating during the procedure. The scheduled coronary artery bypass graft was aborted because of poor visualization of the targets for the left anterior descending artery, marginal, and RV branches secondary to complete encasement of the ventricular surface. They proceeded with the Dor procedure. After a CPB time of 147 minutes, separation was achieved for approximately 10 minutes, at which time the patient became hemodynamically unstable, requiring reintubation of CPB. Although the RV ejection fraction was not quantified, it was clinically evident by regional RV wall motion abnormalities and inadequate LV filling. An RV assist device was placed, and separation from CPB was achieved with high inotropic support consisting of epinephrine, norepinephrine, and dobutamine. She was also initiated on nitric oxide, 40 parts per million, for pulmonary artery systolic pressures ranging from 60 to 80 mm Hg. TEE revealed no new regional wall motion abnormalities. The remaining perioperative course was complicated by coagulopathy, multiple organ failure, and death.

Surgical pathology reported the specimen as consisting of fragmented, hemorrhagic, fibrous tissue, measuring 21 x 15 x 4 cm in aggregate. No definite ventricular wall was identified, but there was hemorrhagic tissue which measured 0.2 to 1.0 cm in thickness. The remainder of the tissue was blood clot. The specimen was reported as being consistent with a pseudoaneurysm.

**DISCUSSION**

Our case of concurrent LV pseudoaneurysm and true aneurysm is indeed rare, with only limited reports in the literature (9, 10). Although rare, pseudoaneurysms represent a life-threatening complication of MI necessitating urgent surgery. In our case, a TTE had shown an extensive aneurysm but wasn’t able to delineate it further, and a cardiac MRI had to be performed. The MRI reported the likely possibility of a pseudoaneurysm.

Acquiring optimal precordial images on TTE can be limited by mechanical ventilation, obesity, suboptimal positioning, and/or lines and tubes. TEE may provide a way around these technical limitations (11). This is particularly important because identifying the continuity of the myocardium is a challenging yet distinguishing feature in pseudoaneurysms in comparison to true aneurysms (4).
Cardiovascular derangement occurs in more than 20% of cardiac surgical patients (12). Another benefit of TEE performed during surgical repair and after weaning from CPB is the evaluation for improvements, especially the ejection fraction (4). Although LV failure is mostly studied and assessed, acute RV failure is a major cause of morbidity and mortality. Thus, a comprehensive assessment of RV size, shape, and function may lead to early management of RV failure, making TEE the mainstay in the assessment of perioperative RV function (13).

Although some authors advocate for multimodal cardiac imaging (14), in institutions where advanced technology is limited, precluding the use of MRI for example, TEE is considered superior to TTE in distinguishing between a true aneurysm and pseudoaneurysm (6,7,15). TEE’s portability and ease of examination are added advantages over MRI (16).

Two-dimensional echocardiography can be further enhanced with three-dimensional echocardiography, with one report that suggests better delineation of the size and shape of the rupture site, making it feasible to assess the longitudinal and transverse dimensions, circumference, and area of the rupture site. Additionally, it allows for visualization of the mitral annulus and papillary muscles, which can guide surgical management by assessing severity and/or improvement, possibly precluding the need for mitral valve repair or replacement (17).

In conclusion, with the use of intraoperative TEE, we had the ability to confirm the diagnosis of pseudoaneurysm, evaluate cardiac function before, during, and after surgery, and diagnose RV failure, guiding surgical management.

Conjugal amyotrophic lateral sclerosis

John D. Dewitt, DO, Julia Kwon, DO, Rebecca Burton, DO, and Jeffrey S. Stroup, PharmD

Amyotrophic lateral sclerosis (ALS) is a disease characterized by progressive degeneration of motor neurons in the motor cortex, brainstem, and spinal cord. The incidence of sporadic ALS is 1.5 to 2.7 in 100,000, and the prevalence is 5.2 to 6.0 in 100,000. Conjugal ALS is even rarer than sporadic ALS. We report a case of conjugal ALS encountered in our outpatient neurology clinic.

Amyotrophic lateral sclerosis (ALS) is a progressive degeneration of motor neurons in the motor cortex, brainstem, and spinal cord (1–3). This motor neuron disease occurs sporadically in 90% of cases, with the etiology remaining largely unknown. It is familial in only 5% to 10% of cases, with 20% of those being linked to a mutation in the SOD1 gene and another 2% to 5% of cases being linked to a mutation in the TDP-43 gene (1, 2). Recently, mutations in the FUS/TLS gene and the C9ORF72 gene have also been implicated in familial ALS (4, 5). The average age of onset for familial ALS is 50 years, while sporadic cases have an average age of onset of 60 years (3). Conjugal ALS is rare and is commonly felt to occur as a chance association. We report a case of conjugal ALS in our outpatient neurology clinic.

CASE PRESENTATION

A 45-year-old right-handed white woman was seen in neurological consultation at the Muscular Dystrophy Association Clinic. The patient had seen multiple physicians, including neurologists, regarding her symptoms and received a thorough workup at two major centers, the results of which were reviewed. Her workup included numerous laboratory studies and electrodiagnostic studies, which were not repeated. Her findings were felt to be consistent with motor neuron disease.

The patient initially presented with pain in her neck and shoulders, waxing and waning in character, associated with symptoms of a flaccid bladder. Initially, the pain was attributed to the patient’s occupation, as she had worked as a hairdresser, and she was treated symptomatically without relief. The patient’s laboratory workup was negative except for dyslipidemia, a low folate level, hypothyroidism, and an elevated creatine kinase level of 472 U/L.

The patient had symptoms of dysarthria, dysphagia, difficulty identifying when her bladder was full, and incontinence. The timeline of her symptoms after initial presentation through her death 6 years later is shown in the Table.

Twelve years after her death, the patient’s 66-year-old non-consanguineous husband presented to the same neurology office with dysarthria and diffuse fasciculations in the tongue and all four limbs. The only finding on his neurologic exam was intrinsic hand muscle weakness and +3/4 brisk upper limb reflexes. His symptoms had begun approximately 6 weeks prior to presentation after waking up one morning with a voice change.

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almost overnight. Two to three weeks later, he had started to slur his words and had occasional difficulty swallowing. He then developed muscle twitching in his right arm.

The patient stated that prior to the onset of these symptoms, he had undergone a fundoplication after which he was told he had been hypoxic for an unknown amount of time with an oxygen saturation in the 60s. He stated that since then, he was unable to think well, was unable to do things he used to be able to do, and required in-home assistance.

The patient had a history of hypertension and hyperthyroidism. He had previously had iatrogenic thyrotoxicosis, which had resolved. The patient’s endocrine panel, autoimmune panel, heavy metal screen, tick panel, and serum protein electrophoresis results were normal. Initial electromyography (EMG) of the bilateral lower limbs and left upper limb revealed insertional abnormalities in the form of positive sharp waves, resting fasciculation potentials, and some fibrillation potentials. Voluntary potentials were normal. Motor nerve conduction velocities in the left median, left ulnar, and bilateral tibial and peroneal nerves were normal, as were terminal motor latencies. Distal sensory latencies were absent in the left ulnar, median nerves, and bilateral sural nerves related possibly to an asymptomatic incidental polyneuropathy. Magnetic resonance imaging of the brain was consistent with ischemic white matter changes from small-vessel disease with no evidence of enhancing lesion or acute abnormalities. The patient was diagnosed with bulbar-onset conjugal ALS and referred to another center for a second opinion. An SOD1 mutation analysis was performed for the patient’s daughter, and the result was negative.

One month after initial presentation, the patient presented to the Integris MDA Neuromuscular Center for a second opinion in which the diagnosis of ALS, bulbar onset was confirmed. Three months after initial presentation, the patient developed increasing weakness, multiple falls requiring the use of a walker, dysphagia, and worsening dysarthria. His physical exam revealed bifacial and posterior neck weakness as well as increased atrophy of muscles, and bilateral sural nerves related possibly to an asymptomatic incidental polyneuropathy. Motor nerve conduction velocities in the left median, left ulnar, and bilateral tibial and peroneal nerves were normal, as were terminal motor latencies. Distal sensory latencies were absent in the left ulnar, median nerves, and bilateral sural nerves related possibly to an asymptomatic incidental polyneuropathy. Magnetic resonance imaging of the brain was consistent with ischemic white matter changes from small-vessel disease with no evidence of enhancing lesion or acute abnormalities. The patient was diagnosed with bulbar-onset conjugal ALS and referred to another center for a second opinion. An SOD1 mutation analysis was performed for the patient’s daughter, and the result was negative.

Repeat EMG done at the Integris MDA Neuromuscular Center revealed normal left median motor nerve conduction velocity with prolonged distal latency and reduced amplitude. Left ulnar motor conduction showed prolonged distal latency and reduced amplitudes but no focal conduction block. Left median sensory study showed prolonged peak latency with very small amplitude and no recording from the index finger. EMG of the left arm, leg, and rectus abdominus muscles showed diffuse acute and chronic denervation with fasciculations. Widespread motor neuron disease was suggested. These findings associated with denervation in the tongue met El Escorial criteria for ALS.

Baclofen was initiated for the patient's symptoms of muscle cramping, a neuropsychiatry consult was performed, and speech and swallow evaluation and communication device referral was completed. The use of noninvasive ventilator assistive devices was initiated as the patient developed a rapid progression of diaphragmatic weakness. The patient wished to go on a trip to China, which he completed; however, he died shortly thereafter.

No common exposures were identified between the two patients in regards to environmental toxins, pesticides, metal toxins, or occupational toxins. In addition, they were not farmers and were not exposed to ground water. There was also no history of trauma, alcoholism, or military service.

**DISCUSSION**

The most commonly used diagnostic criteria for ALS are the 1994 El Escorial criteria and the revised 2000 Airlie House criteria (1, 2). These criteria are used mainly for research studies, however, as the diagnosis remains mostly clinical. The El Escorial criteria classify the ALS through signs and symptoms as definite, probable, probable with laboratory support, possible, or suspected (1).

Patients presenting with the spinal-onset form of ALS will experience an insidious progressive painless weakness beginning with upper or lower extremities, atrophy of muscles, and fasciculations (1–3). Patients will usually develop hyperreflexia and an extensor toe sign. On the other hand, 20% to 33% will have a bulbar-onset form of ALS characterized by dysarthria, dysphagia, tongue atrophy, and tongue fasciculations (1–3). Pseudobulbar symptoms such as emotional lability are also common (1–3). Sensation and bowel and bladder function remain intact. Fifty percent of patients do not survive past 3 years, and most succumb to respiratory failure (3).

The incidence of sporadic ALS ranges from 1.5 to 2.7 per 100,000, and the prevalence is 5.2 to 6.0 per 100,000 (1, 2). The lifetime probability of conjugal ALS is more rare, calculated at 1 in 510,000 couples (6). Surprisingly, through 1975, up to 10 conjugal pairs of ALS were recognized in Guam alone (7), where ALS is 50 to 100 times more prevalent (2, 7, 8). The prevalence there is now declining.

Outside of Guam, however, conjugal ALS remains rare. In consideration of the incidence and population in the United States, we would expect to see approximately 4 cases of conjugal ALS per year (3). The incidence, however, is much less. Through 2009, there were reports of 19 conjugal ALS pairs in the literature. This case is the 20th pair. There was a cluster of 9 pairs from France (9, 10), 4 pairs from Italy (7, 11–13), 2 pairs from Brazil (14), 1 pair each from India (15) and Spain (16), and 2 other pairs from the United States (6, 8). As it stands presently, a single unifying or common exposure between pairs cannot be found. No pairs were consanguineous, and all pairs had lived together for at least 10 years prior to diagnosis (10, 11, 13).


High-intensity track and field training in a cardiac rehabilitation program

Kathleen Kennedy, MS, Jenny Adams, PhD, Dunlei Cheng, PhD, and Rafic F. Berbarie, MD

A 65-year-old male athlete with coronary artery disease enrolled in our cardiac rehabilitation (CR) program after successful coronary artery bypass graft surgery following an acute myocardial infarction. Unlike the typical sedentary cardiac patient in his age group, he loved to participate in hurdle events at masters division track meets (competitions for athletes aged 30 years and older). He expressed a strong desire to return to his sport, so we designed a sport-specific, symptom-limited exercise program that enabled him to train safely but at a higher intensity than is typically allowed in conventional CR programs. Although his measured peak heart rates during the sport-specific sessions were significantly higher than the calculated maximum heart rate limits usually imposed on patients during conventional CR exercise training, the patient had no adverse events and safely reached his fitness goal. When developing a CR plan, health care professionals should consider the patient’s goals, not just his or her age.

Cardiac rehabilitation (CR) is an outpatient program that provides exercise, education, counseling, and social support to patients who have had a cardiac event (1). Patients in conventional phase II CR attend the program 3 days per week and perform aerobic activities (treadmill walking and stationary cycling) (2) and may lift 1- to 3-pound hand weights (1). Because a cardiac event is a serious medical condition, the intensity of this exercise training is typically moderate.

To ensure safety during endurance training, CR professionals use responsible and reliable methods to help patients progress gradually. The intensity of exercise training is restricted by setting maximum blood pressure and heart rate limits; staff observations and patients’ subjective responses are also used to determine when increases in intensity are warranted. The maximum allowable systolic blood pressure is 240 mm Hg (1), although in practice, CR staff members typically do not allow patients to reach this threshold. There are three traditional methods of calculating maximum allowable heart rate limits in conventional CR exercise programs when actual peak heart rates from an exercise stress test are not available:

1. Percent maximal heart rate (3) is obtained by calculating the patient’s age-predicted maximum heart rate, or 220 minus the patient’s age in years, then multiplying that value by 70% to 85%. Using the high end of that range yields the following formula: \(220 - \text{age}\) \(\times 0.85\).
2. Heart rate reserve (3), also known as the Karvonen method, takes into account the resting heart rate and is calculated as follows: \([((220 - \text{resting heart rate}) \times 0.85) + \text{resting heart rate}].
3. Resting + 20 (2) is the simplest method of calculating the maximum heart rate limit: resting heart rate + 20 beats per minute.

Throughout the 34 years of our CR program’s existence, we have followed the recommended conservative exercise guidelines. Recently, however, we have become increasingly concerned that the conservative training in conventional programs is inappropriate for patients who plan to return to a physically demanding sport. As a result, we developed a high-intensity, sport-specific exercise program to meet the needs of such patients. Unlike conventional CR exercise training, the high-intensity program incorporates exercises that mimic the patient’s athletic activities, and the training intensity is symptom limited; no calculated maximum heart rate limits are imposed.

In this report, we present data from one of the first athletes to voluntarily participate in the high-intensity, sport-specific exercise program, and we compare the peak heart rates he reached during training with the calculated maximum heart rates that are typically allowed during a conventional CR exercise session.

Case History

A 65-year-old male athlete presented to the emergency department in December 2008 with an elevated troponin level and a non–ST segment elevation acute myocardial infarction. He was taken to the catheterization lab, and four stents were placed: two in the right coronary artery, one in the diagonal coronary artery, and one in the left anterior descending artery.

From the Cardiac Rehabilitation Department, Baylor Jack and Jane Hamilton Heart and Vascular Hospital (Kennedy, Adams), the Institute for Health Care Research and Improvement, Baylor Health Care System (Cheng), and the Division of Cardiology, Department of Internal Medicine, Baylor University Medical Center at Dallas and Baylor Hamilton Heart and Vascular Hospital (Berbarie).

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In January 2009 he had a positive stress test and underwent a second catheterization that revealed in-stent stenosis of the left anterior descending artery. The patient was referred for coronary artery bypass graft surgery and, later, CR.

The patient had an otherwise favorable risk factor profile. At the time of coronary bypass, his total cholesterol was 98 mg/dL; triglycerides, 66; low-density lipoprotein cholesterol, 47; and high-density lipoprotein cholesterol, 38. He had no family history of heart disease and had never smoked. His body mass index was 21 kg/m², and his waist circumference was 33 inches. Medications included clopidogrel (75 mg daily), aspirin (325 mg daily), and rosuvastatin (20 mg daily).

**CARDIAC REHABILITATION EXERCISE TRAINING**

In our CR program in Dallas, Texas, patients are required to attend an orientation session prior to their first day of exercise rehabilitation. During this orientation, an exercise physiologist evaluates each patient’s medical history and current physical condition, and patients are asked to describe the goals they want to reach during their CR stay (6 to 36 sessions, depending on the patient’s schedule and insurance coverage). During this visit, the 65-year-old patient informed the exercise physiologist that he was involved in masters division track and field competitions (for athletes aged 30 years and older), the next of which would occur in 5 months. He wanted to compete in sprinting and hurdlers. At the upcoming meet and asked if that would be a reasonable goal. The exercise physiologist responded favorably, telling the patient that if he was willing to put in the time and effort and his vital signs remained within normal limits, he could very well reach his goal.

## Table. The patient’s heart rate (HR) measurements during high-intensity training and the calculated HR limits used in conventional cardiac rehabilitation

<table>
<thead>
<tr>
<th>Session</th>
<th>Measured HR (Resting, Peak)</th>
<th>Calculated HR limits (Percent maximal, HR reserve, Resting + 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80 (166)</td>
<td>133 (145) 100</td>
</tr>
<tr>
<td>2</td>
<td>86 (166)</td>
<td>133 (146) 106</td>
</tr>
<tr>
<td>3</td>
<td>94 (169)</td>
<td>133 (147) 114</td>
</tr>
<tr>
<td>4</td>
<td>83 (165)</td>
<td>133 (145) 103</td>
</tr>
<tr>
<td>5</td>
<td>70 (143)</td>
<td>133 (143) 90</td>
</tr>
<tr>
<td>6</td>
<td>73 (153)</td>
<td>133 (144) 93</td>
</tr>
<tr>
<td>7</td>
<td>82 (149)</td>
<td>133 (145) 102</td>
</tr>
<tr>
<td>8</td>
<td>75 (162)</td>
<td>133 (144) 95</td>
</tr>
<tr>
<td>9</td>
<td>81 (155)</td>
<td>133 (145) 101</td>
</tr>
</tbody>
</table>

Mean (SD) 80 (7) 159 (9) 133 (0) 145 (1) 100 (7)

During the 18 training sessions, the patient participated in gradually increasing high-intensity exercise. The last nine sessions, specifically designed to simulate the tasks and demands of his hurdlers event, included block starts, sprinting, ladder and agility drills, resistance sprinting, hurdles, and weight training. During CR training sessions, the patient’s heart rate and electrocardiographic rhythm were continuously monitored via telemetry, and his blood pressure was taken every third session. He was monitored for adverse events (ST depression, arrhythmia, shortness of breath, and angina). He had no adverse arrhythmia, blood pressure, or heart rate events while performing the high-intensity, sport-specific training. He did have occasional asymptomatic atrial ectopy (premature atrial contractions), but this did not require any exercise session to be stopped and did not accompany any negative symptoms.

**HEART RATE COMPARISONS**

The Table lists the patient’s resting heart rate and peak heart rate for each high-intensity session, along with the three calculated heart rate limits: percent maximal heart rate, heart rate reserve, and resting + 20.

We used the Wilcoxon signed rank test to determine whether the patient’s peak heart rate was significantly higher than the calculated heart rate limits across all nine sessions. The Wilcoxon signed rank test is a nonparametric test, most suitable for a small sample size when the assumption of normality is usually not met. Comparing the patient’s peak heart rate with the heart rate reserve value yielded a $z$-test statistic of 2.66 with a derived two-sided $P$ value of 0.008. Similarly, comparing the peak heart rate with the percent maximal and the resting + 20 values yielded an identical $P$ value as small as 0.004 ($z$ value, 2.88). Thus, all three Wilcoxon tests suggested that at each high-intensity training session, the patient’s measured peak heart rate was significantly higher than his calculated heart rate limits.

The peak blood pressures that were recorded during four of the nine high-intensity training sessions were 130/82, 142/82, 138/84, and 168/86 mm Hg, indicating that the patient’s peak systolic blood pressure remained well below the safety threshold of 240 mm Hg.

**DISCUSSION**

The patient reached higher peak heart rates during the high-intensity CR exercise sessions than would have been allowed in a conventional program that imposes maximum heart rate limits, yet his peak systolic blood pressure stayed far below the allowable limit. As the Figure shows, this patient reached his goal and has participated in masters track meets at the same physical fitness level required before his cardiac event.

Some patients aspire to return to a high-intensity sport after a cardiac event, but they may be fearful about the level of training that would be required for them to do so. We believe, however, that accelerating patients’ return to athletics can result in improved physical ability and confidence. Therefore,
staff members at our CR facility feel ethically obligated to ensure that patients can safely and confidently resume their desired sport after completing CR training. Tailoring the exercise regimen to meet the goals of each patient, regardless of his or her age, is a major component of meeting that obligation.

The symptom-limited exercise training described in this case report should be implemented carefully and on an individual basis. Conventional CR should be prescribed for patients who have a prolonged perioperative course and/or certain postoperative complications. Nevertheless, as in a previous case report (4), we have demonstrated that high-intensity, sport-specific CR training can be done safely, and we encourage further study of this approach in appropriately selected patients.

Acknowledgments

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 Cardiovascular Research Review Committee for their continued support of cardiovascular rehabilitation research projects. They also thank the patient for graciously allowing his story and photographs to be published. Beverly Peters, MA, ELS, a freelance medical editor, assisted with manuscript development and preparation.

The changing face of health care education: a new surgical simulation center at Baylor University Medical Center

Kristina Stillsmoking, PhD, MEd, BSN, CNOR, and Ronald C. Jones, MD

The first of its kind within the Baylor Health Care System, the Seeger Surgical Simulation Center (Figure 1), which opened at Baylor University Medical Center at Dallas (BUMC) in June 2010, has over 1000 square feet of training space with a variety of simulators. Residents and physicians can access the center any time during the week for training or testing. Currently, BUMC has 48 surgical residents within a 5-year program. Resident training focuses on skills specific to each postgraduate level (Table 1). The curriculum ranges from basic skills during the first year to more advanced skills during the fifth year and includes some element of simulation to enhance the training.

The Seeger Surgical Simulation Center has applied for accreditation as a Level II Education Institute by the American College of Surgeons and thus shares its goals (Table 2).

**PLANNING AND CONSTRUCTION**

The concept of establishing a state-of-the-art surgical laparoscopic simulation laboratory at BUMC was conceived in 2007. Multiple meetings were held with architects to determine the possibility of locating this center in the old Seeger Research Laboratory in the Department of Surgery on the first floor of the A. Webb Roberts Hospital. These meetings resulted in the final suggestion to place the simulation center in the Seeger Research Laboratory, which was initially built as a biochemistry lab. This area was to be enlarged to also accommodate resident carrels, which were in another area of the department. The existing resident carrel area was to be torn out to make room for a new conference room and two staff offices.

![Figure 1. Seeger Surgical Simulation Center.](image-url)

**Table 1. Resident surgical training curriculum by postgraduate level**

<table>
<thead>
<tr>
<th>Year</th>
<th>Curriculum</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Basic knot tying, suturing, instrument handling</td>
</tr>
<tr>
<td></td>
<td>Basics of electrocautery</td>
</tr>
<tr>
<td></td>
<td>Laparoscopy basic skills—nine modules (Lap Mentor)</td>
</tr>
<tr>
<td></td>
<td>Basics of central venous access, ultrasound guided</td>
</tr>
<tr>
<td></td>
<td>Basics of FAST exam</td>
</tr>
<tr>
<td></td>
<td>Basics of ultrasound use</td>
</tr>
<tr>
<td></td>
<td>Lower gastrointestinal case #1 (Accutouch; two times)</td>
</tr>
<tr>
<td></td>
<td>Basics of intracorporeal knot tying</td>
</tr>
<tr>
<td></td>
<td>Basic airway management</td>
</tr>
<tr>
<td></td>
<td>Basic chest tube insertion</td>
</tr>
<tr>
<td>2</td>
<td>Bowel anastomosis suturing</td>
</tr>
<tr>
<td></td>
<td>Gallbladder case #2 (Lap Mentor; two times)</td>
</tr>
<tr>
<td></td>
<td>Lower gastrointestinal case #2 (Accutouch; two times)</td>
</tr>
<tr>
<td></td>
<td>Four laparoscopy procedural tasks (Lap Mentor)</td>
</tr>
<tr>
<td></td>
<td>Gastric bypass case #3 (two times)</td>
</tr>
<tr>
<td></td>
<td>Basics of airway management</td>
</tr>
<tr>
<td></td>
<td>Basic chest tube insertion</td>
</tr>
<tr>
<td>3</td>
<td>Hands-on practice for five FLS skills</td>
</tr>
<tr>
<td></td>
<td>Sigmoidectomy (Lap Mentor; two times)</td>
</tr>
<tr>
<td></td>
<td>Incisional hernia case #3 (Lap Mentor; two times)</td>
</tr>
<tr>
<td></td>
<td>Basics of vascular suturing</td>
</tr>
<tr>
<td>4</td>
<td>Team communication scenario (SimMan)</td>
</tr>
<tr>
<td></td>
<td>Gastric bypass case #3 (Lap Mentor; two times)</td>
</tr>
<tr>
<td></td>
<td>FLS practice</td>
</tr>
<tr>
<td>5</td>
<td>Hands-on practice for five FLS skills</td>
</tr>
<tr>
<td></td>
<td>FLS tests</td>
</tr>
</tbody>
</table>

FLS indicates Fundamentals of Laparoscopic Surgery; FAST, focused assessment with sonography in trauma.

From the Department of Surgery, Baylor University Medical Center at Dallas.

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In March 2008, architectural plans were developed and a budget estimate was finalized, which consisted of $673,450 for construction and $585,000 for simulator and equipment needs, for a total of approximately $1.2 million. Dr. Jones presented the construction budget request to the Seeger Committee for funding from the Hannah Buchanan and Stanley Joseph Seeger Endowment, and the funding request was approved on March 12, 2008.

The American College of Surgeons Accreditation program requires personnel to administer the educational programs within an institute. To meet these requirements, Dr. Jones was designated the medical director and two other staff members were needed, a surgical program director and a director. For the director position, a search was initiated for an individual with a graduate degree to assist the department in the development of the simulation center. In November 2008, BUMC recruited Kristina Stillsmoking, PhD, MEd, BSN, CNOR of Tacoma, Washington. In her previous role with the US Army’s Charles A. Anderson Simulation Center, Ms. Stillsmoking wrote the application for and received the American College of Surgeons award for the military service’s first Education Institute accreditation.

In February 2009, a committee made up of Dr. Jones, Kristina Stillsmoking, and Tammy Fisher, manager of the Department of Surgical Education and research manager, as well as architects began discussing types of simulators to be housed in the center and their installation requirements. Stryker Company, developers of the largest simulation center in the United States at the University of Maryland, hosted a research trip for the group to the Baltimore, Maryland, simulation center. A simulator list was developed, and in February 2009 purchase agreements were signed for a surgical haptic virtual reality simulator; bronchoscopy, upper endoscopy, and colonoscopy simulator; Fundamentals of Laparoscopic Surgery trainers; and a sonogram machine for breast/thyroid and cardiovascular diseases. Also included was a state-of-the-art audiovisual media system. Furniture was selected, as was supporting equipment.

Progress in the development of the simulation center was temporarily delayed while the Department of Internal Medicine considered moving to the medical education area on the first floor of the Roberts Hospital, which would have required additional renovations. In February 2009, the internal medicine department decided not to move, and architectural plans were finalized to meet the American College of Surgeons’ Accreditation of Education Institute specifications to meet Level II standards (1). Funding was then delayed due to a reevaluation of bond status for BUMC until the fall of 2009.

Construction contracts were reviewed and signed in January 2010. Demolition began the next month—approximately 3 years after the first meeting about the possible development of a simulation center. The construction was completed in April 2010. The resident carrel area was then set up, with each carrel having a complete computer system—including hook up to a network printer and hospital intranet and Internet access for both patient information and online educational resources. The simulation center became a reality in mid June 2010, and training began in earnest in July 2010.

On June 1, 2010, Dr. David Arnold agreed to become the medical director of the Seeger Surgical Simulation Center. He continues to work part-time 2 days each week to train junior surgeons in basic laparoscopic and surgery skills, as well as mentoring senior residents in advanced laparoscopic procedures (Figures 2 and 3). Several other physicians provide instruction, including Dr. Andrew Markowski in ultrasound and Dr. John O’Brien in suturing and knot tying. Together they work to provide surgical residents with quality educational opportunities through the use of the simulation center’s resources.

**SIMULATORS**

Simulators are the adjunct training tools that allow a learner to engage in a simulated real-life experience to learn a specific skill, procedure, or team intervention. Numerous types of simulators have been created for specific learning purposes. A task trainer that is static (such as an intravenous access arm) does not interact with the learner in any way. This and similar simulators have been labeled “low fidelity” (not driven by a computerized component), as shown in Figure 4.

Advanced technology simulators are those with a computer-enhanced component controlled by a faculty member.
These types of simulators range from a simple baby simulator (human patient simulator) to the high-end computer-enhanced virtual reality simulator with haptic feedback characteristics. Haptic simulators provide the learner with the "feel" of reality. Advanced technology simulators allow the learner to choose a scenario by type of case and level of expertise. In addition, since these simulators can monitor, record, and score all actions taken by the learner, they are a valuable tool for performance benchmarking.

The laparoscopic simulator provides didactic step-by-step task tutorials, where each task focuses on a skill critical to various procedures. These tasks are in an anatomical setting, with visual signs and instructions on how to carry out a safe procedure, and are aimed at learning the visual clues of traction-countertraction of tissue (using virtual tissue), finding areas of weakness that require additional practice, and developing judgment capabilities and learning interpretation of anatomical and operative findings. Surgeons gain hands-on experience in different techniques, learn alternative approaches for a variety of laparoscopic surgeries, and acquire skills and know-how for safely coping with surgical complications.

The endoscopic simulator for both upper and lower gastrointestinal tracts provides a wide variety of case-based scenarios to hone skills. Didactic modules describe the anatomy of the upper and lower tracts as viewed through a bronchoscope; the correct technique for holding and manipulating the endoscopes; and the indications, contraindications, and complications of the procedure.

**SIMULATION IN HEALTH CARE**

Most people associate simulation with flight training. Flight simulation was the model used to create simulation platforms for physicians, nurses, emergency medical technicians, and other health care professionals. While simulation has been used for health care education for almost 40 years, it has become accepted as an assessment and training tool only within the past 15 years (2). Thus, a new era of health care education has begun where human patient simulators have started to substitute for traditional patient care practice.

Several issues have contributed to simulation’s rise in popularity, including a decrease in patient hospital stays and clinic visits, which has resulted in fewer learning experiences for the student. Also, a recent mandate from the Accreditation Council for Graduate Medical Education limits all residents to an 80-hour work week, thereby impacting their clinical exposure. No educational time was built into this mandate, which has
created many challenges for residency programs to provide clinical exposure or simulation training.

The integration of simulation into health care education provides a partial substitute for real patient practice in a safe environment where students learn from their mistakes. A variety of standardized clinical curricula are used, with 24-7 availability. The simulation learning process creates opportunities to meet the stressful challenges of keeping up with complex new medical findings and technologies, as well as the need to ensure quality, safe patient outcomes through quality educational outcomes (2–4).

The American College of Surgeons implemented a mandated certification program in June 2010. All fifth-year surgical residents must successfully complete a 75-question online test and five psychomotor skills tests before they are approved to take their American Board of Surgery qualifying examination (5). Dr. Ron Jones, chief of surgery, created the Seeger Surgical Simulation Center as part of his efforts to ensure that residents successfully meet this certification requirement.

The catalyst for change—the 1999 report of the Institute of Medicine (IOM), To Err is Human—exposed to the public the significant number of medical errors (4, 6). Gordon outlined how this study reinforced the use of simulation because it “enhances medical safety in the same way as flight simulation” improves air safety (7). The IOM report recommended integrating simulation into training to improve individual and team performance.

The assessment, evaluation, and credentialing or recredentialing of health care providers were also questioned based on results of the IOM report (2). As the public is becoming more technologically savvy, they are demanding accountability for quality patient care, thereby bringing past performance measurements under scrutiny. As levels of performance and ways to measure performance have not been agreed upon, a standardized performance assessment would be of great value (4, 8–10). Using simulation for credentialing or recredentialing is an option but is not without controversy. In Stillsmoking’s Delphi study of 11 simulation experts, five participants agreed that simulation was useful in clinical performance assessment for credentialing; five participants agreed that it was useful but identified several challenges to be resolved before implementation; and one believed it was not useful (11). Other studies have also pointed out some limitations of simulation in this environment (12).

In the 21st century, it has become apparent that simulation is an educational adjunct to facilitate movement away from a totally apprenticeship learning model and is an excellent resource for cognitive, psychomotor, task, and procedural skill training as well as team training (2, 5). Simulation is a natural evolution from traditional apprenticeship to development of a safe, confident learner who will provide safe patient outcomes. Simulation provides a safe environment for assessing and validating skill proficiency and competence. Within the simulation environment, the learner can deliberately practice and learn from mistakes (2, 13). Aside from the exciting “shock and awe” of the simulator, it is important to remember that “simulation is a technique not a technology” (3).

Simulation is a means to “replace or amplify real experiences with guided experiences that evoke or replicate substantial aspects of the real world in a fully interactive manner” and should be embedded in the “daily fabric of health care delivery” (3, 5). Recently, the Association of American Medical Colleges (AAMC) began to study the spread of simulation use and organizational resources within the health care education field. “The AAMC hopes the results will help the educational community define the prevalence of simulation, share information about other institutions’ activities, and support research on simulation” (14).

CONCLUSION

The IOM report has shown that traditional educational and credentialing models for health care professionals have not eliminated medical errors. Therefore, a paradigm shift is needed towards a model of achieving and maintaining quality health-care provider training, and simulation is a powerful tool in this effort (3). Clinical personnel, teams, and systems can improve their performance “by undergoing continual systematic training, rehearsal, performance assessment, and refinement of their practice” (3). With the financial assistance of the Baylor Health Care System Foundation and the Seeger Endowment, the BUMC Department of Surgery has met this challenge by developing a fully equipped state-of-the-art surgical simulation center that provides medical students, residents, fellows, and staff the opportunity to practice and improve their surgical skills.

Dissecting Darwinism

Joseph A. Kuhn, MD

John Hunter, the acclaimed “father of scientific surgery,” understood human anatomy through a process of careful dissection. From 1750 to 1793, he revolutionized modern surgical anatomy through the dissection of thousands of human samples derived from fresh human cadavers, which came from fresh graves (1). He was credited with educating over 2000 surgeons globally based on the doctrine of observation, experimentation, and application of scientific evidence, rather than a reliance on potions, humors, and superstitions to manage disease. The early American surgeons who attended these highly desired anatomy courses included Philip Syng Physick, William Shippen, John Morgan, and many others who helped establish the foundations of American medical education.

John Hunter was also a brilliant biologist and naturalist, having dissected and stored thousands of animals and plants. His considerable samples represented the entire initial display of the Royal College of Surgeons Museum. In two lengthy volumes, entitled Essays and Observations on Natural History, Anatomy, Physiology, Psychology, and Geology, he identified the remarkable similarity of muscles and organs between various species. John Hunter proposed a gradual formation of species 70 years before Charles Darwin published his observations in On the Origin of the Species. Therefore, history reveals that surgeons are uniquely capable of gathering information, making observations, and reaching conclusions about scientific discoveries.

As the scientific community is faced with new challenges to time-honored conclusions regarding the origin of the species, the origin of humans, and evolution, it is appropriate to dissect this new corpus of information with fairness and modern knowledge. Hence, the purpose of this paper is to review the arguments that have been leveled against the concept of evolution as proposed by Charles Darwin and John Hunter, surgeon and biologist extraordinaire.

Since this review is offered by a physician and surgeon, it might be appropriate to provide evidence of qualification and credibility for such a scientific endeavor. Medicine is a field that attracts some of the brightest minds, based on competitive test scores and undergraduate performance. Modern premedical education commonly includes a typical bachelor’s of science degree in biology, chemistry, mathematics, biochemistry, or molecular biology. Medical education includes 2 years of basic science education in molecular biology, biochemistry, biology, anatomy, physiology, and pharmacology, among other topics. Participation in clinical or basic research is common during medical education or residency. Physicians then continue their education by practical application of basic science into problem-solving situations with the human body. Regarding the human body, physicians also have an intimate and integrated knowledge of the complete interrelationships, biochemistry, and molecular processes involved with various systems. In fact, the physician represents the penultimate expert on applied molecular pathways as they relate to human conditions. Many surgeons, including this author, are actively involved with gene therapy, vaccine therapy, and the latest molecular targeting based on the incredible breakthroughs in our understanding of the science of DNA (2–4). Therefore, the physician is indeed an excellent source to dissect evolution based on modern science and applied medicine.

In a 2005 survey of 1472 physicians, almost 78% favored a belief in evolution as an explanation for the origin of the species (5). Among the nation’s scientists and biologists, 99% believe in Darwinian evolution (6). The definition of evolution has changed over the years. However, the basic tenets of Charles Darwin suggested that random mutations occur and natural selection continually acts on the surviving mutation, leading to slight improvements and changes in species over time. Neo-Darwinism was coined in 1895 and reflected knowledge of reproduction and recombination, leading to potentially greater shifts in species. The “modern synthesis” of evolutionary thought was proposed in 1950 to incorporate the knowledge of genetics, systematics, paleontology, and other fields. Taken together, the basic concepts recognize that random mutations occur and natural selection continually acts on the surviving mutation, leading to improvements and changes in species over time. These mutations can occur gradually or rapidly via a term called saltation or punctuated evolution. This process of mutation and natural selection has been proposed to explain the descent from a common ancestor, even from the original prokaryocytes billions of years ago. On the basis of natural
selection and time, it has been theorized that single cellular organisms may have arisen from a primordial mixture of ancient elements and energy.

Several academic organizations have developed guideline statements to promote Darwinian evolution (including neo-Darwinism, modern synthesis, and punctuated evolution) as the single basic principle to be taught in high schools, universities, and colleges (7). School systems have debated the educational merits of Darwinian evolution and have found themselves in various state and federal courts. In Kitzmiller v the Dover Area School District, the US District Court ruled in 2005, among other things, that the school board could not require teachers to denigrate or disparage the scientific theory of evolution (8). In 2010, the Texas State Board of Education accepted testimony for 3 days from scientists and citizens regarding the teaching of evolution. Representatives of the National Center for Science Education testified that teaching the weaknesses of evolution would unfairly mark future high school seniors as poorly prepared to compete for college positions based on an education that might be considered nonscientific (9). However, numerous other scientists, citizens, and educators brought forth evidence that emphasized the weaknesses of Darwinian evolution. Ultimately, the board took a controversial position and voted to require future textbooks in the state to explain the weaknesses and the strengths of Darwinian evolution.

Two specific strengths of Darwinian evolution are generally agreed upon:
1. Species adapt to a change in environment (bird beak changes, bacterial resistance, fruit fly experiments). This is called microevolution.
2. There is similarity in the DNA across species (called homology).

During the Texas State Board of Education testimony, weaknesses were raised about three issues:
1. Limitations of the chemical origin of life data to explain the origin of DNA
2. Limitations of mutation and natural selection theories to address the irreducible complexity of the cell
3. Limitations of transitional species data to account for the multitude of changes involved in the transition

In the sections below, I discuss these three weaknesses and then provide some concluding thoughts on paradigm shift.

CHEMICAL ORIGIN OF LIFE

In 1953, the field of abiogenesis took a large step forward when Stanley Miller and Harold Urey reported that a collection of five simple amino acids could be formed from placing a combination of chemicals in a jar and subjecting the jar to energy in the form of electricity (10, 11). This experiment continues to be used in high school and college texts as the unquestioned fundamental explanation for the origin of life based on a purely natural process (12). Unfortunately, the experimental conditions of a low-oxygen, nitrogen-rich reducing environment have been refuted by many (13–15). The experiment actually produces a racemic mixture of amino acids that would inhibit the production of useful proteins.

After Watson and Crick unveiled the double helix nature of DNA in 1953, the origin-of-life research began to focus on the nucleotides and the complex chemical processes that might create the energy for the primitive cell. Modern textbooks expand on the largely debunked Miller-Urey experiment and further propose that the nucleotides form together in a primitive environment with explanations that include the RNA world hypothesis (16), thermogenesis (17), and hypercycles (18). Unfortunately, the student is not taught that those theories still require complex and specified information contained in functioning proteins, which cannot be explained or self-generated (19). Furthermore, the student is not taught that the four nucleotides do not spontaneously form in nature (20).

There is no self-organizing principle that would guide or facilitate alignment of nucleotides (21, 22). Any experimentally manufactured nucleotides are mixtures of L (left-oriented) and D (right-oriented) isomers. Since DNA is composed of only D isomers, the probability of alignment of thousands of specified D isomers becomes even more remote (23, 24). Even if there was a self-organizing pattern, the probability of even a short strand of nucleotides occurring in a precisely specified linear pattern that would code for even the smallest single-celled organism with approximately 250 genes has been calculated to be 1 in $10^{150}$—1 in $10^{70}$ less than the chance of finding a particular electron in the entire universe (25).

In addition to the lack of evidence for self-formation of proteins or nucleotides, the fundamental and insurmountable problem with Darwinian evolution lies in the remarkable complexity and inherent information contained within DNA (26). Modern scientists have unraveled the incomparable elegance and protein-coding information of DNA over the past 50 years. The fundamental blueprint of the cell is found in the DNA, which is composed of four different nucleotides (adenine, cytosine, thymine, and guanine). The individual human cell has 5 billion nucleotides arranged in precise order, allowing for the coding and formation of 25,000 complex enzymes and proteins.

This protein development process involves at least 200 unique proteins and cofactors (Figure 1). First, transcription involves the copying of the DNA into a matching strand of messenger RNA composed of similar nucleotides and slightly different sugar molecules. Second, the messenger RNA migrates out of the nucleus into the cytoplasm and is translated into a protein in a ribosome, which coordinates the delivery of a specific transfer RNA-amino acid moiety. A codon, composed of three specific nucleotides, allows for the integration of a single specific amino acid into a long series of amino acids, which then folds into a specific three-dimensional structure called a protein. The 25,000 enzymes and proteins being coded for in each cell of the human body have thousands of minute functions, including signal transduction from the surface, maintenance of specific electrolyte concentrations within very tight limits, storage and utilization of energy, manufacture of proteins, and cell division. In summary, the DNA within each cell is responsible for the production and processing of carefully orchestrated and interrelated functions within the cell. As an analogy, DNA far surpasses the complexity of the blueprints and production of a
30-story building with elevators, electricity, plumbing, computers, and air-conditioning.

Based on an awareness of the inexplicable coded information in DNA, the inconceivable self-formation of DNA, and the inability to account for the billions of specifically organized nucleotides in every single cell, it is reasonable to conclude that there are severe weaknesses in the theory of gradual improvement through natural selection (Darwinism) to explain the chemical origin of life. Furthermore, Darwinian evolution and natural selection could not have been causes of the origin of life, because they require replication to operate, and there was no replication prior to the origin of life.

IRREDUCIBLE COMPLEXITY OF CELLULAR SYSTEMS

The physician studies and understands the enormous complexity of the human body and the human cell. Some aspects of Darwinian evolution in the human body are readily agreed upon—for example, mutation and natural selection acting to influence malarial resistance, skin characteristics, and many other minor changes within the species. However, the origin of and explanation for the formation of complex organs remains unclear. Starting from a single germ-line cell, the DNA is sufficient to code for and control development of 50 trillion cells that organize into complex organs based on expression of different sections of DNA, leading to entirely different “factories” that have such diverse functions as the liver, the brain, the heart, and the eye.

Proponents of mutation and natural selection point to a scientific publication regarding eye evolution. Nilsson offered a simulation explaining how a light-sensitive spot with a light-absorbing layer gradually transitioned to a cup, then a hemisphere filled with a transparent substance, and then, with the ends brought together, an aperture (27). Natural selection would theoretically lead to a gradually improved species, which would evidently mate and create progressively better eyes, including the natural formation of a lens, a retina, and the neural transmission to the brain.

However, biochemists have shown that even a simple light-sensitive spot requires a complex array of enzyme systems. When light strikes the retina, a photon interacts with a molecule called 11-cis-retinal, which rearranges within picoseconds to trans-retinal. The change in the shape of the retinal molecule forces a change in the shape of the protein rhodopsin. The protein then changes to metarhodopsin II and sticks to another protein, called transducin. This process requires energy in the form of GTP, which binds to transducin. GTP-transducin-metarhodopsin II then binds to a protein called phosphodiesterase, located on the cell wall. This affects the cGMP levels within the cell, leading to a signal that then goes to the brain. The recognition of this signal in the brain and subsequent interpretation involve numerous other proteins and enzymes and biochemical reactions within the brain cells. Thus, each of these enzymes and proteins must exist for the system to work properly. Many other mathematical and logistical weaknesses to the Nilsson example of eye evolution have been uncovered (28). In summary, the eye is incredibly complex. Since it is unreasonable to expect self-formation of the enzymes in perfect proportion simultaneously, eye function represents a system that could not have arisen by gradual mutations.

The concept of irreducible complexity suggests that all elements of a system must be present simultaneously rather than evolve through a stepwise, sequential improvement, as theorized by Darwinian evolution (29). Within each individual cell, there are tens of thousands of additional interrelated complex actions, enzymatic steps, and processes that automatically maintain cellular homeostasis, protein transport, self-protection, and replication. The fact that these irreducibly complex systems are specifically coded through DNA adds another layer of complexity called “specified complexity” (30). Geoffrey Simmons, MD, has presented 17 examples within the human body of irreducibly complex systems that could not have formed by sequential or simultaneous mutation, since all components must be present to work correctly (31). These infinitely complex systems include vision, balance, the respiratory system, the circulatory system, the immune system, the gastrointestinal system, the skin, the endocrine system, and taste. In addition, virtually every aspect of human physiology has regulatory elements, feedback loops,
and developmental components that require thousands of interacting genes leading to specified protein expression. These functions and the corresponding specification of the DNA code are too inconceivably complex to have arisen by accidental mutation or change.

When John Hunter and Charles Darwin saw similarities in muscles and body structure across species, they had no knowledge of the enormous complexity inherent within those organs. In the 1850s, Hunter and Darwin might have accomplished the same simulation as Nilsson with the simple alignment of a series of eyes from less complex to complex and the assumption that some sort of gradual evolution over billions of years would be possible. Modern scientists applying knowledge of the intrinsic complexity within each cell would understand that each sequential mutation in the DNA within the eyeball would require simultaneous mutations in bone structure, nerves, brain function, and hundreds of proteins and cell signaling pathways to make even the smallest change in only one organ system. Such changes would require far more than could be expected from random mutation and natural selection. Since these systems are irreducibly complex and individual mutations in one organ would not be beneficial for the organism, these random mutations in all aspects of vision would need to occur simultaneously. Therefore, the human body represents an irreducibly complex system on a cellular and an organ/system basis.

TRANSITIONAL SPECIES DATA

The transitional species from primitive primates to man have been illustrated in textbooks for over 100 years. These drawings form the visual imagery that supports Darwinian evolution for high school students, university students, medical students, and the public. However, honest dissent exists in the accuracy of most of the transitional hominoids, with many found to be frauds or animal species. Reconstructions based on fragmentary and scattered bones, surface bones, and gross morphologic features are limited. Anomalous findings of stone tools, bones, and hundreds of other artifacts have suggested that Homo sapiens were actually present 2 to 7 million years ago (at the same time as early proposed transitional species) (32). Certainly, there has been no additional transitional mutant or species change from the first generally accepted Homo sapiens over 200,000 years ago. The DNA homology between ape and man has been reported to be 96% when considering only the current protein-mapping sequences, which represent only 2% of the total genome. However, the actual similarity of the DNA is approximately 70% to 75% when considering the full genome, including the previously presumed “junk DNA,” which has now been demonstrated to code for supporting elements in transcription or expression (33). The 25% difference represents almost 35 million single nucleotide changes and 5 million insertions or deletions (34). The ape to human species change would require an incredibly rapid rate of mutation leading to formation of new DNA, thousands of new proteins, and untold cellular, neural, digestive, and immune-related changes in DNA, which would code for the thousands of new functioning proteins. This rate of mutation has never been observed in any viral, bacterial, or other organism. The estimation for DNA random mutations that would lead to intelligence in humans is beyond calculation. Therefore, the recently discovered molecular differences between apes and humans make the prospect of simple random mutation leading to a new species of Homo sapiens largely improbable (35).

The 2004 transitional species between water- and land-based creatures (Tiktaalik roseae) was based on a recovered bone fragment representing the wrist structure that would be necessary for moving on land (36) (Figure 2). Even though this species has been disparaged by scientific circles, it is important to realize that any transition from a water-based organism to an air-breathing land-based organism would also require thousands of simultaneous mutations in the basic physiology of the eyes, nose, alimentary system, lungs, muscles, and bones. This would entail thousands of discrete mutations in the DNA, which would code for the underlying changes in the individual cellular systems and enzymes responsible for the changes. A transitional species change would also require a simultaneous change in another organism, allowing for reproduction and duplication of the markedly mutated DNA.

The transitional species concept has been most extensively studied through invertebrate species of plants, shells, and mollusks in carefully preserved fossil fields in Japan, Malaysia, and Asia. Thousands of specimens were available at the time of Darwin. Millions of specimens have been classified and studied in the past 50 years. It is remarkable to note that each of these
fossil beds shows a virtual explosion of nearly all phyla (35/40) of the animal kingdom over a relatively short period during the Cambrian era 525 to 530 million years ago (37) (Figure 3). Since that time, there has been occasional species extinction, but only rare new phyla have been convincingly identified (38). The seminal paper from paleoanthropologists J. Valentine and D. H. Erwin notes that the absence of transitional species for any of the Cambrian phyla limits the neo-Darwinian explanation for evolution (39).

Finally, bacterial evolution or adaptation offers an excellent opportunity to see mutation in a species with rapid cell division. Evolutionary biology can be modeled over a relatively short time (30 years), while observing DNA mutations over $10^{20}$ generations (40). This is analogous to observing mutations in man or any mammal over 200 million years. A recent review of numerous papers related to viral and bacterial evolution over the past 40 years revealed that the vast majority of mutations led to a loss or slight modification of function that conferred resistance or survival benefit (41). These specific mutations included simple deletions, substitutions, frame shift mutations, inversion, and insertion. No gain-in-function mutations were observed in any of the long-term bacterial evolution studies. There were only two gain-of-function mutations in the long-term viral evolution studies. The absence of mutations leading to a single new protein suggests the difficulty of using mutation to explain the development of numerous new proteins coded specifically by thousands of nucleotides in a precise order, interacting with numerous other enzymes in a simultaneous fashion to accomplish a single cellular action such as the cellular manufacture of a single nucleotide.

The complexity of creating two sequential or simultaneous mutations that would confer improved survival has been studied in the malaria parasite when exposed to chloroquine. The actual incidence of two base-pair mutations leading to two changed amino acids leading to resistance has been shown to be 1 in $10^{20}$ cases (42). To better understand this incidence, the likelihood that *Homo sapiens* would achieve any single mutation of the kind required for malaria to become resistant to chloroquine (a simple shift of two amino acids) would be 100 million times 10 million years (many times the age of the universe). This example has been used to further explain the difficulty in managing more than one mutation to achieve benefit.

In all fairness, there is convincing evidence, that is widely acknowledged, that random mutation and natural adaptation (Darwinian evolution) does occur within species, leading to minor changes in areas such as beak size, skin pigmentation, or antibiotic resistance. Some of these changes involve a simple biologic survival advantage for a population, without a mutation in DNA. Others might be influenced by a single deletion or insertion within the DNA strand. However, the modern evolution data do not convincingly support a transition from a fish to an amphibian, which would require a massive amount of new enzymes, protein systems, organ systems, chromosomes, and formation of new strands of specifically coding DNA. Even with thousands of billions of generations, experience shows that new complex biological features that require multiple mutations to confer a benefit do not arise by natural selection and random mutation. New genes are difficult to evolve. The bacteria do not form into other species. A reliance on gross morphologic appearances, as with fossils, drawings, and bone reconstructions, is severely inadequate compared to an understanding of the complexity of the DNA and coding that would have been required to mutate from a fish to an amphibian or from a primitive primate to a human.

**PARADIGM SHIFT**

In his landmark book, *The Structure of Scientific Revolutions*, Massachusetts Institute of Technology Professor Thomas S. Kuhn gave the term paradigm its contemporary meaning when he used it to describe universally recognized scientific achievements that, for a time, provide model problems and solutions to a community of practitioners (43). A paradigm shift can be heralded by the occurrence of “counterinstances or anomalies,” which represent exceptions of the logic or exaggerations of the evidence. According to Kuhn, these shifts lead to conflict, debate, and great resistance, even with accusations that the new theorists have ignored “science.” Examples of these gradual paradigm shifts, which began as chinks in the established armor of science, include Copernicus versus Ptolemy in astronomy, Lavoisier versus Priestly in gases, and Einstein versus Newton in relative dynamics.

The primary conflicts or anomalies with neo-Darwinian evolution lie in the failure of mutation and natural selection to account for the formation of DNA, the information of DNA, or the complexity of the human cell. In all fairness, many physicians, medical students, and college students have not been shown the weakness of Darwinian evolution. They haven’t been shown the failure of the Miller-Urey experiments to explain DNA, RNA, or protein formation; the paucity of fossil data; or the refutations of transitional species based on a growing biochemical understanding of complex systems and the limits of DNA mutation to account for the formation of new DNA, new chromosomes, and therefore new species.

In contrast, how is it possible that the majority of National Academy of Science members (who should know the above
weaknesses) fully believe that random mutation and natural selection can explain the origin of DNA and the subsequent generation of a vast array of protein systems within complex cells? It is possible that the biologist, the paleontologist, and the anthropologist are each studying a small portion of the picture and do not have the education and training to see the full picture. More likely, their previous research relies on the established paradigm of Darwinian evolution to provide structure for their work. As the limitations of existing paradigms become apparent, adoption of a new paradigm typically requires at least a full generation, since existing practitioners and scientists often hold on to the old paradigm.

When the Texas State Board of Education voted to recognize the weaknesses of Darwinian evolution in explaining the origin of the species, it was a result of 3 full days of intense debate and scientific dispute. In 2011, when new textbooks were presented to the State Board of Education, 9 out of 10 failed to provide the mandated supplementary curricula, which would include both positive and negative aspects of evolution (44). Moreover, several of the textbooks continued to incorrectly promote the debunked Miller-Urey origin of life experiment, the long-discredited claims about nonfunctional appendix and tonsils, and the fraudulent embryo drawings from Ernst Haeckel. In essence, current biology students, aspiring medical students, and future scientists are not being taught the whole story. Rather, evidence suggests that they continue to receive incorrect and incomplete material that exaggerates the effect of random mutation and natural selection to account for DNA, the cell, or the transition from species to species.

The Texas State Board of Education guidelines do not propose teaching any other alternatives to Darwinian evolution. Rather, the students of tomorrow and teachers of today should appropriately recognize that there are weaknesses that have been pointed out by reasonable scientists. In this dissection of Darwinism, we have cut into the weaknesses of the fossil evidence for human evolution, the failure of the fossil data to demonstrate substantial transition species, and the awareness of the sudden formation of most species in a short window of time, with no significant subsequent variation. More importantly, this physician-perspective article emphasizes the extreme impossibility of the natural formation or self-formation of billions of nucleotides in a specific sequence, allowing for the coding of RNA and proteins in a complex cell with thousands of interrelated and irreducibly complex functions. The article also enlightens the reader regarding the conflicts and difficulty of using natural selection and mutation to explain the simultaneous or sequential changes in cellular DNA, involving entirely new strands of DNA and thousands of new proteins, which are necessary for the formation of new species.

John Hunter and Charles Darwin were limited to gross observation of physical appearance. The human cell appeared to be a glob of jelly under a primitive microscope. Both scientists observed mutation and adaptation, which clearly exist today. For almost 150 years following their proposal, thousands of articles and biology departments across the world made observations based on the paradigm of random mutation and natural selection to account for changes within species. These changes are uncontested truths. However, regarding the origin of the species and life (DNA), even Darwin commented, “If it could be shown that complex systems could not arise by small sequential steps, then my theory would completely break down.” Irreducibly complex systems involving thousands of interrelated specifically coded enzymes do exist in every organ of the human body. At an absolute minimum, the inconceivable self-formation of DNA and the inability to explain the incredible information contained in DNA represent fatal defects in the concept of mutation and natural selection to account for the origin of life and the origin of DNA. As new theories emerge that explain the origin of life, the inevitable emotional accusations of heresy and ignorance are not surprising in a period of scientific revolution. It is therefore time to sharpen the minds of students, biologists, and physicians for the possibility of a new paradigm.


The theme of Dr. Kuhn’s paper is that Darwin’s theory of evolution to explain the origin of species is inadequate, and that the 2010 decision by the Texas State Board of Education to require textbooks to present the weaknesses, as well as the strengths, of Darwin’s theory was appropriate. The three limitations of Darwin’s theory concern the origin of DNA, the irreducible complexity of the cell, and the paucity of transitional species. Because of these limitations, the author predicts a paradigm shift away from evolution to an alternative explanation.

The intellectual problem, in my opinion, is not that evolution has “fatal defects,” but rather that it remains a suspect theory for most Americans >150 years after the publication of The Origin of Species (1859). While the Texas State Board of Education may have debated the issue for 3 full days in 2010, its recommendation in the end will probably be ignored by scientists who write textbooks. I suppose the Texas decision represents progress. Tennessee’s Butler Act made it unlawful to teach evolution, giving rise to the Scopes trial in 1925, in which John T. Scopes, a high school teacher, was accused of violating that law. After an 8-day trial, a guilty verdict was reached.

To embrace the idea that all forms of life, great and small, plant and animal, primate and nonprimate, were derived from a common primordial cell or organism requires a scientific perspective. The various religions, current and extinct, typically elevate humans above other forms of life. Most Homo sapiens believe that the different species on planet earth were created independently by a God, in sequential batches, placed in certain locales, with the Homo sapiens inherently superior, made in the image of the creator—thus, the resistance to the concept of evolution.

With respect to the origin of DNA as a weakness of Darwinism, our knowledge of DNA, from my reading, has added to, not subtracted from, the evidence of evolution. In the 2006 preface to the 30th anniversary edition of The Selfish Gene (first published by Oxford University Press in 1976), author Richard Dawkins wrote:

Let me repeat and expand the rationale for the word “selfish” in the title. The critical question is which level in the hierarchy of life will turn out to be the inevitably “selfish” level, at which natural selection acts? The Selfish Species? The Selfish Group? The Selfish Organism? The Selfish Ecosystem? Most of these could be argued, and most have been uncritically assumed by one or another author, but all of them are wrong. Given that the Darwinian message is going to be pithily encapsulated as The Selfish Something, that something turns out to be the gene, for cogent reasons which this book argues.

The notion of “irreducible complexity” in a cell, as an argument against evolution, is beyond my present understanding. Knowing that life has existed on planet earth for billions of years, however, I suspect that there has been time enough for evolution, no matter how complex, with reducibility.

With respect to transitional species, a brief glance through recent issues of National Geographic shows no paucity of data from paleontologists. Human lineage can be traced back >6 million years, with fossils discovered in East Africa from all three major phases of hominid evolution—Ardipithecus, Australopithecus, and Homo—with a divergence from living ape species (chimpanzee and bonobos) roughly 8 to 6 million years ago. Transitional species have been identified in numerous other groups. The whale, for example, accomplished an enormous transformation, with fossil evidence. Fifty million years ago it was semi-terrestrial; now it is fully aquatic.

Seven billion Homo sapiens now inhabit planet earth. World population in AD 1 (the time of Christ) was about 200 million. In the struggle for survival in the next century and beyond, the hand of natural selection will be at work, I believe, and evidence of evolution, to explain the origin, modification, and behavior of species, will continue to increase.

—Charles Stewart Roberts, MD
Cardiovascular Surgery
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Editor’s note: Gregory Dimijian, MD, is also preparing a full-length article on Darwinism, which Proceedings will publish in an upcoming issue.
A brief history of cross-species organ transplantation

David K. C. Cooper, MD, PhD

Cross-species transplantation (xenotransplantation) offers the prospect of an unlimited supply of organs and cells for clinical transplantation, thus resolving the critical shortage of human tissues that currently prohibits a majority of patients on the waiting list from receiving transplants. Between the 17th and 20th centuries, blood was transfused from various animal species into patients with a variety of pathological conditions. Skin grafts were carried out in the 19th century from a variety of animals, with frogs being the most popular. In the 1920s, Voronoff advocated the transplantation of slices of chimpanzee testis into aged men whose “zest for life” was deteriorating, believing that the hormones produced by the testis would rejuvenate his patients. Following the pioneering surgical work of Carrel, who developed the technique of blood vessel anastomosis, numerous attempts at nonhuman primate organ transplantation in patients were carried out in the 20th century. In 1963–1964, when human organs were not available and chronic dialysis was not yet in use, Reemtsma transplanted chimpanzee kidneys into 13 patients, one of whom returned to work for almost 9 months before suddenly dying from what was believed to be an electrolyte disturbance. The first heart transplant in a human ever performed was by Hardy in 1964, using a chimpanzee heart, but the patient died within 2 hours. Starzl carried out the first chimpanzee-to-human liver transplantation in 1966; in 1992, he obtained patient survival for 70 days following a baboon liver transplant. With the advent of genetic engineering and cloning technologies, pigs are currently available with a number of different manipulations that protect their tissues from the human immune response, resulting in increasing pig graft survival in nonhuman primate models. Genetically modified pigs offer hope of a limitless supply of organs and cells for those in need of a transplant.

The increasing demand for organs, tissues, and cells for purposes of clinical transplantation, and the relative lack of improvement in the number of deceased human organs that become available each year, have increased interest in the possibility of using organs and cells from an animal species (1, 2). The concept of cross-species transplantation (or xenotransplantation) is not new, and there has been a surprisingly large number of clinical attempts during the past 300 years or more (1, 3, 4). The barriers to xenotransplantation are considerable but are steadily being overcome, largely by our ability to genetically engineer pigs to make their tissues more resistant to the human immune response.

XENOTRANSPLANTATION IN MYTHOLOGY

A review of Greek mythology and of religious tracts—particularly, for example, from the Hindu religion—draws attention to the fact that humans have been interested in the possibility of merging physical features from various animal species for hundreds of years. For example, the chimera has been used to represent the allotransplantation of organs and cells (transplantation between members of the same species), and the lamassu (Figure 1) has been selected as the mythological figure to represent the International Xenotransplantation Association and its official scientific journal, Xenotransplantation.

The late Keith Reemtsma pointed out that possibly one of the earliest examples of xenotransplantation was the attempt by Daedalus and his son, Icarus, to fly across the sea from Crete to mainland Greece with the help of bird wings attached to their...
arms (5). Icarus failed in the attempt, and Reemtsma put this forward as a possible case of hyperacute rejection (very rapid rejection of the graft), though he thought it was more likely to be related to failure of a thermolabile adhesive. However, Daedalus successfully made the journey, providing this pair with an enviable 50% success rate.

**BLOOD XENOTRANSFUSION**

If we look beyond the realm of mythology and legend, we come to the 17th century, when Jean Baptiste Denis (Figure 2) began the clinical practice of blood transfusion from animals to humans (6). Perhaps not surprisingly, the results were mixed. As a result, xenotransfusion was banned in France for a number of years. Today, with the increasing risk of transfer of infectious agents with human blood transfusions, a strong case could be made for using an animal such as a pig (housed under ideal "clean" conditions and monitored at intervals to ensure that no infectious agent would be transferred) as the source of blood cells and blood products in the future (6). In fact, this approach has recently been explored again by several groups (7).

**SKIN XENOTRANSPLANTATION**

In the 19th century, skin grafts became relatively popular between various animal species and humans (8, 9). The grafts were either free skin grafts or pedicle skin grafts. Pedicle grafts were complicated because they required the donor, for example, a sheep, to be strapped immobile to the patient for several days, during which time the graft would reputedly be vascularized by the recipient. If this occurred, the graft could be disconnected during which time the graft would reputedly be vascularized by the recipient. If this occurred, the graft could be disconnected from the donor. It is almost certain that none of these grafts was successful, although some “successes” were reported.

The fact that many of the species used as donors—sheep, rabbits, dogs, cats, rats, chickens, and pigeons—had hair, feathers, or fur growing from the skin did not appear to discourage the surgeons involved, but the trend was to use animal species in which these accoutrements were not present. The ideal graft would appear to have been from frogs, which were sometimes “skinned alive.” It is possible that some of these grafts were “successful” in this way, when used to cover a skin ulcer, they provided protection, at least for a number of days, while the ulcer healed beneath the graft. However, probably none of the grafts actually became permanent.

**CORNEAL XENOTRANSPLANTATION**

Remarkably, in 1838 the first corneal xenotransplantation (from a pig) was performed in a patient, whereas the first corneal allograft (human-to-human) was not carried out until more than 65 years later, in 1905. The field of corneal xenotransplantation has recently been reviewed by Hara and Cooper (10, 11).

**ALEXIS CARREL AND BLOOD VESSEL ANASTOMOSIS**

More scientific efforts had to wait until the 20th century, when the French experimental surgeon, Alexis Carrel (Figure 3), working first in France and subsequently in North America, developed surgical techniques for anastomosing blood vessels, which enabled organ transplantation to be carried out successfully for the first time. For this work he was awarded the Nobel Prize in 1912. He developed an interest in cross-species transplantation, at least from an experimental perspective, and in 1907 wrote these prophetic words:

> The ideal method would be to transplant in man organs of animals easy to secure and operate on, such as hogs, for instance. But it would in all probability be necessary to immunize organs of the hog against the human serum. The future of transplantation of organs for therapeutic purposes depends on the feasibility of hetero [xeno] transplantation.

> It is remarkable that, more than 100 years ago, Carrel indicated what we are now trying to do, which is to genetically modify pigs to make their tissues resistant to the human immune response. Carrel was clearly a man of vision.

**SERGE VORONOFT AND “REJUVENATION” BY CELL XENOTRANSPLANTATION**

A few years later, Serge Voronoff (Figure 4), a Russian émigré working in Paris, developed the concept of transplanting cells that produced a hormone in which the recipient was deficient. This is another example of a visionary scientist who was ahead of his time. Today we are doing exactly what he envisaged, namely transplanting human pancreatic islets that produce insulin in patients with severe type 1 diabetes. In view of the limited number of human pancreases that become available each year, there is growing interest in using pig islets for this purpose (see below).

Voronoff’s main interest, however, was in reversing the effects of aging in elderly men who had lost their “zest for life.” He carried out a significant number of chimpanzee or baboon testicular transplants in male human recipients (12, 13). His
technique was to slice up the animal testicle and insert the slices into the recipient’s testicle. (It can be looked upon as the Viagra of the 1920s.) The procedure became popular on both sides of the Atlantic, and several hundred of these operations were performed. It is inconceivable that any of them had any beneficial effect whatsoever except psychological, but there were reports of remarkable “rejuvenation” of men who reported much increased energy after the operation. The complications of the operations must have been significant because presumably on occasions the slices of donor testicle would have necrosed and set up inflammatory or infectious complications. Surprisingly, reports of such complications appear to have been uncommon.

Voronoff was certainly a man ahead of his time because he also applied to the authorities in Paris to carry out what would have been the first kidney allotransplant, using the kidneys from a criminal who was to be guillotined. His request was refused, and this allowed his Russian compatriot, Yurii Voronoy, to become the first surgeon to perform kidney allotransplantation in 1933 (14).

The concept of transplanting glandular tissue to produce hormones that would benefit the recipient was continued in the United States by a much less scientific doctor, John Brinkley, whose work was carried out largely in Kansas and Texas (15). His chosen donor was the goat, as he had been convinced by a local farmer of its sexual potency. It would appear that Brinkley was a charlatan rather than a serious transplant surgeon, and, although it made him a fortune, his work fell into serious disrepute, and he was eventually driven out of business by the American Medical Association.

Nevertheless, this concept of cell xenotransplantation has been sustained until the present time, with the establishment of several clinics, particularly in Europe, in which animal tissue or serum is injected into patients for a variety of conditions. The results have been controversial (16).

KEITH REEMTSMA AND CHIMPANZEE KIDNEY XENOTRANSPLANTATION

By the 1960s, Keith Reemtsma (Figure 5)—at that time at Tulane University in Louisiana—hypothesized that nonhuman primate kidneys might function in human recipients and thus be a successful treatment for renal failure. At that time, the concept of kidney transplantation had been established largely by French and American surgeons, but the availability of kidneys from deceased humans was extremely limited and chronic dialysis was not yet being undertaken. In Reemtsma’s opinion, therefore, there was little alternative to death for the patient unless organs could be made available from nonhuman species. He selected the chimpanzee as the source of organs because of its close evolutionary relationship to humans. He carried out 13 of these transplants, on each occasion transplanting both kidneys from the chimpanzee (which generally weighs significantly less than an adult human) into the recipient (17).

Most of the transplants failed within 4 to 8 weeks, either from rejection (because of the limited immunosuppressive agents available at the time) or from an infectious complication (because of the overadministration of these agents). Nevertheless, one of Reemtsma’s patients lived for 9 months, returning to work as a schoolteacher and evidently remaining in good health until she suddenly collapsed and died. At autopsy, the chimpanzee kidneys appeared normal and showed no signs of acute or chronic rejection (Figure 6). It was suggested that she had died from an acute electrolyte disturbance. This is possible since the transplantation of nonhuman primate kidneys into patients was frequently associated with an immense diuresis in the early posttransplantation period, often exceeding 20 liters in 24 hours, and there could have been a late electrolyte imbalance.

The concept of using nonhuman primates as kidney donors was expanded by several surgeons, particularly by Tom Starzl (Figure 7), who used baboons as donors in Colorado (18); his results were similar to those of...
of Reemtsma, except that he did not achieve any relatively long-term survivors. Others in the US and in France also had small experiences (3).

JAMES HARDY AND THE FIRST HEART XENOTRANSPLANT

James Hardy (Figure 8), who had carried out the first human lung allotransplant in 1963, visited Reemtsma and was impressed by the health of some of the patients with chimpanzee kidney transplants. In 1964, Hardy was determined to carry out the first clinical heart transplantation and decided to acquire some chimpanzees as potential "donors" in case he could not identify a deceased human donor. He had a less-than-ideal patient who would not be accepted for heart transplantation today, as he had widespread atheromatous vascular disease throughout his body—for which he had undergone amputations of both legs—and was in a semicomatose state at the time the transplant was undertaken. However, as the patient was rapidly dying, Hardy was stimulated to transplant a chimpanzee heart (19). The chimpanzee heart was not large enough to support the circulation and failed within a couple of hours.

In contrast to the response to the attempted lung allotransplantation, the public and medical professional response to the heart xenotransplantation was adverse and dissuaded Hardy and his colleagues from carrying out any further attempts. The procedure of cardiac allotransplantation was later established by Barnard and his colleagues in 1967 (20), who later also carried out two cardiac xenotransplants (21).

It is of interest to note that the consent form for Hardy’s operation—which, in view of the patient’s semicomatose condition, was signed by a close relative—stipulated that no heart transplant had ever been performed, but made no mention of the fact that an animal heart might be used for the procedure. Such was the medicolegal situation at that time that this “informed” consent was not considered in any way inadequate.

LEONARD BAILEY AND “BABY FAE”

Perhaps the best known clinical cardiac xenotransplantation since Hardy’s attempt was that by Leonard Bailey (Figure 9), who transplanted a baboon heart into an infant girl, known as Baby Fae, in 1983. At that time, it was almost impossible to obtain human organs from infants, particularly those with anencephaly, for transplantation into infants with life-threatening congenital heart disease. The surgical procedure in Baby Fae was technically successful, but the graft underwent acute rejection and the patient died 20 days later (22). As the graft was necessarily taken from a baboon that was ABO-incompatible with the recipient—as the O blood type is essentially not found in baboons—this might have added to the severity of rejection. Even though cyclosporine had become available by this time, the immunosuppressive therapy was not sufficient to prevent xenograft rejection.

This procedure did little to advance progress in xenotransplantation, but it did draw public and medical attention to the dearth of deceased human organs available for infants in need of a transplant. Following the procedure, particularly with the immense publicity associated with it, the situation with regard to donation of organs from infants became very much improved, and Bailey went on to develop an extremely successful cardiac allotransplantation program in infants and children at Loma Linda University.

THOMAS STARZL AND LIVER XENOTRANSPLANTATION

Tom Starzl (Figure 7), who is one of the greatest pioneers in the field of kidney and liver allotransplantation, performed a handful of liver transplants between nonhuman primates and young patients in Colorado in the 1960s without lasting success (23–26). When the addition of tacrolimus had improved the immunosuppressive armamentarium, he and his team in Pittsburgh performed two liver transplants from baboons in adult patients in the 1990s, with one patient surviving for 70 days (27). The results, however, were not successful enough to warrant continuing this experimental clinical trial.

Most of the early attempts at clinical organ xenotransplantation used nonhuman primate species as sources of the organ, although there have been a few attempts using the pig (28) and other nonprimate mammals, but without significant success (3).

CARL-GUSTAV GROTH AND THE FIRST ISLET XENOTRANSPLANTATION

There are an estimated 2 to 3 million patients with type 1 diabetes in the USA alone. As pig insulin differs from human insulin by only one amino acid, and pig insulin was administered successfully for the treatment of diabetic patients for decades until recombinant human insulin became available, it is reasonable to anticipate that successful pig islet transplantation will result in normoglycemia. The Swedish group headed by Carl Groth (Figure 10) was the first to attempt pig islet transplantation in patients with diabetes in 1993 (29). Although porcine C-peptide was documented in the blood of some of the patients, indicating that some islets survived, no clinical benefit was obtained.
In recent years, there have been encouraging results from islet allotransplantation in patients with type 1 diabetes, but with such large numbers of patients suffering from the disease, the number of human pancreata that become available will never be sufficient to treat all of the potential patients, particularly as often two (or even three) human pancreata are required to provide enough islets to render a single recipient normoglycemic.

**XENOTRANSPLANTATION USING PIGS AS SOURCES OF ORGANS AND CELLS**

The advantages of xenotransplantation, particularly if we could use a readily available animal source, such as the pig, would be numerous (Table 1) (30). First, there would be an unlimited supply of “donor” organs, which would resolve the current increasing and severe shortage of human organs.

Second, these organs would be available electively whenever required, which is an equally important point. Currently, a patient may wait several months in an intensive care unit or with a left ventricular assist device while awaiting a heart transplant, or even several years on chronic dialysis awaiting a kidney transplant. If transplantation could be carried out as soon as the patient experiences irreversible organ failure, then immediate transplantation would almost certainly result in significantly improved survival.

Third—a point that is generally overlooked—brain death has numerous adverse effects on the donor organs, particularly the heart, that may lead to primary graft nonfunction or other injury (31, 32). In the case of the xenotransplantation of pig organs, this would be avoided as organs would be excised from a healthy pig under anesthesia.

Fourth, almost no year passes without a novel microorganism being transferred from the donor to the recipient with the graft. In recent years, West Nile virus, rabies, and other microorganisms have been transferred with fatal results. While there has been some concern that a porcine microorganism might be transferred with a pig organ (33–35), the pig herd for transplantation will be housed under ideal conditions and be monitored at regular intervals for infectious agents, providing a much greater chance that the donor animal would be free of all known pathogenic organisms than the average deceased human donor.

In several countries, there are cultural barriers to deceased organ donation, e.g., Japan, and yet there are no barriers to xenotransplantation; thus, the number of transplants performed would be vastly increased. The lack of deceased human donors, particularly with regard to liver transplantation, has popularized living donor liver transplants, in which almost two thirds of the donor liver is transplanted in an adult, and there have been a number of donor deaths after these procedures (estimated donor mortality, 0.1% to 0.8%). These tragedies would be avoided if pig organs could be used for transplantation.

The immunological and pathophysiological problems associated with pig xenotransplantation, however, are significant and probably reflect the fact that it has been 80 million years since the pig and human diverged on the evolutionary scale. Therefore, in the words of Claus Hammer, what we are trying to do is “outwit evolution.”

**OVERCOMING THE PROBLEM OF THE GAL ANTIGEN**

Nevertheless, very significant progress has been made since we began to develop the ability to genetically modify large animals, particularly the pig. The “creation” of “Dolly” the sheep, the first cloned mammal, opened the gates to the possibility of rendering pig tissues resistant to the human immune response. It is only through this route that we will overcome the remaining barriers. Many of the barriers have been identified, and some have been overcome.

---

**Table 1. The advantages and disadvantages of the pig vs baboon as a potential source of organs and cells for humans**

<table>
<thead>
<tr>
<th></th>
<th>Pig</th>
<th>Baboon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Availability</td>
<td>Unlimited</td>
<td>Limited</td>
</tr>
<tr>
<td>Breeding potential</td>
<td>Good</td>
<td>Poor</td>
</tr>
<tr>
<td>Period to reproductive maturity</td>
<td>4–8 months</td>
<td>3–5 years</td>
</tr>
<tr>
<td>Length of pregnancy</td>
<td>114 ± 2 days</td>
<td>173–193 days</td>
</tr>
<tr>
<td>Number of offspring</td>
<td>5–12</td>
<td>1–2</td>
</tr>
<tr>
<td>Growth</td>
<td>Rapid (adult human size within 6 months)*</td>
<td>Slow (9 years to reach maximum size)</td>
</tr>
<tr>
<td>Size of adult organs</td>
<td>Adequate</td>
<td>Inadequate*</td>
</tr>
<tr>
<td>Cost of maintenance</td>
<td>Significantly lower</td>
<td>High</td>
</tr>
<tr>
<td>Anatomical similarity to humans</td>
<td>Moderately close</td>
<td>Close</td>
</tr>
<tr>
<td>Physiological similarity to humans</td>
<td>Moderately close</td>
<td>Close</td>
</tr>
<tr>
<td>Relationship of immune system to humans</td>
<td>Considerable</td>
<td>Close</td>
</tr>
<tr>
<td>Knowledge of tissue typing</td>
<td>(in selected herds)</td>
<td>Limited</td>
</tr>
<tr>
<td>Necessity for blood type compatibility with humans</td>
<td>Probably unimportant</td>
<td>Important</td>
</tr>
<tr>
<td>Experience with genetic engineering</td>
<td>Considerable</td>
<td>None</td>
</tr>
<tr>
<td>Risk of transfer of infection (xenozoonosis)</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Availability of specific pathogen-free animals</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Public opinion</td>
<td>More in favor</td>
<td>Mixed</td>
</tr>
</tbody>
</table>

*Breeds of miniature swine are approximately 50% of the weight of domestic pigs at birth and sexual maturity and reach a maximum weight of approximately 30% of standard breeds. At full size, miniature swine are easier to house and to handle. Furthermore, inbred herds are available, though cloning of any pig can result in inbred herds, if needed. Although MHC-identical miniature swine may have some specific immunologic advantage, the disadvantage is that they cannot be cross-bred with other pig strains in which a genetic modification has been introduced; if cross-breeding is carried out, clearly MHC identity is lost.
For example, whereas the human vascular endothelium expresses the ABH blood group antigens, the pig’s vascular endothelium expresses a galactose oligosaccharide, Galα1,3Gal (Gal) (36). The presence of Gal in the pig and its absence in humans, who thus generate anti-Gal antibodies, has proved a major challenge (37–40). When a pig organ or cells are transplanted into a human, these antibodies immediately bind to the cells of the graft and activate complement, resulting in hyperacute rejection that occurs within minutes or hours. This problem has largely been overcome by the development of pigs homozygous for α1,3-galactosyltransferase gene-knockout (GTKO), which no longer express Gal epitopes (41–43).

A second way of negating the problem of human antibody binding to pig antigens is to provide the pig with increased resistance to human complement-mediated injury. This has been achieved by inserting into the pig genes one or more human complement-regulatory proteins, such as CD55 or CD46 (44, 45). The combination of GTKO and expression of CD46 and/or CD55 has made hyperacute rejection a rarity in experimental organ xenotransplantation studies (46).

CURRENT RESULTS OF EXPERIMENTAL PIG ORGAN OR CELL XENOTRANSPLANTATION

The experimental results of cell xenotransplantation, e.g., islet or neuronal cells, are currently significantly better than those of pig organ xenotransplantation. For example, pig islets have continued to function effectively in immunosuppressed nonhuman primates for periods of more than a year (47–50). Indeed, a clinical trial of encapsulated pig islet transplantation is under way in diabetic patients in New Zealand (51).

There are an estimated 8 million patients in the US with a neurodegenerative disease, such as Parkinson’s disease. Human embryonic neural precursor cells can restore local motor activity in patients with Parkinson’s disease, but the use of human embryos is largely precluded on ethical grounds or on logistic grounds as too few become available. Genetically engineered pig embryos might provide an alternative source. Indeed, a European group has reported encouraging improvement for >1 year in locomotor function in monkeys with a Parkinson-like condition after the transplantation of genetically modified pig dopamine-producing cells into the brain (52–54).

There is also a great need for corneas, particularly in Asia and Africa; for example, it is estimated that 4 million patients need corneal transplantation in China alone (11). Experimental corneal xenotransplantation has made significant progress in recent years; pig lamellar grafts have survived in monkeys for periods of more than 1 year, with the recipient receiving only corticosteroid injections into the eyes (55). Partly because the risk to the recipient would be small, it is likely that corneas will be the first xenotransplants to be carried out as a clinical trial, perhaps followed soon after by neuronal cell or islet cell transplantation.

With regard to pig organ xenotransplantation in nonhuman primates, we have been able to achieve pig heterotopic cardiac graft survival up to 8 months (56–59) (i.e., non–life-supporting grafts in which the graft is placed in the abdomen and, by being supplied with recipient blood, beats, thus allowing monitoring for rejection) and life-supporting pig kidney survival up to almost 3 months (60, 61). Transplantation of pig livers (62, 63) and lungs (64, 65) in nonhuman primates has been significantly less successful, with grafts functioning for only days. Pig hearts and livers may initially be used as a bridge while the patient is awaiting a human graft; this will give us experience with organ xenografts in humans. Because dialysis maintains life for a number of years in many patients with renal failure, clinical pig kidney transplantation will probably be delayed.

SAFETY AND REGULATORY ASPECTS OF XENOTRANSPLANTATION

The major concern of national regulatory authorities is whether pig organ or cell xenotransplantation will prove safe from the perspective of the transfer of porcine microorganisms with the graft to the recipient and perhaps into the general population (33–35). As mentioned earlier, to prevent this, pigs will be housed under strict barrier conditions and will be screened for potentially pathogenic microorganisms at regular intervals (34). Organs and cells from these pigs should, therefore, be safer from this perspective than an allograft taken from a recently brain-dead human, where there has been insufficient time to monitor for all potential infectious agents.

With regard to xenotransplantation, most concern has related to endogenous retroviruses that are present in the genome of every porcine cell (33, 35). These will inevitably be transferred with the donor tissues. This potential risk gave considerable concern some years ago, but it is now generally believed that these are weak viruses and are unlikely to be problematic, even in an immunosuppressed recipient. There has been no documentation of transfer of these viruses in humans or nonhuman primates exposed to pig tissues. Strict monitoring for infectious complications in the recipient and archiving of tissues from the source pig will be required by the regulatory authorities for a prolonged period of time (66).

PREDICTING FUTURE PROGRESS

In 1969, Sir Peter Medawar, the British scientist who won the Nobel Prize for medicine in 1960 and is considered the father of transplant immunology, stated, “We should solve the problem [of organ transplantation] by using heterografts [xenografts] one day if we try hard enough, and maybe in less than 15 years.” This indicates that even Nobel Prize winners can get their prophecies wrong. In contrast, in 1995, Sir Roy Calne, another great pioneer in organ transplantation, stated that xenotransplantation “is just around the corner, but it may be a very long corner.” He has been proved correct. At least he and Sir Peter Medawar were optimistic about the development of xenotransplantation, whereas Norman Shumway, the pioneer of heart transplantation, stated rather pessimistically that “xenotransplantation is the future of transplantation, and always will be.”

Nevertheless, there is clear evidence that xenotransplantation will become successful in the relatively near future. There
is a Native American proverb, “Timing has a lot to do with the success of a rain dance.” With the increasing variety of genetically engineered pigs now becoming available, it is likely that the remaining problems will be resolved and the timing for xenotransplantation will be right. For example, in Pittsburgh, we have available to us (through our colleagues at Revivicor Inc., of Blacksburg, VA) pigs with no fewer than nine different genetic manipulations, of which at least five have been combined in a single pig (Table 2). With interbreeding between these various pigs—and with new genetic modifications being introduced—it is likely that the problems of rejection and coagulation dysfunction (which is the present major barrier [67]) will soon be overcome. Although there are relatively few hard data at present, the current evidence is that the function of pig organs and cells in humans may be adequate (68).

The words of George Orwell in Animal Farm will be appropriate to pig organ transplantation in humans. “The creatures outside looked from pig to man, and from man to pig, and from pig to pig again; but already it was impossible to say which was which.” I believe the same will one day be said for the doctor examining a patient with an organ transplant—the doctor will not be able to determine whether the organ is an allograft or a xenograft. Eventually, allotransplantation will be of historic interest only.

Acknowledgments

The author thanks Burcin Ekser, MD, for preparing Table 2. Work on xenotransplantation in the author’s laboratory in the Thomas E. Starzl Transplantation Institute at the University of Pittsburgh has been supported in part by National Institutes of Health grants U01 AI068642, R21 AI074844, and U19 AI090959, and by sponsored research agreements between the University of Pittsburgh and Revivicor, Inc., Blacksburg, VA.

Table 2. Genetically modified pigs currently available for xenotransplantation research*

<table>
<thead>
<tr>
<th>Gal antigen deletion or <em>masking</em></th>
</tr>
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<tbody>
<tr>
<td>• α1,3-galactosyltransferase gene-knockout (GTKO)</td>
</tr>
<tr>
<td>• Human H- transferase gene expression (expression of blood type O antigen)</td>
</tr>
<tr>
<td>• Endo-beta-galactosidase C (reduction of Gal antigen expression)</td>
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<tr>
<th>Complement regulation by human complement-regulatory gene expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>• CD55 (decay-accelerating factor)</td>
</tr>
<tr>
<td>• CD46 (membrane cofactor protein)</td>
</tr>
<tr>
<td>• CD59 (protectin or membrane inhibitor of reactive lysis)</td>
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<table>
<thead>
<tr>
<th>Anticoagulation and antiinflammatory gene expression or deletion</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Human tissue factor pathway inhibitor (TFPI)</td>
</tr>
<tr>
<td>• Human thrombomodulin</td>
</tr>
<tr>
<td>• Human CD39 (ectonucleoside triphosphate diphosphohydrolase-1)†</td>
</tr>
<tr>
<td>• Von Willebrand factor–deficient (natural mutant)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Suppression of cellular immune response by gene expression or downregulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Porcine CTLA4-Ig (cytotoxic T-lymphocyte antigen 4 or CD152)</td>
</tr>
<tr>
<td>• LEA29Y (inhibition of the B7/CD28 costimulatory pathway of T-cell activation)</td>
</tr>
<tr>
<td>• CIITA-DN (MHC class II transactivator knockdown, resulting in swine leukocyte antigen class II knockdown)</td>
</tr>
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<table>
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<tr>
<th>Human TRAIL (tumor necrosis factor-α–related apoptosis-inducing ligand)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• HLA-E/human B2-microglobulin (inhibits human natural killer cell cytotoxicity)</td>
</tr>
<tr>
<td>• Human CD47 (for species-specific CD47-SIRPα natural interaction on macrophages)</td>
</tr>
</tbody>
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<table>
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<tr>
<th>Human FAS ligand (CD95L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Human CD39 (ectonucleoside triphosphate diphosphohydrolase-1)†</td>
</tr>
<tr>
<td>• Human GnT-III (N-acetylgalactosaminyltransferase III) gene</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Anticoagulation, antiinflammatory, and antiapoptotic gene expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Human A20 (tumor necrosis factor-alpha–induced protein 3)</td>
</tr>
<tr>
<td>• Human heme oxygenase-1 (HO-1)</td>
</tr>
<tr>
<td>• Human TNFR1-Fc (tumor necrosis factor-alpha receptor I-Fc)</td>
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</table>

<table>
<thead>
<tr>
<th>Prevention of porcine endogenous retrovirus (PERV) activation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• PERV siRNA</td>
</tr>
</tbody>
</table>

*Kindly collated by Burcin Ekser, MD. Pigs with combinations of genetic modification, e.g., GTKO with added transgenes, are available. †Personal communication from Drs. S. Robson and P. Cowan.


59. Mohiuddin MM, Corcoran PC, Singh AK, Azimzadeh AM, Hoyt RF, Thomas MP, Eckhaus MA, Ayares D, Pierson RN III, Horvath KA. Over six month survival of cardiac xenograft is achievable but heterotopic placement of the graft may limit consistent prolonged survival (Abstract TTS-1383). Transplantation 2010;90(Suppl):325.


Physician behavior and bedside manners: the influence of William Osler and The Johns Hopkins School of Medicine

Barry D. Silverman, MD

The practice of medicine changes with time as we develop better techniques for diagnosis and improved therapies for treatment. The art of medicine remains constant over the millennia because human nature is unchanging. Patients bring fear, anxiety, and self-pity into the exam room. It has always been the doctor’s responsibility to calm their fears and provide hope. The accomplished doctor has a bedside manner that is humane and compassionate, empathetic and supportive.

Students are taught bedside skills, the art of medicine, by our senior, most experienced clinicians. However, in the past 20 years, more of these professors are laboratory scientists, often deficient or unpracticed in their bedside skills. Bernard Lown, the famous Boston cardiologist, wrote in 1996 in his book *The Lost Art of Healing* how essential bedside behavior is to good medical care. He expressed his concern that important bedside skills are disappearing in our technology-focused practice of medicine.

Several medical schools have recommended a new emphasis on improving professionalism. Jock Murray, former dean of the Dalhousie Medical School, speaking to the American College of Physicians in 2006, commented on the general erosion of professionalism and a growing public cynicism about the profession. He called for a new focus on the three core principles of professionalism: competency, the primacy of patient welfare, and social justice. Professionalism is not an attempt to protect physicians’ power and status, he noted, but a call to practice medicine in patients’ best interests.

No physician has exerted a greater influence on how physicians should behave than Sir William Osler. His essays on the practice of medicine, his leadership in medical organizations, and his personal charisma established a paradigm that has served as a model for physician behavior at the bedside. His textbook of medicine, *The Principles and Practice of Medicine*, first published in 1892, was the bible of rational medical therapy for 30 years. He was the first chief of medicine at the Johns Hopkins Hospital and Medical School, and his leadership at Johns Hopkins transformed American medical care. He led the effort to bring a scientific approach to the care of the patient. Osler famously said, “The practice of medicine is an art based on science” (Figure).

Osler was a unique personality and practiced at a propitious time in medicine. At the end of the 19th century and the beginning of the 20th century, medicine was evolving from a practice based on superstition and tradition into a rational biological science. His bedside manners were based on Victorian morals and their notion of the duties of a gentleman. But like the technophobe and iPad enthusiast of today, he eagerly embraced scientific medicine as the new hope for tomorrow. How did William Osler and the Johns Hopkins Medical School influence our current bedside behavior?

Figure. Osler at the bedside of a patient. Photo from the Mark Silverman collection.

From Piedmont Hospital, Atlanta, Georgia.
Presented at the meeting of the American Osler Society, Boston, Massachusetts, May 2008.

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HIPPOCRATIC THOUGHT ON BEDSIDE MANNER

We begin with the Greeks in the 4th century BC, as does almost everything in Western culture. The Greeks were very specific about physician bedside manners. Included in the Hippocratic corpus is this comment:

The physician ought also to be confidential, very chaste, sober, and not a winebibber, and he ought to be fastidious in everything, for this is what the profession demands. He ought to have an appearance and approach that is distinguished. Everything ought to be in moderation, for these things are advantageous, so it is said. Be solicitous in your approach to the patient, not with head thrown back (arrogantly) or hesitantly with lowered glance, but with head inclined slightly as the art demands.

He ought to hold his head humbly and evenly; his hair should not be too much smoothed down, nor his beard curled like that of a degenerate youth. Gravity signifies breadth of experience. He should approach the patient with moderate steps, not noisily, gazing calmly at the sick bed. He should endure peacefully the insults of the patients since those suffering from melancholic or frenetic ailments are likely to hurl evil words at physicians (5).

Physicians’ manners, dress, bearing, deportment, and conduct were vital and necessary elements of patient care, a tradition that extended from the earliest shamans to the emergence of scientific medicine. The Hippocratic corpus has many references to appropriate conduct and medical etiquette, with several devoted just to physician behavior. The importance of bedside manners was taught by medical scholars for 1500 years, from Hippocrates and Galen to Avicenna and the early Christian monks who began hospital care in the Middle Ages.

MODERN CHANGES AND THE REDEVELOPMENT OF PROFESSIONALISM

In the 17th century, medical practice changed with competition between physicians, surgeons, and apothecaries and the growth of new institutions including infirmaries, clinics, and hospitals. The professional institutions were unconcerned with moral matters, and legal regulation of medical practice was nonexistent. Only personal character served as a guarantor of a physician’s conduct. In the 18th century, when civility had fallen to a low point in England, John Gregory reintroduced appropriate physician behavior into the curriculum at Edinburgh.

In 1769, John Gregory of Edinburgh, a friend of David Hume and a member of the Scottish Enlightenment, was teaching that duty and benevolence were the duties of the physician (6). The physician was an educated, superior individual obligated to serve his fellow man. In 1789, conflict broke out at the Manchester Infirmary over medical staff privileges and care for the poor during a typhus epidemic. Thomas Percival, a pupil of John Gregory, was asked by the board of trustees to mediate. In response to this conflict, he wrote Medical Ethics (7). His book was a set of rules on how physicians should behave with patients and their colleagues and is considered the beginning of modern medical ethics. The book is much more a manual of etiquette than a code of ethics.

In America, the American Medical Association (AMA) was founded in response to a crisis over professionalism and professional standards. This crisis was the result of a change in the method of training physicians. The traditional apprentice system for training doctors was displaced when in 1803 Harvard College granted an MD degree. This diploma was soon recognized in Massachusetts as the qualification to practice medicine. In a very short time, there were 40 diploma schools with >1000 graduates a year, and the diploma quickly became the preferred method to qualify as a medical practitioner. The schools had no standard curriculum, and the training was deficient with didactic lectures and little opportunity for the students to participate in patient care (8). The curriculum was completed in just 16 weeks a year with courses repeated over a 3-year program. The early 19th century American attitude of Jacksonian antiliterism resulted in the repeal of all medical licensure requirements in every state of the union. There were no requirements to qualify for the practice of medicine, and a rapid decline in the quality of American medical education and the American practitioner followed.

In response to this deterioration of medical practice, Nathan Smith Davis organized in 1846 a convention to establish a national medical organization to improve medical education. This response to the gross unprofessionalism in American medicine was the beginning of the AMA. Isaac Hayes recommended a second convention to meet the following year in Philadelphia to develop excellence in medical training and establish a code of ethics. This convention was successful in adopting a code of ethics modeled on Thomas Percival’s Medical Ethics and the writings of the American physician, medical educator, and founding father, Benjamin Rush (9). It became the first official code of ethics for any professional organization. Reform in medical education itself would have to wait for the Flexner Report in 1910.

Before the Civil War, there were many types of medical care in America. These included homeopathy, hydropathy, electric medicine, and botanical healing. The AMA Code of Ethics was meant to exclude practitioners who did not have formal training in a recognized scientific school of medicine. The AMA hoped that by restricting ethical consultation to those trained at scientific-based medical schools, the code would become a weapon to drive the irregular practitioners (homeopaths) out of business. Homeopathy was popular in America, and the homeopaths frequently referred their patients to university physicians. They were an important source of income for many of the academic centers. In a very short period of time, there developed a conflict between practicing physicians and academic physicians over the clause in the code that restricted referrals from homeopathic physicians to members of the AMA (8).

In 1895, the University of Michigan had both a school of medicine and a school of homeopathy. Victor Vaughn, the dean, wanted to merge the schools to save money. In anticipation of objections, Vaughn wrote prominent physicians around the country to solicit their opinions. William Osler responded: “I concur in the suggestion. It is high time that the profession and the public were made aware of the fact that any system of
therapeutics does not embrace the whole scope of medicine and surgery. After all, the differences which, in matter of treatment, separate members of the rational school are not greater than those which separate some of us from our homeopathic brethren” (10). Osler expanded on this egalitarian attitude in his 1902 essay “Chauvinism in Medicine” (11). He stated that medicine is progressive because of its scientific basis and its eagerness for improvements. Medical practice is based on four principles: emancipation from priest craft, science, the Hippocratic oath, and the behavior of a gentleman.

Osler was leading a crusade to establish a scientific approach to patient care. It was the beginning of our current evidence-based medicine. If his recognition of the importance of science in medicine was visionary, his attitudes concerning physician behavior were deeply rooted in 19th century Victorian attitudes. If Thomas Percival and the AMA introduced ethics, decorum, and etiquette to American medicine, William Osler and the Johns Hopkins School of Medicine established scientific medicine in this country. When Johns Hopkins was founded, the English philosopher Thomas Henry Huxley gave the principal address on medical education, stressing that medicine was a branch of experimental physiology. Huxley made no reference to morals, religion, or ethical behavior, a deletion that was commented on in the Baltimore papers (12). Johns Hopkins was to shape a new conception of professional competence based on science.

**OSLER’S AND CURRENT VIEWS OF PHYSICIAN BEHAVIOR**

At the bedside, Osler’s attitude was one of noblesse oblige. In his biography of William Osler, Michael Bliss (12) related that Osler was described by his colleague, “Everyone loved the Chief. He was so warm, so friendly, so happy and charming, so funny, so interesting and interested that he enchanted everyone, from patients to his most senior colleagues.” But what was the bedside manner of this charming, compassionate, charismatic medical scientist? Bliss reported that he spent only a short time with private patients, coming in and out of the room quickly. While walking on the wards, he sometimes stopped to grasp the toes of a patient. Ward visits were an unusual combination of informality and dignity. The students imitated every Osler gesture: his walk, his expression, and his accents.

Until the 19th century, it was the character and behavior of the physician that convinced patients to have confidence. Osler and Hopkins changed that; good science became the preeminent requirement. Although he stressed good behavior, he accepted as a given that physicians fit the mold of a Victorian gentleman. Our concepts of a gentleman have changed with our culture. In Shakespeare’s time, a gentleman was a member of the aristocracy, but Osler’s gentleman was the Victorian man of breeding and education, which placed the physician on an elevated pedestal of superior rank. Today, I think it would be difficult to define Sir William Osler’s physician gentleman. If art reflects reality, we have progressed from the kindly, compassionate Dr. Marcus Welby of the 1970s TV series to the arrogant, self-absorbed, rude, and even hostile Dr. Gregory House of the current TV series *House*. This is an individual who places science above any consideration of compassion and empathy.

Abraham Verghese, one of those senior medical professors who has been concerned about a loss of the art of medicine, addressed the importance of bedside manners in a scene from his book, *Cutting for Stone* (13). A case was presented at grand rounds where a young man died with a critical emergency. After the housestaff presentation of the case, the surgical professor at the Boston Mecca Hospital stood to read a letter he had received from the patient’s mother. The mother wrote that when her son’s condition became critical, she was quickly escorted from the room. As she left, she noted how anxious and afraid her son appeared. She described the doctor’s lone concern as preparing the patient for surgery; only a nurse held the patient’s hand and provided comfort. The professor asked the students and residents what should be the most important responsibility of the surgeon in this situation. No one had an answer except the book’s hero, who had read the professor’s textbook. He responded that the surgeon should whisper words of comfort into the patient’s ear. The story is noteworthy because Verghese recognized that the humanity of the patient is often forgotten and only his disease is considered. It is also incredible that I cannot remember in the past 30 years when the feelings of a patient or the family were seriously discussed at a medical conference.

Another example deserves mention, the movie *50/50* (14). This is a true story written by a Will Reiser, a cancer survivor. After completing Will’s evaluation, the oncologist sat down with him to describe his computed tomography scan. The physician started by describing a large tumor on his spine without first preparing him for this devastating diagnosis. Later when Will underwent a complex surgical procedure, the surgeon met the family postoperatively and began with a discussion of the surgical problems she faced before letting the family know that Will was doing well and had a good outcome.

Atul Gawande, an observer of medical behavior and practice, commented:

> It is unsettling how little it takes to defeat success in medicine. You come as a professional equipped with expertise and technology. You do not imagine that a mere matter of etiquette could foil you. But the social dimension turns out to be as essential as the scientific matter of how casual you should be, how formal, how reticent, how forthright. Also how apologetic, how self confident, how money minded. In this work against sickness, we begin not with genetic or cellular interactions but with human ones (15).

Osler was the prophet and communicator who brought the importance of scientific medicine to the practicing physician. But his was a generation of noblesse oblige, a generation where it was expected that honorable and generous behavior was the characteristic of rank and education. By not encouraging the teaching of the art of medicine, and by not including a guide to physician behavior in his textbook, he contributed to the slide down that slippery slope of professional behavior to misconduct, offense, and occasional outrage.
10. Osler W. Letter from the historical archives of the University of Michigan.
Sir William Osler’s speech at Troy: a Trojan horse?

Michael E. Moran, MD

Troy, New York, is a city of 55,000 people in upstate New York located along the Hudson River. A city of surprisingly rich cultural heritage, it was the home of New York state’s first hospital outside New York City. The 50th anniversary celebration of Troy’s hospital brought William Osler to the city as the keynote speaker. This speech, delivered on November 28, 1900, is one of Sir William’s less well known addresses. Osler began his comments with Sir Thomas More’s *Utopia* and talked at length about the hospital, its obligations, the influences it has upon the community, and the role of physicians and surgeons. He broached one of his old saws, the salary of attending physicians and their needed role in hospital management. His words were published in the diamond jubilee’s records, but the hospital did not outlive its prominent guest professor, and it closed its doors in 1914. Just like the great historical city of Troy, New York’s own Troy was on the brink of decline, and its hospital would be the first fatality. Therefore, it is almost prescient that the words of Osler, taken into historical context juxtaposed against the socioeconomic forces at work, are akin to the Greek’s offering of a wooden edifice to end the Trojan War.

At the crossroads of development of the modern image of America lie the metaphoric ruins of cities, towns, industries, and relics such as the Erie Canal, which represented the ideals of this new nation. One such city is Troy, New York, which developed, prospered, and declined as America developed. America’s medical profession likewise has followed an evolutionary pathway similar in many aspects to the rise and fall of its cities. A curious coupling of medicine, medical education, hospitals, and health care provides a backdrop for review of one of the 19th and early 20th centuries’ giants of medicine, Sir William Osler. His opinions from a little known address given on November 28, 1900, in Troy, New York, form the basis of this treatise. His talk was given on the occasion of the golden jubilee of the Old Troy Hospital but also serves as a metaphor, or perhaps more precisely an allegory, of the Trojan horse of Homer’s *Iliad*. The wooden horse was a Greek trick to seduce the Trojans into accepting a hidden invading army into the city’s midst. Though Osler was invited into the confines of the Old Troy Hospital as a visiting dignitary, the downfall of the hospital was indeed imminent, and his choice of material for his talk is hauntingly prophetic, starting with Thomas More’s *Utopia* and linking the hospital to the financial success of the community. William Osler was then the chief of medicine at the Johns Hopkins, sole author of the *Principles and Practice of Medicine*, and the star of modern American medical education; he was at his zenith and much in demand as a speaker (1).

THE CITY OF TROY

Troy, New York, is a bustling city in upstate New York on the shores of the Hudson River and its confluence with the Mohawk. Troy’s history has a remarkable cultural heritage. The foundations of the city are linked to the early colonization of the New England region. The first settlers were Dutch, followed by the English. In 1609, Henry Hudson found the mouth of the river that is now named in his honor. He sailed up the Hudson River on the *Half Moon* and by September 1609 was forced by sandbars to stop at the northward boundary that is now the city of Albany. Lubbert Gijsbertsz established the first colony, then called “Lubbert’s Land,” in 1634. Between 1656 and 1663, 18 Dutch families were living and thriving in this area called Fort Orange, later to be Albany, New York. The village of van der Heyden prospered, and in January 1789 the residents met at Stephen Ashley’s tavern to discuss the future of the town. In records recovered and on display in Troy’s library, the freeholders of van der Heyden met to establish a name for the town that they felt could be a modern metropolis (2).

A majority of voices, it was confirmed, that in the future, it should be called and known by the name of TROY. From its present improved state, and the more pleasing prospects of its mercantile line, it may not be too sanguine to expect, at no very distant period, to see Troy, as famous as her trade and navigation as many of our first towns.

With these words, the people of Troy expressed enthusiasm at the future prospects of their fair city. By the late 18th century,
Troy was beginning to rise in prominence in early America as an industrial center. Hannah Lord Montague in 1794 developed a detachable collar. By the early 19th century, removable collars became the height of gentlemen’s fashion in the United States and the world. Troy, New York, was the center of the manufacture of these collars, and it received the nickname “the Collar City.” The War of 1812 created a need for rations for troops, which were encamped throughout upstate New York. Troy’s Sam Wilson, nicknamed Uncle Sam by locals and family, was a meat packer who rose to his patriotic duty to provide much-needed rations for these troops. Soldiers garrisoned in upstate New York knew of him and began calling rations stamped with “U.S.” as coming from Uncle Sam. The popular myth spread rapidly and was culminated by the political cartoonist, Thomas Nast, in his image of Uncle Sam. Troy, New York, was poised on the forefront of early American greatness (2).

What made Troy, New York, such an early American success? This can be traced to many factors, including its location on the upper Hudson River at the confluence of the Mohawk River. Shipping provided an early inexpensive method for transportation throughout New York, and the location of the Hudson River along the northeast passageway down to New York City, connecting it to the natural resources of the Adirondack region of upper New York, came to serve this purpose. Labor was readily available from a large influx of immigrants, primarily coming into the New York City region, especially the Irish. The Adirondack region provided a wealth of resources, including iron, coal, and endless supplies of wood. Finally, the hills around Troy had numerous waterfalls for early hydroelectric power development.

The final key to the success of Troy’s early American legacy was the proposed construction of the Erie Canal in 1724. The early proponents intended to connect the Hudson River to Lake Erie and provide cheap water access from New York City in the Atlantic Ocean to the inner hub of early America. Almost a century later, “the great canal bill” was proposed to Congress in 1817. The canal was opened in October 1823 with huge celebrations, particularly in Troy, New York. The Watervliet lock on the Erie Canal was considered an engineering wonder of its time. This canal was championed by New York’s first governor, Dewitt Clinton, and was often referred to in the early 19th century as “Clinton’s Ditch.” The canal was 340 miles long and 4 feet deep with 82 locks. It influenced the country’s early economy, and in particular New York’s vastly expanding financial hold in the early United States (2).

THE OLD TROY HOSPITAL

By 1845, the influx of immigrant labor and the rise of early industrial establishments, particularly factories, allowed for the development of overcrowded, squalorly conditions. This in turn resulted in epidemic outbreaks of smallpox, yellow fever, cholera, and typhoid fever (3). The community responded by 1845: the Sisters of Charity of St. Vincent de Paul moved to form a hospital that they felt was necessary for the success of the burgeoning community at Troy. The hospital was initially designed by Markus P. Cummings with a French II empire architecture.

The first hospital was hastily constructed, but the primary hospital was located at 8th Street and Fulton. The cornerstone of the future hospital was placed by the Right Reverend J. J. Conroy, Bishop of Albany, on June 28, 1868. The Troy Hospital became the first full-service hospital outside of New York City (3).

The hospital was clearly linked to its surrounding community, and its style and full-service concept reflected the bright industrious people from the town of Troy. Most notable was Henry Burden, who was an industrialist, innovator, and inventor of early American manufacturing. He was intimately associated and linked with the Rensselaer Polytechnic Institute, which graduated the future entrepreneurial engineer of the Chicago World Fair, George W. G. Ferris, in 1881. Troy was also the backdrop for Clement Moore, a New York City minister, who upon visiting Troy read “A Visit from St. Nicholas” and published it in the Troy Record on December 3, 1823. This piece would later become more fondly known as “Twas the Night Before Christmas.” The stove industry reached its zenith with 17 foundries and $2.8 million in revenue by 1821. One manufacturing plant, the Meanly Bells Company, produced over 50,000 church bells. Corning Winslow and Company obtained a contract to construct the iron cladding for the U.S.S Monitor and proceeded to do this in less than 100 days. The end of the Civil War, however, was linked clearly with the beginning of the end of Troy’s early American success story (2).

The hospital in Troy attracted several physicians of note. Dr. John Thorn was the first appointed physician. Thorn trained in England, was one of early Troy’s most famous residents, and was twice elected mayor. At the end of the Civil War, the growth of Troy and two fires at the old hospital site resulted in plans for a new and larger hospital, which was located at Fulton and 8th Streets. The new Old Troy Hospital was completed in the fall of 1871 in the “Grant style” of building and attracted young, newly minted physicians to the upgraded facility that was thought to be on the leading edge of health care in the U.S. The Sisters of Charity were justly proud of their efforts and meticulously recorded their accounts, daily activities, and photographic archives. In 1895 the hospital added a “special operating room suite” and began a nursing school (3).

SURVEYING OSLER’S COMMENTS AT TROY HOSPITAL’S GOLDEN JUBILEE

Troy’s reputation at this time carried more luster than the town held during Osler’s visit. By the time of the golden jubilee of Old Troy Hospital, there was a significant feeling of an impending depression. Osler’s lecture (Figure 1) emphasized the hospital’s link to its community; these comments were fortuitous, as the ties binding the medical staff to the hospital and to the town cannot be fully appreciated except in retrospect. Both the town and the hospital would fall before a score of years passed.

Osler commenced his comments with remarks from Thomas More’s Utopia: “But first and chiefly of all, respect is had to the sick, that be cured in the hospitals” (4). This was the key element of his talk; it formed the foundation for which he would go on to speak throughout his address, and it tied the city’s future to
that of the hospital and its community. He switched in his next statements to the idea of the Good Samaritan, “not so the problem of the sick, poor, which charity answers with the smile.” Osler proceeded to his main theme: “The hospital centers all that is best and highest in the profession of medicine. . . . In it . . . we doctors live and move and have our beginnings.”

This address represents a classic Oslerian oration. He began with a theme from a classical author, in this case Sir Thomas More and *Utopia* (5). Osler next moved into his “old saw” about the ability of good men in medicine to contribute greatly. Neither Osler nor his audience were fully aware of the financial peril that both the city and the hospital were facing. This was particularly eerie in light of his choice of *Utopia*. In *Utopia*, More painted the picture of a community no longer scrapped by financial considerations. The hospital was the primary reference in his work, where he poignantly referred to man’s potential greatness, especially when removed from financial considerations (4).

The 1902 annual report of the Troy Hospital (Figure 2) commented, “After this pleasing picture, it is with reluctance that we refer to our deficit for current expenses and a number of requirements, which are absolutely needed for future demands.” Expenditures and indebtedness of the hospital stood then at a staggering $72,700 (6). The town of Troy had only one remaining active foundry at the time of Osler’s visit. Manufacturing had left the area for the upstart communities of Pittsburgh and Chicago. Waves of labor strikes had taken their toll on the once thriving city of Troy. Medicine and medical education were also crossing the Hudson River; the downfall of Troy’s medical practice became a blessing for the rising Albany Medical College.

The Old Troy Hospital is now West Hall at Rensselaer Polytechnic Institute (6) (Figure 3). It no longer serves the “sick” of the community, and like long ago Troy, it is now a legacy of the past. It is supposedly haunted by Betsy the ghost, who roams the first two floors only (7). This is intriguing since these were two active floors of patient wards during the heyday of the Old Troy Hospital; the third floor housed the women’s ward. Osler stated early in his address that “society is built upon a tripod—the schoolhouse, the hospital, and the jail” (4). Could he have known that the Old Troy Hospital would fail in its service to the sick and then become a schoolhouse? This is improbable given the enthusiastic and upbeat nature of his address at the time of the golden jubilee.

We can only speculate what brought the central figure of early American medicine to the city of Troy to give this golden jubilee address. Osler made several comments regarding specific physicians during his talk, especially the hospital’s pathologists and surgeons. Troy had become a center for training of surgeons, especially the orthopedists and the laryngologists (3). Osler specifically alluded to their contributions to medicine, particularly training resident physicians (4).

**CONCLUSION**

At the January 5, 1789, foundation, the fathers of Troy, New York, felt that the naming of their fair city, Troy, would bring great commerce to their town. In fact, Troy did become a center of early American manufacturing and trade. But for Troy, New York, the era had come and gone by the golden jubilee of the Old Troy Hospital. As evidenced in the hospital’s annual report, deep financial concerns were gathering.

It is impossible when reading these interactions from a less hectic medical past not to find similarities between Osler’s address and the Trojan horse. In the New York Troy, the Greeks were not the cause of the downfall, but a rapidly changing America. Almost poignantly, we can conclude with Sir Thomas More’s quote: “For where money beareth all the swing, there
many vain and superfluous occupations must needs be used, to serve only for riotous superfluity and unhonest pleasure” (5).


Reader comments

T.R., J.F.K., and 50-mile hikes


“The Strenuous Life” was a speech given by Theodore Roosevelt in Chicago in 1899. He argued that strenuous effort and overcoming personal hardships were ideals to be embraced by Americans. As a youngster, Roosevelt was sickly and asthmatic and was compelled by his father to take up boxing, a practice he continued for years along with tennis, hiking, rowing, polo, and horseback riding.

Much later, in 1960, President-Elect John F. Kennedy published an article entitled “The Soft American” in Sports Illustrated. He was alarmed at the decline of physical fitness among American youth, who lagged far behind Europeans at the time. (Before this, President Eisenhower had created a Council on Youth Fitness in 1956.)

As president, Kennedy had a particular interest in the fitness of the military, and in February 1963, the White House discovered a 1908 executive order from Theodore Roosevelt that all Marines should be able to cover 50 miles in 3 days. The records showed that some officers in 1908 had covered the distance in 1 day. A challenge was made to the commandant of the Marines, General David Shoup, to see if the 1963 Marine Corps officers were as fit as those of 1908. General Shoup ordered the Marine officers at Camp Lejeune, North Carolina, to prepare for a 50-mile march with a standard of completion of 20 hours. On February 12, 1963, 34 officers marched all day wearing helmets, pistols, and a 25-pound pack. The fastest time was 9 hours and 53 minutes by a Marine who was a long-distance runner and completed the march half running and half walking.

The 50-mile hike became a national craze as the public took to the streets in record numbers. But after Kennedy’s assassination in November 1963, the movement disappeared quickly. However, one individual, Buzz Sawyer of Hagerstown, Maryland, kept the spirit alive by organizing the JFK 50-Mile Memorial in 1964.

The JFK 50-mile race is the oldest ultramarathon run in the United States and is always held in Washington County, Maryland, on the Saturday before Thanksgiving. Around 1000 runners return every year for this grueling event, which starts in Boonsboro, Maryland, goes up South Mountain to the Appalachian Trail for 13 miles, moves down to Harpers Ferry, and then proceeds 26 miles along the Chesapeake and Ohio Canal Towpath before finishing in Williamsport, Maryland, with a time limit of 14 hours.

Years ago, I became fascinated by this race, especially since my Confederate grandfather had been wounded in the Battle of South Mountain, near the race course. I was fortunate to have finished four separate JFK 50 ultramarathons years ago. The event was my favorite and brings back great memories.

Why would anyone attempt to run 50 miles? Aside from the personal satisfaction of achievement, the usually cited possible benefits of long-distance running include improved cardiovascular fitness, weight loss, social camaraderie, and mental effects. The ultramarathon is different than regular marathons, with frequent walking and rest breaks and use of new muscles, with a goal of simply finishing rather than setting a record time. It is a unique challenge and adventure.

—S. Robert Lathan, MD
Atlanta, Georgia

January 2012
Baylor Health Care System deploys AT&T Healthcare Community Online

Baylor Health Care System (BHCS) is one of the first hospital systems in Texas to create an enterprise health information exchange (HIE) to improve access to patient information across the community of care. Baylor is deploying AT&T Healthcare Community Online to help more than 4000 physicians on the medical staffs at Baylor facilities exchange patient information and share applications in a highly secure manner.

“When patients go to different Baylor locations, they expect us to know them and recognize their information. Physicians need the right information at the right time, not only in their offices and facilities, but also from home or in the car,” said David Muntz, senior vice president and chief information officer of BHCS.

In fiscal year 2010, Baylor recorded more than 2.6 million patient encounters. Baylor’s network has more than 250 access points, including 26 hospitals, 23 joint-ventured ambulatory surgical centers, 50 satellite outpatient locations, four senior centers, and 156 HealthTexas Provider Network physician clinics. AT&T will work with Baylor to create a marketing outreach program to promote physician adoption of the HIE solution.

“Baylor is focused on honoring the sacred trust between a doctor and patient, and our networks are designed to share and protect critical information,” said Xavier Williams, senior vice president, public sector and health care at AT&T.

With AT&T Healthcare Community Online, physicians can
- Exchange information such as patient profiles, medical history, and prescriptions
- Improve workflow efficiency and streamline processes associated with physician orders and referrals, lab orders and results, medications, and discharge planning
- Locate millions of patient records
- Analyze patient information and help bring evidence-based information to the point of care
- Integrate with existing practice management systems in their offices
- Send clinical messages among health care providers
- Access 58 important applications such as dictation, claims, and eligibility

The Joint Commission names five Baylor hospitals as “Top Performers on Key Quality Measures”

Five Baylor hospitals are recognized as “Top Performers on Key Quality Measures” in the Joint Commission’s 2011 annual report on quality and safety, Improving America’s Hospitals. They are:
- Baylor Jack and Jane Hamilton Heart and Vascular Hospital
- The Heart Hospital Baylor Plano
- Baylor Medical Center at Garland
- Baylor Regional Medical Center at Grapevine
- Baylor Regional Medical Center at Plano

These five hospitals are among 405 organizations identified as attaining and sustaining excellence in accountability measure performance for 2010 and represent approximately 14% of Joint Commission–accredited hospitals and critical access hospitals that report core measure performance data. The Top Performers on Key Quality Measures program is designed to inspire better performance on 22 accountability measures for heart attack, heart failure, pneumonia, surgical care, and children’s asthma care.

The Heart Hospital Baylor Plano and Baylor Jack and Jane Hamilton Heart and Vascular Hospital win Press Ganey Summit Awards

The Heart Hospital Baylor Plano has achieved a milestone few other hospitals can claim. It is one of only 87 recipients of the 2011 Summit Award in two areas—emergency department and inpatient satisfaction—in the all Press Ganey database. Baylor Jack and Jane Hamilton Heart and Vascular Hospital also achieved the Summit Award for inpatient satisfaction. The Summit Award is one of Press Ganey’s most prestigious awards, honoring hospitals that sustain an overall rank above the 95th percentile for at least the past 3 consecutive years. There are approximately 1800 hospitals in the inpatient survey database and about 1500 emergency departments in the all Press Ganey database.

Baylor Jack and Jane Hamilton Heart and Vascular Center and The Heart Hospital Baylor Plano were also included on the most recent list of Becker’s Hospital Review’s “50 Physician-Owned Hospitals to Know,” which recognizes high-performing leaders in patient care and clinical quality.

Baylor collaborates with other top health care organizations to improve health care, lower costs

BHCS has joined the Mayo Clinic, Cleveland Clinic, and other top national health care organizations as a member of the High Value Healthcare Collaborative (HVHC). Members of the HVHC share critical information and resources, such as outcomes data, care pathways,

ACCOLADES

F. David Winter, MD, has been named president of HealthTexas Provider Network. He will also continue in his role as chairman and chief clinical officer. Dr. Winter has been a board-certified practicing physician for over 30 years and has been affiliated with BHCS since the mid 1970s.

The American Medical Group Association recognized HealthTexas Provider Network as an Acclaim Award Honoree at their September 2011 Institute for Quality Leadership annual conference. The Acclaim Award honors organizations that embrace the Institute of Medicine’s aims by incorporating the six attributes of an ideal health care delivery system as identified by the Commonwealth Fund Commission. HealthTexas Provider Network was recognized for its “transforming healthcare delivery through patient-centered care” initiative, which centers on its strategy of clinical transformation—a commitment to continually improve the quality of patient care through the redesign of key clinical processes.

Emily Hebert, MD, received the 2011 Texas Medical Association Anson Jones, MD, Award in the Physician Excellence in Reporting category for her work as the medical expert on the local ABC television affiliate, WFAA Channel 8. This marks the third consecutive year that a BHCS physician has received this award.
and costs, as they adopt best practices and expanded measurement standards. The goal of the collaboration is to improve quality of care while lowering health care costs. Baylor’s strong research-based quality improvement program, advanced health information technology, solid financial and operational resources, committed staff, and history of working with other institutions are reasons Baylor was invited to join the collaborative.

### Baylor Quality Alliance formation making progress

BHCS is making progress forming the Baylor Quality Alliance (BQA). First announced in July 2011, the goal of BQA is to improve health care access and delivery while lowering costs for both patients and providers. Currently, the innovative alliance is forming six committees focusing on various aspects of providing health care: best care/clinical integration, membership and standards, finance and contracting, compliance, population management, and information technology. These committees will include both independent and HealthTexas Provider Network physicians. Besides recruiting for these committees,
developing the legal and operational structure of BQA also is well under way. BQA is a key step for Baylor becoming an accountable care system, which is part of Vision 2015—Baylor’s path to becoming consistently recognized as a “Top 5” health care system in the country. In addition, BQA complements Baylor’s patient-centered medical homes initiative, which enhances quality of care while reducing costs by developing better ways to care for patients when they are not in a physician’s office or a Baylor hospital.

Baylor Charles A. Sammons Cancer Center joins Multiple Myeloma Consortium
Baylor Charles A. Sammons Cancer Center at Dallas is now a member of the Multiple Myeloma Research Consortium (MMRC). The MMRC is an early stage drug development consortium comprising 16 world-renowned research institutions from across the country, including City of Hope, Dana-Farber Cancer Institute, H. Lee Moffitt Cancer Center and Research Institute, Mayo Clinic, and Mount Sinai School of Medicine. Since its inception in 2004, the MMRC has partnered with pharmaceutical and academic sponsors to facilitate 19 phase I and phase II clinical trials

PHILANTHROPY NOTES

Baylor receives $12 million pledge to benefit geriatric patients
BHCS Foundation is proud to announce that the Deerbrook Charitable Trust has pledged more than $12.4 million over the next 3 years to improve care for geriatric patients. Deerbrook has a strong interest in advancing care for the elderly. The trust approached the BHCS Foundation with the seed of an idea and called upon Baylor to strategically plan, develop, and execute programs that advance the field of geriatric care.

Rosemary Luquire, PhD, RN, FAAN, NEA-BC, corporate chief nursing officer at Baylor, worked with Cynthia Krause, vice president at the foundation, to forge a collaborative effort among Deerbrook representatives, Baylor clinical leaders, and foundation employees. This team took this vision and created several innovative new programs.

This extraordinary commitment will help advance elder care in many ways. It will allow Baylor to 1) create specialized geriatric nursing education programs; 2) refine a comprehensive volunteer program for hospitalized older patients; 3) create education and best-practice partnerships with skilled nursing homes; 4) create a consortium with regional geriatric experts in nursing universities throughout North Texas; and 5) assess risks for chronically ill patients and refine a transitional care model to reduce their hospital readmissions and emergency room visits.

The findings from these initiatives will be presented in research publications that could improve care for geriatric patients. Baylor will freely disseminate best practices, educational programs, and teaching tools developed from these programs with nursing schools, health care organizations, and virtual centers of learning throughout the country.

Celebrating Women raises $2 million, offers promise of hope to breast cancer patients
BHCS Foundation hosted its 12th annual Celebrating Women luncheon in October at the Hilton Anatole hotel in Dallas. The event, presented for the seventh consecutive year by Tom Thumb, raised more than $2 million to benefit BHCS’s fight against breast cancer.

The event, chaired by Fredye Factor and Sarah Losinger, recognized the Ernestine and Bradley Wayne Family with the Circle of Care Award. The award is given to those who have served as advocates, volunteers, educators, or donors and have made a difference in the campaign against breast cancer. The Joan and Andy Horner Family served as this year’s honorary chairmen. Kimber Hartmann, Angie Kadesky, Daffan Nettle, Cathy Coughlin, and Sophia R. Johnson were this year’s underwriting chairmen.

Featured speaker, award-winning actress and breast cancer survivor Diannah Carroll, charmed the audience of more than 1200 with stories about her illustrious career and struggle with breast cancer.

Funds raised at this year’s Celebrating Women luncheon will be used to create a Celebrating Women Education Fund, which will support the training of the next generation of nurses, oncologists, and breast surgeons at Baylor University Medical Center at Dallas. Over the last 12 years, Celebrating Women has raised more than $18 million for the fight against breast cancer at Baylor. These gifts have been focused in four main areas: research, capital and technology, patient-centered programs, and the education of medical leaders.

Participants in diabetes fun run/walk stick it to diabetes
Runners and walkers, including professional basketball player Corey Brewer, took to the streets of South Dallas in October for the second annual Diabetes Health and Wellness Institute Fun Walk/5K Run. The event, presented by MedAssets, had 850 registrants and raised nearly $135,000.

The institute, which opened last year, is the area’s first and only diabetes health and wellness facility addressing the region’s health care needs relative to diabetes. A public/private partnership between BHCS and the City of Dallas, the institute uniquely focuses on prevention, wellness, and improving the overall health of the South Dallas community. Residents in South Dallas have a higher incidence of diabetes, more complications from the disease, and a 17% higher rate of related hospitalization than those living anywhere else in Dallas County.

The institute offers a clinic staffed by physicians, nurses, care coordinators, and diabetes education specialists. It also offers cooking and exercise classes, affordable medications, and other medical supplies, as well as a farmers market selling fresh foods.

Grand Rounds generates record amount for graduate medical education
More than 200 golfers helped BHCS Foundation raise $290,000 to support graduate medical education programs at Baylor University Medical Center at Dallas by playing in the 10th annual Grand Rounds Golf Tournament, presented by Bank of Texas.

Following the day’s rounds, players enjoyed dinner and a golf talk with guest speaker Hank Haney. Hank, recognized worldwide as one of the foremost authorities on the game of golf, has had the pleasure of teaching the best golfer in the world, Tiger Woods, and one of the worst, Charles Barkley.
involving novel treatment strategies aimed at high-priority targets. This unique capability will enable participation in and initiation of new treatment approaches for this disease. In addition, the MMRC will facilitate studies in the tumor immunology and immunotherapy of myeloma within Baylor Institute for Immunology Research and Baylor Sammons Cancer Center.

Baylor Institute for Rehabilitation outpatient services opens new clinic in Rockwall

Baylor Institute for Rehabilitation has opened its newest outpatient services clinic at 810 East Ralph Hall Parkway, Suite 170, in Rockwall, Texas. This new location offers physical therapy services for individuals with orthopedic and musculoskeletal conditions and sports- and work-related injuries, as well as specialized programs for spine care and balance and vestibular disorders. Individualized treatment options include joint mobilizations and manipulation, soft tissue release and massage, and kinesiotaping. The new Rockwall clinic joins a network of more than 30 Baylor Institute for Rehabilitation outpatient services locations in the greater North Texas region.

The Heart Hospital Baylor Plano first in Texas to implement Odyssey Cinema Studio and Epoch platforms

The Heart Hospital Baylor Plano recently implemented the Odyssey Cinema Studio and the Epoch platform to enhance interventional cardiology and electrophysiology services. Odyssey Cinema Studio is a fully integrated, real-time information management system that promotes online education and collaboration by allowing physicians to remotely access live and recorded procedure data across the hospital system and around the world. The Epoch platform for the hospital’s robotic ablation system (Niobe) is an advanced computer controlled technology that allows physicians to navigate within the patient’s heart with robotic precision. With technologically advanced magnetic navigation, Epoch allows electrophysiologists to provide faster, more efficient, quality magnetic catheter control for cardiac ablation procedures for the treatment of complex cardiac arrhythmias.

Baylor Sammons Cancer Center turns green design into LEED Gold

The new Baylor Charles A. Sammons Cancer Center at Dallas is no longer just recognized for its advanced approach to fighting cancer. It is now being recognized for an advanced approach to sustaining the environment. On November 7, 2011, the Baylor Sammons Cancer Center was awarded the Leadership in Energy and Environmental Design Core and Shell 2.0 (LEED CS 2.0) Gold Certification—an environmental certification few projects of its size and scope can claim. The Baylor Sammons Cancer Center, which opened in March, is 14% more energy efficient than energy code minimums require, and 30% more efficient in its water usage than code minimums. Additionally, 70% of the building energy usage is carbon offset.

In addition, the Heart Hospital Baylor Plano performed its first robotic-assisted thoracic surgery on November 11, 2011, and is the first cardiovascular specialty hospital in North Texas to specialize in the minimally invasive da Vinci Surgical System for cardiovascular and thoracic procedures.
Primary cutaneous angiosarcoma of the breast after breast trauma

Ying Cao, MD, PhD, Laura Panos, MS, CGC, Robbie L. Graham, MD, Thornwell H. Parker III, MD, and Robert Mennel, MD

Primary angiosarcoma of the breast is a rare malignant tumor. We report a case of breast primary cutaneous angiosarcoma in a patient with a strong family history of malignancy. For definitive diagnosis, a tissue biopsy is needed, with immunostaining for the presence of blood vessel endothelial markers CD31 and CD34. Total mastectomy is the preferred method of surgical treatment. Chemotherapy has not been shown to increase overall survival, but in some instances it may improve local control and disease-free survival. Surgery combined with radiation may increase local control, but patients at high risk of recurrence may benefit from adjuvant treatment as well. We discuss the potential benefits from various treatments for primary cutaneous breast angiosarcoma.

Angiosarcoma of the breast is a very rare malignant tumor, with few patients surviving long term (1). It may occur as a primary tumor, as a complication of radiation therapy after breast conservation, or during pregnancy (2–4). True primary angiosarcomas account for <0.04% of malignant breast neoplasms (5), and primary angiosarcomas of the breast have a reported incidence of 17 new cases per million women (6). We describe a case of primary cutaneous angiosarcoma of the breast in a patient with a family history of malignancy.

CASE REPORT

A 54-year-old Caucasian woman visited her dermatologist with complaints of a "rash" on her breast present for approximately 3 months. She was referred for biopsy, which revealed cutaneous angiosarcoma. She presented to our office with complaints of thickened, purple discoloration located around the 4:00 position on the right breast (Figure 1). The patient's history was unremarkable except for a history of breast implants along with a record of several breast surgeries, most recently in 2006, for correction of fibrotic capsulation around the implant. She also had trauma to her right breast following a skiing accident about 4 to 5 months before presentation. A punch biopsy showed findings suggestive of chronic inflammation and malignancy. Magnetic resonance imaging (MRI) of the breast revealed hematoma associated with skin thickening. A second punch biopsy of the lesion revealed an atypical intradermal vascular proliferation suspicious for malignancy.

A full-thickness skin biopsy was then performed. Histologically, the tumor consisted of nodules of vascular proliferation with atypical spindle cells in a cuff-like appearance (Figure 2a). The neoplastic cells showed moderate to focally marked pleomorphic nuclei, a high mitotic index, and an overall infiltrative pattern. Immunostaining indicated that these cells strongly expressed CD34 (Figure 2b) and CD31 (not shown) but did not express HHV8. These findings led to a diagnosis of angiosarcoma.

The patient had a negative metastatic workup (complete blood count, complete metabolic profile and computed tomography scan). She then received a right mastectomy. The pathology of the tumor revealed a grade 2 (7) tumor 4.5 cm in diameter. The patient is currently undergoing adjuvant chemotherapy with single-agent paclitaxel every 3 weeks.

She has a strong family history of malignancy. Her father died at the age of 64 of chronic leukemia, reportedly diagnosed from the Departments of Oncology (Cao, Panos, Mennel) and Pathology (Graham), Baylor Charles A. Sammons Cancer Center and Baylor University Medical Center at Dallas; and Skin Cancer Consultants, Dallas, Texas (Parker).

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angiosarcoma of the breast

DISCUSSION

Paternal aunt was diagnosed with breast cancer in her 60s. Lymphoma, initially diagnosed at the age of 43. In addition, her grandmother was 5.9 cm (5). Mammographic findings tend to be nonspecific in angiosarcoma cases, the mean tumor size of the mass at presentation is third of patients and is thought to be attributable to the vascular nature of the tumor (5). In a study of a series of 24 breast angiosarcoma cases, the mean tumor size of the mass at presentation was 5.9 cm (5). Mammographic findings tend to be nonspecific for angiosarcoma, while with ultrasound, angiosarcoma typically presents as a heterogeneous, hyperechoic, hypervascular mass (5). MRI is more likely to image an angiosarcoma; however, this was not true in our case. An MRI of angiosarcoma shows a heterogeneous mass with low signal intensity on T1-weighted images, but signal intensity is high in images that are heavily T2-weighted (5, 12). Although not definitive, MRI is useful in ascertaining the extent of the disease and in planning surgery. Positron emission tomography (PET) with 18F-fluorodeoxyglucose (FDG) may be used for staging of angiosarcoma (13). One case report showed focal, intense accumulation of FDG in angiosarcomas of the heart, with a standard uptake value of 7.5 (14).

A definitive preoperative diagnosis may be achieved with fine-needle aspiration cytology or a core needle biopsy (15). Immunohistochemical stains for epithelial markers (pancytokeratin), endothelial markers (CD34 and CD31), and other sarcoma markers are helpful in making the correct diagnosis (16). Rosen’s method for grading breast angiosarcoma correlates well with the clinical outcome, as a low grade is associated with a better outcome (7). His system is very similar to the French soft tissue sarcoma grading system, where various histologic aspects of the tumor are scored (tumor differentiation, mitotic count, tumor necrosis) and added together to give a final histologic grade (17). Rosen’s study gave estimated probabilities of disease-free survival of 5 years following initial treatment: stage I, 76%; stage II, 70%; and stage III, 15%. Our patient had stage II disease (7). Thus, prompt localization and identification of angiosarcoma is vital in the treatment of this disease.

Total mastectomy alone is the preferred method of surgical treatment (18). Sarcomas are less likely to spread to the lymph nodes, as Sher et al demonstrated (3). Sarcomas most commonly spread to the lung. In 31 cases of breast angiosarcoma, only two had lymph node invasion (3). Studies examining the efficacy of adjuvant chemotherapy are lacking, due in part to the low incidence of breast angiosarcomas. One retrospective study revealed that 36% of patients with primary angiosarcoma received chemotherapy in an adjuvant or neoadjuvant setting (7). Sher et al reported that adjuvant chemotherapy using an anthracycline and ifosfamide or gemcitabine and a taxane did not significantly improve recurrence-free survival compared with patients who did not receive chemotherapy (38 vs. 31 patients; hazard ratio, 0.47; P = 0.11). However, administration of chemotherapy at the time of recurrence resulted in a 48% response rate (3). In the case of secondary angiosarcomas induced by radiation treatment, docetaxel showed promise for treating secondary breast angiosarcomas that were refractory to anthracycline-based chemotherapy (19). Bevacizumab, the anti–vascular endothelial growth factor antibody, has been used as treatment for angiosarcomas to block blood vessel growth, but the results have been variable. Currently two phase II clinical trials are investigating the use of bevacizumab in cases of sarcoma, including angiosarcoma. The goal of the first trial, which has completed accrual, is to determine the effect of treatment with bevacizumab alone and to measure disease-free survival in patients with angiosarcoma (20). The second trial, which is still accruing patients, involves treatment with bevacizumab in combination with gemcitabine and docetaxel in patients with various sarcomas, including angiosarcoma (21). Once results of these studies are available, we may better know the effect of this adjuvant therapy in cases of primary breast angiosarcomas.

Figure 2. Histology of the grade II tumor. (a) Angiosarcoma stained with hematoxylin and eosin (original magnification 400×). (b) Angiosarcoma stained with antibody to CD34 (original magnification 400×).
For patients with sarcomas of the breast, it has been suggested that radiation therapy after surgical resection may have a beneficial effect on outcome, especially for patients with microscopically positive margins (18). There was no statistical correlation of adjuvant radiation therapy with survival in this study, due to the small number of patients and the retrospective nature of the study. But, patients at high risk of recurrence (with large, high-grade tumors) may benefit from adjuvant treatment with improved local control and disease-free survival (18). Adjuvant radiation therapy should be administered especially when the margins of resection are microscopically involved after definitive surgical treatment, such as in this case.

Li-Fraumeni syndrome

Li-Fraumeni syndrome (LFS) is a cancer predisposition syndrome associated with soft tissue sarcoma, osteosarcoma, premenopausal breast cancer, brain tumors, adrenocortical carcinoma, and a variety of other neoplasms (22). More than 70% of individuals diagnosed clinically have an identified disease-causing germline mutation in TP53, the only gene known to be associated with LFS (23).

Since our patient had a personal history of sarcoma, as well as a family history of brain tumors, leukemia, and lymphoma, she met with a genetic counselor to assess the possibility of LFS. Using sequencing and deletion/duplication studies, no mutation was found in her p53 gene. Based on the patient's family history of malignancy, there is likely a genetic predisposition to cancer. At this time, it is not known what gene(s) are contributing to this familial cancer risk.

Conclusion

Primary cutaneous angiosarcoma of the breast is a very rare disease. PET–computed tomography is useful for staging workup. Definitive diagnosis is based on pathology results. Total mastectomy is the preferred treatment. Although no clinical trial proves the benefit of adjuvant chemotherapy or radiation therapy, both therapies should be considered in patients at high risk of recurrence.

References

A 21-year-old African American woman presented to the emergency department with a 3-week history of heavy vaginal bleeding; she had experienced varying amounts of bleeding but never needed more than a pad per hour. She was known to be less than 12 weeks pregnant but was unsure of the date of her last menstrual period. She was gravida 3 and parity 2, with a spontaneous vaginal delivery approximately 5 years earlier and an “abdominal” (presumed ectopic) pregnancy removed by laparotomic surgery 5 months earlier at an outside institution. Other medical history included hypertension, depression, bipolar disorder, and surgery for a “hernia repair.” All laboratory values were within normal limits, and her human chorionic gonadotropin level was 8009 mIU/mL. Differential considerations at this time were threatened or spontaneous abortion and recurrence of ectopic pregnancy.

Upon transvaginal sonography, a bicornuate uterus was identified (Figure 1). No adnexal abnormalities were appreciated. Within the right cornua, a gestational sac, yolk sac, and fetal pole were identified and diagnosed as a cornual ectopic pregnancy (Figure 2). Fetal heart tones measured approximately 120 beats per minute. No appreciable myometrium surrounded the gestational sac (Figures 3 and 4). The left cornua demonstrated a thick endometrium, most likely related to hyperestrogenemia from a pregnant state, without any other abnormality.

**DIAGNOSIS:** Cornual ectopic pregnancy.

**DISCUSSION**

Ectopic pregnancy is one of the most common gynecologic abnormalities and emergencies that can afflict a potential mother. With ectopic pregnancy occurring in approximately 2% of all pregnancies, the myriad of locations have a hierarchy of prevalence as well as associated mortality and morbidity (1). The most common location for ectopic pregnancy continues to be the fallopian tubes (accounting for roughly 90% of all ectopic pregnancies), followed by the far less common interstitial pregnancies, which comprise 2% to 4% of extrauterine cavity pregnancies (2). While often the terms *interstitial* and *cornual* pregnancy are used interchangeably, there is a specific difference. Cornual pregnancy describes the presence of an eccentrically located gestational sac surrounded by a thin rim, specifically <5 mm of myometrium (2). The only semantic difference between the terms is that interstitial pregnancy refers to an ectopic location of the gestational sac in the intramyometrial segment of the fallopian tube in a normally configured uterus, while cornual pregnancy pertains to an ectopic location of the gestational sac in

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the intramyometrial segment of the fallopian tube in a bicornuate uterus (2).

Fortunately, interstitial and even less frequent cornual pregnancies (occurring in <1% of all ectopic pregnancies) are very rare, as the complications of these diagnoses can be grave. There is often a delay in diagnosis for interstitial pregnancies, as this segment of the fallopian tube has increased distensibility, leading to less pain. (Up to half of all ectopic pregnancies are asymptomatic to begin with.) Researchers have documented diagnosis being made as late as 16 weeks gestation (3). Timely diagnosis is essential, as rupture of these specific ectopic pregnancies can be life-threatening secondary to their close proximity to the cardinal vessels, specifically the uterine artery.

Radiographically, the finding most suggestive of interstitial pregnancy is what is known as the “interstitial line” sign, which represents an echogenic line that extends from the endometrial canal into the upper regions of the cornua and borders the margin of the intramural gestational sac. The interstitial line sign is more specific than sensitive, with 80% sensitivity and 98% specificity reported (2).

Another interesting finding in this patient is an associated urinary tract anomaly, which happens commonly with uterine configuration variants. The uterine bud and female genital tract arise from the mesonephric duct embryologically, and commonly with uterine duplication anomalies there can be urinary tract abnormalities such as renal agenesis, cystic dysplastic kidney, cross-fused renal ectopia, and duplicated collecting systems (4). Renal agenesis is the most common, and that is what our patient had, as evidenced by a prior nonenhanced computed tomography scan (4) (Figure 5).

While attempts can be made to treat some ectopic pregnancies medically with agents like methotrexate when the patient is hemodynamically stable and has a low risk of rupture, surgical intervention (usually reserved for rupture, as most ectopic pregnancies can be removed laparoscopically) is generally curative with little mortality if diagnosed in a timely fashion. Current data provide a 9% to 14% overall mortality rate for ectopic pregnancies, and that is the leading cause of death in the first trimester of pregnancy (3). Morbidity is relatively patient specific according to the location of the ectopic pregnancy, in that a patient may lose a fallopian tube or a horn of her uterus or may have to succumb to a total hysterectomy.

For cornual pregnancies, possible surgical considerations are cornuostomy (excision of the gestational sac out of the cornua while preserving myometrium), salpingectomy, imaging- or laparoscopic-guided injection of cytotoxic agents (etoposide, potassium chloride, etc.) into the affected cornua, or, what has become the standard treatment, cornual wedge resection by laparotomy (3).
The clinical course of our patient consisted of a minilaparotomy, which showed a bicornuate uterus with a right cornual pregnancy (Figure 6). Surgeons performed a wedge resection of the right cornual pregnancy with preservation of the left uterine horn in hopes of preserving fertility. She was discharged in stable condition on hospital day 2 with pain control and further follow-up as well as plans for long-term birth control until full healing could take place.

Acknowledgments

We thank Dr. Sharon Bakos for involving us in this case and for providing the intraoperative photos.

Hermansky-Pudlak syndrome complicated by pulmonary fibrosis

Brett W. Carter, MD

A 45-year-old woman from Puerto Rico presented to the emergency department with progressively worsening dyspnea over a 3- to 4-day period. She had been diagnosed with type 1 Hermansky-Pudlak syndrome complicated by pulmonary fibrosis 4 years earlier. Previous renal biopsy demonstrated nephrosclerosis secondary to Hermansky-Pudlak syndrome. A brother also had Hermansky-Pudlak syndrome complicated by pulmonary fibrosis. Despite receiving 6 L of oxygen via nasal cannula at home, her oxygen saturation had fallen to 80% to 85%. She was subsequently admitted to the intensive care unit and intubated. Broad-spectrum antibiotics were initiated for a presumptive diagnosis of pneumonia.

A chest radiograph obtained at the time of admission showed reticular opacities throughout the bilateral lungs (Figure 1). There was no evidence of consolidation. Contrast-enhanced chest computed tomography (CT) demonstrated extensive subpleural honeycombing, consistent with pulmonary fibrosis (Figures 2 and 3). Patchy ground-glass opacity was also present bilaterally. The patient had been scheduled for lung and kidney transplant but had fatal cardiac arrest in the intensive care unit and died.

DISCUSSION

Hermansky-Pudlak syndrome is a genetic disorder characterized by oculocutaneous albinism, platelet dysfunction, and accumulation of ceroid-lipofuscin, a lipid-protein complex, in lysosomes (1). The diagnosis is typically made by the presence of skin and hair hypopigmentation, characteristic ocular abnormalities, and the absence of dense bodies in platelets on microscopic evaluation. It is inherited in an autosomal recessive manner. Nine types of Hermansky-Pudlak syndrome have been described, most of which are associated with a mutation in the HPS gene on the long arm of chromosome 10. Most of the patients in whom the disorder has been identified and characterized are of Puerto Rican descent (2, 3).

The disease primarily affects the lungs, heart, gastrointestinal tract, and kidneys. Symptoms are predominantly related to pulmonary fibrosis, its major complication, and result from deposition of ceroid-lipofuscin within the lungs. The interalveolar septa are typically thickened by fibrous tissue (4). Patients with type 1 Hermansky-Pudlak syndrome due to a mutation in the HPS1 gene are more likely to develop pulmonary fibrosis and typically have lung disease of a greater severity than patients without this mutation. The prognosis is poor, and patients usually die from pulmonary fibrosis in the fourth to fifth decades of life.

Important preventive health measures include influenza and pneumococcal vaccinations and avoidance of cigarette smoke. Patients are typically treated with oxygen in an attempt to alleviate dyspnea. High-dose corticosteroids have not been shown to be effective. An antibiotic, pirfenidone, may slow the progression of pulmonary fibrosis but is effective only in patients with significant residual lung function. The only definitive treatment for pulmonary fibrosis related to Hermansky-Pudlak syndrome is lung transplantation, few cases of which have been successfully performed (5, 6).

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Chest radiographs may be normal in patients with Hermansky-Pudlak syndrome at the time of presentation. The most common abnormalities detected on radiography include reticular opacities, perihilar fibrosis, pleural thickening, and peribronchovascular opacities (6, 7). The predominant findings on high-resolution chest CT differ somewhat as the disease progresses. For instance, the most common abnormalities in cases of minimal severity include interlobular septal thickening, reticular opacities, ground-glass opacity, and subpleural honeycombing. In cases of moderate severity, reticular opacities and subpleural honeycombing are present to a greater extent than in cases of minimal severity. Additionally, a wider range of findings is typically present, including bronchiectasis, peribronchovascular thickening, and pleural thickening. Interlobular septal thickening is not a prominent feature, as in cases of minimal severity. In severe cases, subpleural honeycombing and bronchiectasis are more common than in cases of moderate severity. Subpleural reticular opacities, ground-glass opacity, and peribronchovascular thickening are also present. In general, these imaging findings predominantly occur within the periphery of the lung. As the disease progresses, the central portions of the lung become involved. Additionally, an atypical pattern has been described in which the peripheral lung is spared. Patients with greater severity of lung disease at the time of imaging typically have lower forced vital capacity on pulmonary function tests and decreased survival time compared with patients whose lung disease is less severe (6).

Presented is a patient with papillary tumor of the pineal region (PTPR), an uncommon and recently recognized neoplasm. As its name implies, PTPR does not arise from the pineal gland itself. The cell of origin is thought to be the specialized ependymocytes of the subcommissural organ. Primary tumors of the pineal region include pineal parenchymal neoplasms, germ cell neoplasms, and tumors arising from adjacent structures, including meningiomas, astrocytomas, and ependymomas. Like other masses in this location, PTPR often leads to obstructive hydrocephalus. Due to the relative paucity of reported cases of PTPR, its natural history is unknown.

A 32-year-old man presented with worsening headaches and visual disturbances of several months’ duration. Noncontrast computed tomography (CT) revealed a 1-cm mass near the posterior aspect of the third ventricle, which resulted in obstructive hydrocephalus. The third and lateral ventricles were enlarged (Figure 1).

Brain magnetic resonance imaging (MRI) was subsequently performed before and after intravenous administration of gadolinium contrast material. A precontrast sagittal T1-weighted image showed a mass in the region of the pineal gland, with a thin rim of intrinsic signal hyperintensity and enlargement of the third and lateral ventricles (Figure 2).

Postcontrast sagittal and axial T1-weighted images showed avid enhancement of this mass with no additional enhancing lesions (Figure 3). A third ventriculostomy was performed, and the mass was biopsied. Tissue sampling revealed histologic results consistent with PTPR.

Figure 1. CT of the brain showing a small mass in the region of the pineal gland (arrow) with enlargement of the third and lateral ventricles (arrowhead).

Figure 2. Precontrast sagittal T1-weighted MRI showing a mass in the region of the pineal gland, with a thin rim of intrinsic signal hyperintensity (arrow).

Figure 3. Postcontrast (a) sagittal and (b) axial T1-weighted images showing an avidly enhancing mass (arrows).
DISCUSSION

The normal pineal gland secretes melatonin and is located in the supratentorial midline, above the superior colliculi and below the vein of Galen. Tumors of the pineal region account for <1% of intracranial neoplasms in adults (1). Primary tumors of the pineal region include pineal parenchymal neoplasms, germ cell neoplasms, and tumors arising from adjacent structures, including meningiomas, astrocytomas, and ependymomas (1). Pineal parenchymal tumors include the relatively indolent pineocytoma and the highly malignant pineoblastoma. Both of these entities appear as lobular, enhancing masses centered in the pineal gland that displace the normal pineal calcifications peripherally (1). Germ cell tumors include germinoma and teratoma. Pineal cysts are considered a normal finding, occurring in up to 40% of patients (1). When they occur in the pineal region, dermoid and epidermoid cysts image similarly to those that occur elsewhere in the central nervous system. Metastases to the pineal gland often result from primary tumors of the lung, breast, colon, and kidney (1).

As its name implies, PTPR does not arise from the pineal gland itself. The cell of origin is thought to be the specialized ependymocytes of the subcommissural organ (2). The subcommissural organ is involved in the secretion of glycopeptides and is located below the posterior commissure at the level of the cerebral aqueduct, just anterior to the pineal gland. It is the glycopeptide content that is thought to be the source of intrinsic T1 hyperintensity commonly reported in PTPR (3).

On imaging, PTPR appears as a heterogeneously enhancing mass arising from the pineal region. Like other masses in this location, obstructive hydrocephalus is a common secondary finding (1). No specific imaging features are pathognomonic for PTPR. However, intrinsic T1 hyperintensity has been reported as a potentially characteristic feature of this neoplasm (3). Hemorrhagic and lipid-containing lesions of the pineal region can also demonstrate T1 shortening and may be excluded from the differential diagnosis by the use of additional sequences such as fat suppression and susceptibility weighted imaging (2). The entire neuraxis should be imaged, as leptomeningeal seeding has been documented (2). Surgical resection followed by radiotherapy is the preferred treatment (4).

Due to the relative paucity of reported cases of PTPR, its natural history is unknown. Histologic grading criteria remain undefined, but will likely correspond to World Health Organization grade II or III (1).

Echinococcus granulosus infection presenting as right upper-quadrant abdominal pain

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A 67-year-old Lebanese man presented with vague abdominal pain in the right upper quadrant. No other symptoms were reported. He has lived in the United States for 10 years and last traveled to Lebanon 2 years prior to presentation. While in Lebanon, his diet included lamb liver. His blood pressure was 134/62 mm Hg; pulse, 82 beats per minute; respirations, 12 breaths per minute; temperature, 98°F; weight, 187 lbs; and height, 5’3”. The patient was anicteric. Hepatomegaly was present, but his lungs and cardiac examination were within normal limits and his abdomen was nontender to palpation.

Computed tomography (CT) and ultrasound demonstrated multiple hepatic and splenic cystic lesions. Magnetic resonance imaging (MRI) performed for further lesion characterization demonstrated multiple lesions in the liver and spleen. These were well-circumscribed cystic lesions with predominantly fluid-signal intensity containing linear serpiginous filling defects. The lesions had local mass effect without surrounding inflammation or edema. Following the administration of intravenous gadolinium contrast, images showed mild peripheral capsular enhancement (Figures 1–4).

DIAGNOSIS: Echinococcus granulosus infection.

DISCUSSION

Echinococcosis is a parasitic infection caused by the larvae of the cestode Echinococcus. The three species most commonly associated with human disease are E. granulosus, E. multilocularis, and E. vogeli. E. granulosus is the most common form of the disease, resulting in unilocular cystic lesions, contrasted with the multilocular alveolar lesions of E. multilocularis.

The adult form of the Echinococcus tapeworm lives in the small bowel of dogs, wolves, and other definitive canid hosts. Eggs are passed into the stool and subsequently ingested by intermediate hosts such as sheep, goat, camels, horses, swine, and humans. Once ingested, the eggs hatch and the resultant embryos (also known as oncospheres) penetrate the intestinal...
Mucosa and travel via the portal system to the liver. Once in the liver, the embryos either infect the hepatic cells or travel via the systemic circulation to other organ systems, including the lungs, brain, kidneys, and spleen. Once in these organ systems, the larvae develop into cysts, which slowly fill with fluid and produce daughter cysts containing protoscolices (Figure 5). Infection of the definitive host occurs at this stage, as the hydatid-containing organs of the intermediate host are ingested by the definitive host. The protoscolices are then released as scolices, attach to the host intestinal mucosa of the small bowel, and develop into adults within 32 to 80 days. The life cycle is shown in Figure 6.

*E. granulosus* occurs worldwide but is more prevalent in areas where livestock is raised, such as China, central Asia, the Middle East, eastern Africa, and Australia. The most important mode of transmission for human infection relates to environmental interaction with infected dogs. This is particularly common in settings where the dogs have dietary access to the viscera of home-slaughtered sheep or other livestock. Canine infection leads to environmental contamination with echinococcus eggs, which then leads to human infection (1). *E. multilocularis* is found in the Alpine, sub-Arctic, or Arctic regions of Canada, the United States, Europe, China, and central Asia. *E. vogeli* is known to be located only in Central and South America.

Echinococcal cysts produce symptoms via mass effect, as their slowly expanding size eventually causes space-occupying effects to the particular organ, usually the liver or lung. The liver is involved in about two thirds of *E. granulosus* infections and nearly all *E. multilocularis* lesions. The clinical presentation is dependent on the number of cysts, their location, and their rate of growth; a latent period of 5 to 20 years is common.

Hepatic echinococcosis is characterized by abdominal pain or a right upper-quadrant mass. The cysts may mimic cholelithiasis, causing biliary obstruction resulting in jaundice. Mass effect on the hepatic vasculature can lead to occlusion or thrombosis. Rupture or leakage of the hydatid cyst can produce allergic effects, such as fever, pruritus, eosinophilia, and even anaphylaxis.

Pulmonary echinococcosis symptoms include cough, hemoptysis, salty phlegm, dyspnea, and chest pain due to rupture of the cysts into a bronchus. Rupture can also result in systemic dissemination of the protoscolices, creating more cysts.

The imaging findings of *Echinococcus granulosus* depend on the stage of infection. The World Health Organization (WHO) has published a classification scheme based on the sonographic findings relating to the viability of the hydatid cyst. During the early active stage, the infection typically presents as unilocular cysts. Sonography will often demonstrate free-floating protoscolices in the cysts. This hydatid sand appears as the “snowflakes” sign (Figure 7). Daughter cysts will eventually develop, which partly or completely fill the mother cyst (Figure 8). The resulting images demonstrate a mother cyst with internal daughter cysts producing a “wheel-like” or “honeycomb-like” appearance (2). These single or multiloculated cysts contain viable organisms or protoscolices. When the viability of the parasite is lost, the
pressure within the cyst decreases. The endocystic membranes/germinal layer will then detach and float within the cyst fluid. This is the transitional stage according to the WHO classification. The imaging appearance at this stage is that of intracystic serpiginous linear filling defects known as the “water-lily sign.” The MRI images on our current case correspond to this transitional, nonviable stage of infection (Figure 2). The inactive stage will show a degenerated cyst that has a sonographic appearance of a solid-looking pseudotumor that may show a “ball of wool sign” (2). Dead cysts are characterized by a calcified wall, which varies from partial to complete. The calcification is often serpiginous and peripheral, having the appearance of a decompressed or crenated lesion.

While treatment of echinococcosis is based on the size, location, and severity of the cysts, surgery has been the traditional definitive therapy. Medical management only with albendazole is utilized in many cases. Recently, PAIR (percutaneous aspiration, infusion of scolicidal agents, and reaspiration) has gained ground for specific types of lesions. Albendazole is administered 4 days before and several weeks after treatment, regardless of which procedure is performed. Ultrasound is first utilized for WHO criteria staging. The different stages of cyst include active (CL, CE1, and CE2), transitional (CE3), and inactive cysts (CE4 and CE5). Surgical removal is preferred for pulmonary hydatid cysts and small calcified hepatic cysts. PAIR is contraindicated for superficial cysts, cysts with multiple thick internal septa, and cysts communicating with the biliary tree (3). Aspiration is generally performed with ultrasound or CT guidance, as diagnosis can be confirmed with demonstration of the protoscolices in the aspirate.

Echinococcal infection of the liver causing Budd-Chiari syndrome

A 37-year-old woman of Middle Eastern descent had a hepatic infection with *Echinococcus granulosus* diagnosed in her home country based on clinical and sonographic findings. The patient presented to Baylor University Medical Center with signs and symptoms of cirrhosis and portal hypertension. The echinococcal infection led to chronic compression and obstruction of the intrahepatic inferior vena cava (IVC), leading to Budd-Chiari syndrome.

Computed tomography (CT) images in Figures 1 and 2 demonstrate an inactive stage of echinococcal infection with a decompressed, peripherally calcified echinococcal cyst. Chronic occlusion of the intrahepatic IVC led to typical late-stage changes in the hepatic parenchyma with cirrhosis. Intrahepatic venous collaterals have developed within the medial aspect of the posterior segment right lobe. These intrahepatic collaterals connect the subhepatic IVC to the suprahepatic IVC. A discussion of echinococcal infection appears in our earlier article (1).

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Figure 2. Axial CT venous-phase intravenous contrast–enhanced images best demonstrate the typical heterogeneous enhancement and cirrhotic morphologic changes related to chronic Budd-Chiari syndrome.
A 69-year-old Caucasian man presented with a lesion on his forehead which “grew overnight” (Figure 1). It was located at the edge of a scar of a previously removed squamous cell carcinoma. The patient has had numerous squamous cell carcinomas and mild hyperlipidemia. What is your diagnosis?

Over the ensuing week, the patient developed two fresh ulcers on his forehead “overnight” (Figure 2). There was no erythema, flaking, pain, numbness, or tingling in the areas prior to the development of the ulcers. The two new lesions were tender. There was no known trauma. Now, what is your diagnosis?

DIAGNOSIS: Herpes zoster.

Herpes zoster is the reactivation of varicella zoster virus. It typically presents with a prodrome of pain, tingling, or tenderness, and then an eruption of grouped vesicles on an erythematous base occurs within a sensory dermatome. The most common complication is postherpetic neuralgia, which is a neuropathic pain syndrome that develops after the rash has resolved (1–3). It is typically described as burning, stabbing, or shocklike pain in the area where the rash was located (1, 4). Postherpetic neuralgia occurs in 14% to 20% of patients with herpes zoster (2).

**Figure 1.** Right frontolateral forehead. A 5-mm well-circumscribed superficial ulcer with a rolled pink border and surrounding telangiectasias at the medial edge of a scar. Superolateral to the lesion, there is a second scar from a previously treated nonmelanoma skin cancer.

**Figure 2.** The blue circle (A) is a superficial ulcer with an overlying hemorrhagic crust along the scalp fringe to the right of the midline. The red circle (B) is a superficial ulcer with a rolled border within the right eyebrow. The yellow circle indicates the primary lesion.
A vaccine for the prevention of herpes zoster and postherpetic neuralgia, Zostavax, was approved by the Food and Drug Administration in 2006 (5). It is a live virus vaccine composed of at least 19,400 plaque-forming units of the Oka/Merck strain of the varicella zoster virus. The potency of this vaccine is 14-fold higher than that used in children (2). Zostavax reduces the risk of developing herpes zoster by 51% and decreases the incidence of postherpetic neuralgia by 67% (3, 4); further, it decreases the burden of illness of herpes zoster by 61% and decreases the duration of postherpetic neuralgia by 57% (3, 4). Therefore, disease severity is decreased in patients who experience a herpes zoster outbreak despite vaccination (3, 4). Most recently, Zostavax was shown to decrease the risk of ophthalmic involvement, therefore decreasing the risk of serious vision-threatening sequelae (4). Zostavax is recommended by the Centers for Disease Control and Prevention for use in patients >60 years of age who are not immunocompromised (3, 4).

Our patient had received the Zostavax vaccine 2 weeks prior to his initial presentation. The patient is otherwise healthy and is not immunocompromised. To date, there are no reports of the Zostavax Oka/Merck varicella virus strain causing herpes zoster itself. However, there are reports of a herpes zoster–like reaction occurring at an average of 16 days after vaccination (4, 6). Wild-type varicella zoster virus DNA was isolated by polymerase chain reaction from the active lesions of the vaccinated patients with a herpes zoster–like reaction, confirming the reactions were likely not due to the vaccine (6). Thus, our patient experienced a herpes zoster–like reaction from the vaccine given 2 weeks prior to the onset of his facial lesions.

The case highlights the importance of conducting a thorough history, including a vaccination history. It exemplifies how a vaccine-dampened outbreak of herpes zoster can clinically mimic nonmelanoma skin cancer. Therefore, truncated herpes zoster should be included in the differential diagnosis for nonmelanoma skin cancer for recently vaccinated individuals; a biopsy of the lesion is necessary for confirmation of disease.

Secondary syphilis and HIV

Shagun Dhaliwal, Mahir Patel, MD, and Alan Menter, MD

Syphilis has been termed the “great mimic” due to its versatile and varied disease presentations. Dermatological findings are associated with the secondary phase of the disease and typically consist of a generalized papular eruption that can involve the palms and soles, genitals, and mucous membranes. Patients with syphilis and concomitant HIV infection may have altered presentations. We report a case of a 41-year-old HIV-positive man who presented with a papular rash of a few months’ duration and was diagnosed with secondary syphilis.

Syphilis is a sexually acquired infectious disease that has been the target of many aggressive public health interventions by the US government since the 1940s. Initial intervention resulted in a marked decrease in the incidence of the disease, but in more recent years syphilis has re-emerged. Syphilis frequently presents in tandem with newer conditions such as HIV (1). Because of this more recent association, little knowledge is available about the diagnosis and treatment of syphilis in a patient with concurrent HIV. This case study reviews the disease presentations of syphilis manifesting in a patient with HIV disease.

CASE PRESENTATION

A 41-year-old white man was admitted to Baylor University Medical Center at Dallas complaining of a diffuse head-to-toe erythematous, papular rash of 3-months’ duration. The rash involved all areas of the skin, including the palms, soles, and genitalia. The rash was neither painful nor pruritic and had changed minimally since its onset 2 months earlier. Review of systems was remarkable for fever, chills, sore throat, odynophagia, dry cough, and sinus congestion. His past medical history included HIV diagnosed 25 years earlier (age 16) with an unknown CD4 count. The patient was a nonsmoker, nondrinker, and reported he had not been sexually active over the past year. He had a history of methamphetamine abuse, but had quit using the substance 6 months earlier. He also had allergies to sulfonamides, penicillin, ciprofloxacin, Bactrim, and amoxicillin.

He had a diffuse erythematous, papular eruption involving the face, trunk, and upper and lower extremities (Figure 1). Discrete papular lesions with minimal scale measured approximately 1 cm and involved the palms and soles (Figure 2) as well as the genitals. No evident lip or buccal mucosal lesions were noted.

His blood work revealed anemia, with hemoglobin levels at 7.9 g/dL and hematocrit levels at 24.1%, an overall lymphocytopenia with a markedly decreased CD4 count (102), and a viral load of 1.43 million. A serum rapid plasma reagin test was positive at a titer >1 to 512, indicating the presence of syphilis infection. The cerebrospinal fluid appeared grossly bloody with a glucose level of 50 mg/100 mL, protein level of 348 mg/100 mL, red blood cell count of 42,000, and white blood cell count of 42, with a differential of 28 lymphocytes, 45 neutrophils, 2 basophils, and 4 monocytes. The high white blood cell and neutrophil count was indicative of an active infection, with the low lymphocyte count compatible with his HIV infection. The cerebrospinal fluid Veneral Disease Research Laboratory test was nonreactive, thus ruling out the presence of neurosyphilis. The patient also had a positive tuberculosis QuantiFeron...
gold test result but a negative subsequent chest x-ray, suggesting an inactive *M. tuberculosis* infection. The patient tested positive for blastomyces antibody, which suggested previous exposure to *Blastomyces dermatitidis*. Epstein-Barr virus was detected via polymerase chain reaction. A skin punch biopsy demonstrated chronic dermatitis with positive cell-rich inflammatory reactions containing plasma cells, suggestive of syphilitic dermatitis. Subsequent staining of the skin sample indicated the presence of spirochete organisms.

A comprehensive analysis of the laboratory data resulted in a diagnosis of secondary syphilis as well as Epstein-Barr virus, Blastomyces exposure, and confirmation of HIV. The patient was administered a 14-day course of 24 million units daily of intravenous penicillin. He was started on highly active antiretroviral therapy and tuberculosis prophylaxis and placed on a 2-week course of valacyclovir, 1 g orally three times daily, for varicella zoster virus. He was also given dapsone 100 mg orally daily as prophylaxis against pneumocystis pneumonia. The patient was instructed to follow up daily at his physician’s office for penicillin infusion and further infectious disease workup.

**DISCUSSION**

Syphilis is a sexually transmitted disease caused by the spirochete microorganism *Treponema pallidum* (1). Concomitant syphilis and HIV infection are particularly common among men who have sex with men, intravenous drug abusers, and prostitutes (2). Although syphilis presentation in patients with HIV is largely similar to that in patients without HIV, differences in disease manifestation may be present.

The first stage of syphilis, known as primary syphilis, is marked by the presence of a chancre, a well-demarcated, relatively painless, ulcerated lesion evolving from a papule with resolution within 3 to 6 weeks. Unilateral or bilateral inguinal adenopathy may also be present in primary syphilis (1). Patients infected with both HIV and syphilis show changes characteristic of primary syphilis, although these changes may be more numerous, larger, and deeper (3). Chancre as compared to HIV-negative patients are also more likely to persist in to the secondary stage. Our patient, however, did not exhibit any evidence of an active or healed primary chancre.

Secondary syphilis has several symptoms. Patients frequently present with systemic symptoms that include fever, headache, anorexia, weight loss, sore throat, and myalgia. Our patient presented with both a fever and a sore throat. The most characteristic finding in secondary syphilis is that of a diffuse, papular rash that usually covers the torso, extremities, palms, and soles. The lesions are generally 0.5 to 2 cm in diameter with a moderate degree of peripheral (collarette) scale specifically notable on the palms and soles (see Figure 2). Other dermatologic signs include mucosal lesions, condylomata lata, alopecia, and generalized lymphadenopathy (4). Secondary syphilis in patients with concurrent HIV may present with a broad spectrum of cutaneous morphologies, which include papulosquamous, lenticular, annular, and pustular lesions and those resembling eczema, leprosy, and mycosis fungoides (5). In patients with advanced HIV, secondary syphilis may present as malignant secondary syphilis. This is characterized by severe ulcerating lesions and gummatous infiltration of mouth, eye, subcutaneous tissue, bone, joints, and cerebrospinal system (1). Thus, one should be careful to note that secondary syphilis is a disease that is more aggressive in HIV patients. Our patient did not present with any signs of malignant secondary syphilis. In this patient, the rash was diffuse, generalized, erythematous, and papular and covered the entire body, including genitals, palms, and soles (Figures 1 and 2). This unique combination of symptoms in the patient’s history is what initially suggested secondary syphilis as a possible diagnosis.

Latent syphilis follows secondary syphilis and is a period of relatively few symptoms and a decreased chance of passing on the infection. As many as 25% of untreated patients in the latent stage will progress to tertiary syphilis, a stage characterized by cardiovascular and neurologic features as well as gummatous lesions (1).

Cardiovascular features of tertiary syphilis, such as coronary ostitis, aortic regurgitation, and aortic aneurysm, are the most common of the three tertiary manifestations and develop anywhere from 10 to 30 years after initial infection (1). Previous cases have shown that aortitis may develop more rapidly in HIV-coinfected individuals (3). Gumma formation may begin as soon as a year after infection but is most likely to occur 15 years after the initial infection. Gummatous lesions may form in any organ and can lead to ulcers (1). Neurosyphilis occurring at the tertiary stage is known as late neurosyphilis, while neurosyphilis occurring at the earlier stages is known as early neurosyphilis. During early stages of syphilis, spirochetes infiltrate the central nervous system, resulting in early neurosyphilis which includes such symptoms as meningitis, stroke, seizure, myelopathy, brainstem abnormality, cranial nerve abnormalities, vestibular disease, and ocular disease. Late neurosyphilis primarily involves the brain and spinal cord parenchyma, resulting in dementia, tabes dorsalis, general paresis, sensory ataxia, and bowel or bladder dysfunction (1).

In HIV-negative individuals, confirmatory diagnosis of secondary syphilis is possible through serologic testing; however, in
individuals with untreated HIV, as in this case, serologic tests are more likely to be inaccurate. In such cases the serologic tests can be repeated at a later date and/or a skin biopsy can be performed (1). In this case, an ultimate diagnosis of syphilis could be arrived at when the patient tested positive on both a serologic test, rapid plasma reagin, and in the skin biopsy. Penicillin G, at a dose of 2.4 million units intravenously, is the recommended antibiotic in early syphilis. Treatment is followed by a reexamination at 6 and 12 months to ensure a reduction in nontreponemal antibody and thus to confirm a response to treatment. If no such reduction is seen, a follow-up course of benzathine penicillin is administered.


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**Avocations**

Sunflower septals close-up and sunflower image on a water droplet. Photos © Rolando M. Solis, MD. Dr. Solis is an interventional cardiologist on the medical staff of Baylor Medical Center at Garland.
A 19-year-old woman with congenital HIV infection was admitted to the hospital after experiencing nausea, vomiting, diarrhea, and fatigue for 1 week. Her CD4 count was 27. She had undergone percutaneous endoscopic placement of a gastrostomy tube for feeding 5 months earlier. In addition, she had extensive genitoanal ulceration due to infection with herpes simplex virus complicated by secondary bacterial infection. Her home medications included tenofovir disoproxil fumarate, sulfamethoxazole and trimethoprim, lamivudine, lopinavir/ritonavir, duloxetine hydrochloride, Nystatin, azithromycin, hydromorphone, and lorazepam.

An electrocardiogram 11 months earlier had been normal except for sinus tachycardia, but in addition to sinus tachycardia the electrocardiogram recorded soon after the current admission showed changes suggestive of severe hypokalemia (Figure 1): sagging ST segments, low T waves, and prominent U waves (which because of the tachycardia fuse with the subsequent P waves). Serum electrolyte concentrations in mEq/L were potassium, 1.4; sodium, 139; chloride, 119; and bicarbonate, 14. Her serum calcium concentration was 7.8 mg/dL, and the creatinine and urea nitrogen concentrations were 1.9 mg/dL and 6 mg/dL, respectively. Urinalysis at that time showed a glucose concentration of >1000 mg/dL while her serum glucose was only 90 mg/dL. Her serum uric acid concentration was 0.8 mg/dL, and serum

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Figure 1. Electrocardiogram recorded soon after admission. See text for explication.
phosphorus was 1.4. The hypercholemic, hypokalemic, metabolic acidosis was thought to be due to therapy with tenofovir. In addition to this, her metabolic acidosis was certainly exacerbated by recent diarrhea. The tenofovir was discontinued because of the suspected Fanconi syndrome.

After 5 days of aggressive fluid therapy and electrolyte replacement, her serum potassium concentration increased to 4.4 mEq/L, and the tenofovir was restarted because of her serious HIV infection. After 5 weeks in the hospital, the patient had improved; her electrocardiogram was normal except for sinus tachycardia (Figure 2), and she was discharged to inpatient hospice care on numerous medications, including electrolyte replacement.

Six days after discharge, the patient was readmitted with confusion and profound weakness. The admission electrocardiogram, seen in Figure 3, showed sinus tachycardia at a rate of 153 beats/minute, right axis deviation, and an intraventricular conduction defect (QRS duration, 0.20 seconds) that suggested hyperkalemia. Serum electrolyte concentrations in mEq/L at this time were potassium, 10.5; sodium, 135; chloride, 120; and bicarbonate, 12. The serum calcium level was 14.5 mg/dL despite a serum albumin level of only 2.2 gm/dL, the highest albumin level recorded during either admission. Her serum creatinine and urea nitrogen concentrations were 2.5 mg/dL and 41 mg/dL, respectively. As the hyperkalemia was treated with oral sodium polystyrene sulfonate, insulin, 50% dextrose solution, and emergent hemodialysis, the QRS duration shortened to 0.12 seconds, and T waves became more peaked and “typical” of hyperkalemia (Figure 4). In addition, the QT interval was noticeably short considering the intraventricular conduction defect (QT interval, 0.25 seconds; QT interval corrected for heart rate, 0.40 seconds), a feature consistent with hypercalcemia.

One of the patient’s discharge medications on her previous admission was potassium chloride, 60 mEq three times per day by mouth, and that dosage in the presence of her renal dysfunction undoubtedly caused the hyperkalemia that occasioned the second admission. She improved, but never sufficiently to leave the hospital. Her stay was complicated by multiple nosocomial infections, pressure sores, and worsened debilitation, and she eventually developed gram-negative sepsis and died 6 weeks after admission.

**DISCUSSION**

Vertical transmission of HIV continues to be a serious health problem in developing countries, with over 95% of congenital HIV occurring in these areas (1). Most of these infected neonates acquire the virus either during or near the time of delivery (2). The widespread use of highly active antiretroviral therapy has decreased this transmission rate from 25% (no treatment) to 2%, and this rate can be further decreased to <1% if prophylactic cesarean section is performed in mothers with viral loads >1000 (2). The potential complications of highly active antiretroviral therapy should never outweigh the benefits of starting this treatment as soon as the infection is found. Data from 2004 showed a 95% decrease in cases of perinatally acquired immune deficiency syndrome when the appropriate treatment and preventative measures were taken (2). Clinicians must always be conscious of the potential complications, however, as they may occur at any time during treatment and can have devastating consequences.

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*Figure 2. Electrocardiogram recorded shortly before discharge. See text for explication.*
The first antiretroviral to be approved to prevent perinatal HIV transmission was zidovudine in the mid 1990s (2). Since that time, many different drugs have been developed, which have successfully reduced transmission to its present rate (2). The use of up to four medications in combination allows for the viral replication cycle to be interrupted at multiple steps (2). Tenofovir is a nucleotide reverse transcriptase inhibitor that prevents replication of the virus by competing for incorporation...
into its DNA (3). The drug’s synergistic actions with other HIV medications make it perfect for use in a multidrug regimen.

Complications of tenofovir therapy include lactic acidosis, Fanconi syndrome, immune reconstitution syndrome, severe acute exacerbation of hepatitis, decreases in bone mineral density, and severe hepatomegaly with steatosis. Fanconi syndrome, a known complication of tenofovir, has occurred in about 1.6% of patients who used the drug and has been characterized by the passage of glucose, amino acids, uric acid, phosphate, and bicarbonate in the urine instead of their being reabsorbed (4). Because of the low incidence of this side effect, it was not widely recognized until tenofovir was used in large populations (3).

The nephrotoxicity of tenofovir is due to mitochondrial dysfunction. This causes a significant decrease in the energy for the sodium-potassium pump in the proximal tubules (3). This disruption allows for electrolytes and small molecules that would normally be reabsorbed to be lost in the urine (3). As Fine described, “The result is a proximal renal tubular acido-sis (usually hypokalemic) with hypophosphatemia, glucosuria, and aminoaciduria (Fanconi syndrome)” (3). Not all of these laboratory abnormalities will be present in every case; many times, the kidneys will compensate and only one or two of these disturbances will be seen (3). Risk factors for tenofovir-associated nephrotoxicity include preexisting kidney disease or elevated creatinine, poorly controlled HIV disease with overall associated nephrotoxicity include preexisting kidney disease or these disturbances will be seen (3). Risk factors for tenofovir-therapy increase risk of progression to nephropathy. Patients with a higher body mass index are at increased risk for developing nephrotoxicity associated with tenofovir therapy (5). African American ethnicity, older age, female gender, and concomitant administration of nephrotoxic agents (5, 6).

Virtually no computer program attempts to read the electrocardiographic changes of electrolyte disturbances. Thus, physicians must recognize these changes on their own. Serum potassium disturbances produce some of the most striking findings. Hypokalemia is characterized by sagging ST segments, low T waves, and prominent U waves (7). One or more of these features may be seen with a serum potassium of 3.0 to 3.5 mEq/L, and below 2.5 mEq/L all three features are usually present (8). With strikingly low levels of serum potassium (Figure 1), the T wave becomes a notch on the upslope of a giant U wave and may fuse with the U, giving the impression of a long QT interval. In the presence of ST-segment depression, the changes may be mistaken for those of ischemia (7). Peaked T waves may be present when the serum potassium rises above 5.5 mEq/L and are present in most patients with levels above 6.7 mEq/L (8). As the potassium rises above 8 mEq/L, the QRS widens diffusely and only rarely resembles typical right or left bundle branch block (Figure 3). The PR interval may lengthen, and the P waves become less distinct and may disappear. Ventricular asystole or fibrillation often occurs when the serum potassium exceeds 12 mEq/L (8). The QTc interval is inversely proportional to the level of the ionized serum calcium (8), and it is the ST segment rather than the T wave that is altered (9). Thus, hypercalcemia causes shortening or virtual disappearance of the ST segment (Figure 4), whereas hypocalcemia causes QTc prolongation by lengthening the ST segment.

In our patient, electrocardiographic changes resulted from multiple electrolyte abnormalities that were corrected during the initial hospitalization. The overcorrection on an outpatient basis was further accentuated by the development of acute renal failure, and tenofovir therapy contributed to it in a debilitated patient with chronic infection. Tenofovir may be used safely in high-risk patients, but close monitoring is necessary to prevent electrolyte abnormalities that may be manifested by life-threatening electrocardiographic changes.

We can’t bank time. That’s the long and short of it. Our minutes slip away one by one, and what becomes important is how well we lived them. Do we live out our dream lives? To do so, we must be extremely good overseers of our time. We tend to view our lives on a daily basis, but Vanderkam asserts that we’d be better off if we viewed them in 168-hour increments, the number of hours in a week. Our days can vary greatly, for what we do on a Sunday usually is far different than what we do on a Thursday, but with the lens broadened to encompass a full week, we can better capture a true picture of our lives. The repeating patterns of 168 hours provide us with the evidence of what we hold important and how our lives will be.

Vanderkam sets out to prove that we can have it all. With careful and deliberate planning, we can find enough time in a week to accommodate 8 hours of sleep a night, full-time work, intense involvement with our families, volunteer work, leisure time, exercise, and anything else that matters to us. It seems overwhelming at first glance to think that it’s all possible. Aren’t we all too busy? That’s the common excuse when we’re asked overworking or underworked. Maybe it’s just that too many hours each week get lost in the shuffle. What if you started out each week with a blank slate and the clear choice as to how you wanted to live out those fleeting 168 hours? You might be surprised to find that you have more time than you think. Once you provide for 8 hours each night to sleep, and let’s say you commit to working 50 hours that week, then that leaves you with 62 hours for other things. The well-lived life will be ever elusive unless we harness our working hours and our free hours to our dreams. That clarity of purpose and disciplined use of time will get us there.

Before you get started constructing how you want to plan for your 168 hours, it’s important to figure out how you are spending them now by keeping a time log, which is available at the website www.My168hours.com. I was not pleased to discover how well I have learned to procrastinate. I check my e-mail way too often, as well as surf my favorite websites. I might be able to get away with the claim that I was surfing for ideas for future articles, but I know better. I’m really just doing the easier thing. Actual writing is hard work. As I have three young children and limited working hours, it’s disappointing to realize how much of my writing time I’m frittering away, but also inspiring to realize how much more I could be accomplishing with a little more discipline.

Another exercise Vanderkam suggests is to compile a List of 100 Dreams. It’s worthwhile to include many of the dreams that you’ve already actualized. For me, there were some I would like to do again, such as living abroad, and others, like parachuting out of a plane, that are checked off my list for good. The key here is to be sure that you’re spending a large portion of your time on activities related to your life goals. Aligned with this should be a focus on your core competencies, the things that are important and meaningful to you and that you do best, and that others can’t do as well or can’t do at all.

It seems integral to the concept of a well-lived life that you choose the right job, one that plays to your core competencies. How fortunate are those who know from a young age what they want to do in life; for others of us, we might discover it a bit late, if at all. And, to ever be world class at anything, you’ll need at least 10,000 hours of deliberate practice at the craft to get there, at least according to the findings of K. Anders Ericsson (now of Florida State University) and his colleagues. With the right job choice, those thousands of hours can be a source of joy and satisfaction.

To create the ideal work situation, Vanderkam recommends implementing a four-part process:

- Seize control of your schedule.
- Do not mistake things that look like work for actual work.
- Get rid of non-core-competency tasks by ignoring, minimizing, or outsourcing them.
- Boost efficiency by getting better at what you do.

The promise here is that you can reach your professional goals without relinquishing what you value in your personal life. If nurturing your children is one of your core competencies, then you’ll need to spend some real quality time with them. The good news is that parents today are doing just that. Both mothers and fathers now spend more time with their children than parents did back in 1965, even though more than 50% more mothers are now in the workforce. What gives is the amount of time spent on housework.
Unless you don’t mind a messy house, the author recommends outsourcing for all the demands of life maintenance, citing cooking, laundry, and cleaning as opportunity costs. Instead, you could be spending more “quality time” with your kids. To this, I would simply ask: what comprises “quality time” with our kids? Is it just taking them to the park or reading with them? I personally think that “quality time” includes teaching my three children basic life skills and a good understanding of healthy eating habits. If they are asked to pick out the apples at the grocery store, they're more inclined to reach for one when they're ready for a snack. My daughter now takes great pride in helping me cook meals. My older boy likes to set the table, and my younger boy, at 6, has become an expert dish washer. He’d probably laugh if you told him that washing dishes was a “chore.” Granted, when he does the dishes, it takes longer and I have to help a bit, but he seems aware that he has contributed to the running of the house and the care of our family.

There is something about the concept of outsourcing our life maintenance that is a bit elitist. Unlike the author, I will not be hiring a personal shopper or a personal organizer. It was hard for me to take seriously the idea that we need a “home team” to support our lifestyles, particularly when an example offered is of “a mom of several young children who ran a hedge fund in her spare time.” It seems for this family there is a need for four full-time workers, including a housekeeper and someone to run errands, at a cost of $200,000 a year. That won’t be happening in my home. I guess my kids will have to learn a bit, but he seems aware that he has contributed to the running of the house and the care of our family.

Instead of outsourcing, I would stress the need for efficiencies in our households. How easy it is to put a chicken in a crock pot in the morning, savor the enticing aroma all afternoon, and have a wonderful meal on the table for dinner. I have most of my meat and seafood delivered quarterly and stored in an outside freezer, thereby freeing up some of my shopping time. And, the big trick is to have your household organized in such a way that maintenance is easy, which can happen only if everything has its place.

While I see the importance of being mindful of how we spend our 168 hours each week, and that careful planning is required to maximize it, I simply don’t feel any desire to schedule every hour of every day of every week. To me, a dream weekend is when I have little planned and am free to do what feels right at the moment.

Still, at its core, I agree with Vanderkam’s thesis that we should focus on our core competencies to live our dream lives, and to do so, we need to simplify. We need to be clear about what we do well—and want to do well—and devote our time to that and strip away the rest; less things, less activities, less errands, less clutter. It takes being self-aware and self-confident to simplify and to know that dream lives are built on the foundation of simplicity.

The reviewer, Fran Roberts Willard, is a freelance writer from Vienna, Virginia.
initially done. “Scrub suits and sterile gloves began in Halsted’s operating rooms.” Other Halsted principles include the gentle handling of tissues, scrupulous hemostasis, tension-free closures, crush-free dissection, and strict application of surgical anatomic knowledge. (“He had memorized Gray’s Anatomy.”)

The proper surgical treatment of hernias, breast cancer, and gallbladder disease all began with Halsted. Today, “500,000 hernia operations are performed annually in the United States.” Prior to Halsted’s surgical approach to hernias, they were said to have “represented a significant economic and physical burden to the individual and to society. . . . Not only are they painful, but they carry the potential to become incarcerated.” Nonsurgical reduction of hernias in Halsted’s times often resulted in “perforation, peritonitis, and death.” When word of Halsted’s surgical treatment of hernias became known, patients traveled from all over America to see him.

“One hundred years ago the breast cancer patient was literally doomed.” Halsted changed all that. He developed an “operation against which all others had to be compared.” For the very first time in history, prolonged remissions and even cures from the malignancy became possible.

Gallbladder disease also was a deadly affliction. At the age of 30, Halsted “successfully performed the first known operation to remove gallstones” to save the life of his own mother. Ironically, he himself would later succumb to complications from this illness as others’ hands proved inadequate to save the master.

Halsted’s surgical career spanned pivotal times in American medicine. The fields of internal medicine, obstetrics/gynecology, and pathology were also in their infancy. Through observation, scientific application, and standardization, Halsted, along with Sir William Osler, William Henry Welch, and Howard Atwood Kelly (“The Very Best Men”), set standards that are still prominent in medicine today.

An endowedness from a successful merchant in Baltimore established Johns Hopkins University and Hospital. Under the leadership of “The Big Four,” this first academic medical school in the country would set standards for all others to follow. As explained by the well-known Bellevue physician, Dr. Austin Flint, “What was accomplished . . . as regards to knowledge of the causes, prevention, and treatment of disease far transcends what would have been regarded a quarter of a century ago as the wildest and most impossible speculation.”

I enjoy biographies that detail greatness and humanness in the same individual and, in that regard, Dr. Imber excels. The author’s title portends the complexity of this innovator, whom he describes as “a formidable and eccentric figure . . . enigmatic and detached.” Dr. Halsted had a dark side. An addiction to cocaine early in his career forced him out of medicine for 7 months. “His hands shook, he often became suddenly drenched in perspiration, and he lost focus.” He “spoke constantly, excitedly, and endlessly, about everything under the sun.” His treatment left him with a second addiction, this one to morphine. While the siren song rang in his ears, his journey was nothing short of heroic.

In this book, Halsted is characterized as “forbidding and nurturing; rigid, proper, and secretive; compulsive and negligent; stimulating and reclusive; addicted and abstemious; oblivious and solicitous.” He had a “quiet, cold demeanor” and was intolerant of talking or excessive noise in his operating room. Levy was out of the question, and the current use of music and nonpertinent discussions during an operation would never have been allowed. In regards to his students, “if one was insecure enough to require reassurance and compliments, one was certain to be sorely disappointed. . . . Abject disapproval would be . . . delivered unemotionally, in a quiet and withering tone, with an expressionless face and unyielding ice blue eyes. In one case Halsted told a resident, in all seriousness, that he should specialize in operating on piles (hemorrhoids), as it would not be too taxing for his abilities.”

His firm, forbidding temperament demanded attention and respect. Relationships with his wife, his colleagues, his patients, and his students were convoluted, often strained. In the operating room, he displayed “intense concentration, . . . unbending demands for excellence” and lavished attention “on even the most trivial detail of his surroundings.” This demeanor carried over into his personal life, as he “became increasingly aloof, and perhaps out of touch with simple human situations.” “No one every remembers him actually laughing.”

Imber proclaims that “every individual in America who undergoes successful surgery owes William Stewart Halsted a nod and deep dept of gratitude.” His “principles of surgery” are still practiced today. “Virtually every academically affiliated surgeon can trace his or her teachers, and his teacher’s teachers to William Stewart Halsted.” Furthermore, “every well-trained surgeon in the world is trained in a Halsted-type system, and all still live by the Halsted principles of surgery.”

I strongly recommend this book to all who are intrigued by the history of medicine, to those who admire pioneers who leave their mark on humanity, and to everyone who has benefited from a surgical operation. A “nod and deep debt of gratitude” indeed is due to this extraordinary man.

The reviewer, F. David Winter Jr., MD, MACP, is a physician in the Department of Internal Medicine at Baylor University Medical Center at Dallas.

BOOKS RECEIVED, November 2010 to November 2011
Call for 2011 Publications

Researchers and staff of Baylor Health Care System, please submit your 2011 publications for inclusion in the publications list to appear in the April issue. Send the citations to cynthiao@BaylorHealth.edu.
Facts and ideas from anywhere

**KAIHOKEN**

In Japanese, the word means “health insurance for all” (1). In 2011, Japan celebrated 50 years of universal health insurance, which started there in 1961, assuring access to a wide array of health services for the entire population. Since then, benefits have become more egalitarian while health expenditures have remained comparatively low: 8.5% of the gross domestic product (GDP) and 20th of countries in the Organization for Economic Co-operation and Development (as of 2008). This achievement is particularly remarkable because the percentage of the population aged 65 years and older has increased nearly fourfold (from 6% to 23%) during these past 50 years. Many factors contributed to this impressive performance, including public health policies, high literacy rates and educational levels, the traditional diet, exercise, economic growth, and a stable political environment.

As described by Reich and colleagues (2) from both Japan and the USA, with the inauguration of Emperor Meiji in 1868, the Japanese government embarked on rapid westernization throughout society. In health care, the government over time succeeded in changing the basis of medical practice from Chinese to Western medicine. Unlike other Asian countries, Japan did not allow independent schools in Chinese medicine to coexist with schools teaching Western medicine. Moreover, the transition was achieved with minimal cost and limited social disruption. For hospitals, however, Japan needed to adopt a new method of delivering care because virtually no public or religious institutions could serve this role. Japan developed hospitals for specific purposes: those for teaching and research, those for army and navy personnel, those for quarantining patients with communicable and venereal diseases (the public hospitals), and—the most numerous—private hospitals that expanded from clinics. In all four cases, the hospital was regarded as the doctor's workplace, and a doctor served as director with clinical and administrative responsibilities. The medical staff of these new hospitals was typically controlled by the professors of prestigious medical schools, notably the University of Tokyo. Physicians were rotated, at the decision of the professor, within the closed network of the university clinical department and its affiliated hospitals.

The most successful private hospitals continued to expand until they rivaled the large hospitals in the public sector. Thus, there was not much distinction between physicians' offices and hospitals. Large medical centers maintained outpatient departments, which patients could visit without referrals. There was also not much distinction between specialists and general practitioners. Those who went into private practice mostly provided primary care because they did not have access to hospital facilities. This basic structure continues today.

In 1945, at the end of World War II, Japan's major cities had been destroyed and an estimated 3.2 million people had died (3, 4). Deep poverty and malnutrition scarred the entire country. Japan's surrender was followed by 7 years of US occupation that sought to restructure the health care system as part of its goal of democratizing the society. The occupying forces strengthened community health institutions. Astounding gains in health status occurred. Between 1947 and 1955, average life expectancy in Japan increased by nearly 14 years. These achievements were attributed to public health policies that were started before the war and facilitated during the occupation, along with reconstruction efforts, and were expanded by the Japanese government after it regained sovereignty in 1952. These early postwar health gains included employee-based health insurance and community health insurance which covered over 70% of the population. Medical education continued during that early postwar period. The hierarchical structure with the University of Tokyo at the top remained intact. Japan now has the world's longest life expectancy.

Japan is currently undergoing several sociocultural changes that are challenging its society, including the rise of part-time and temporary employment for young workers, a growing number of young women who postpone marriage and childbearing, the ever-expanding number of older people, a widening inequality in income, and diversity in values. Japan's fertility rate has declined to 1.37 live births per woman—about the same rate as in Italy and Germany, slightly higher than the rate in Singapore and South Korea, and much less than the replacement rate (2.2 children per woman aged 15 to 45 years). These demographic changes have profound implications for Japan's health care system in the future.

**William C. Roberts, MD**

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ACUTE MYOCARDIAL INFARCTION WITH LOW-DENSITY LIPOPROTEIN CHOLESTEROL LEVELS <70 MG/DL

Lee and 19 other authors (5) from South Korea analyzed 1054 patients with acute myocardial infarction (AMI) who had baseline low-density lipoprotein (LDL) cholesterol levels <70 mg/dL and survived between November 2005 and December 2007. The patients were divided into two groups according to the prescribing of statins at discharge (statin group, N = 607; nonstatin group, N = 447). Statin therapy significantly reduced the risk of the composite endpoint (death, recurrent AMI, target coronary artery revascularization, and coronary artery bypass grafting) at 1 year. Statin therapy reduced the risk of cardiac death by 53% and the risk of coronary revascularization by 55%, but there was no difference in the risk of the composite of all-cause death, recurrent AMI, and repeated percutaneous coronary intervention rates. This study indicates that patients with LDL cholesterol levels <70 mg/dL who take statins have better outcomes than those who do not, despite the relatively low baseline LDL level. Another lesson is that an LDL of 70 mg/dL is not low enough and <50 mg/dL almost certainly would be better.

HOSPITALIZATION AND MORTALITY RATES IN HEART FAILURE PATIENTS ≥65 YEARS

Heart failure (HF) imposes one of the highest disease burdens of any medical condition in the US, with an estimated 5.8 million patients having HF in 2006. The risk of developing HF increases with advancing age, and as a result, HF ranks as the most frequent cause of hospitalization and rehospitalization in older Americans. Heart failure is also one of the most resource-intensive conditions, with direct and indirect costs in the US estimated at $39 billion in 2010.

As the US population grows older, the HF hospitalization rate would be expected to increase, but this may not be the case. Chen and associates (6) from several US medical centers examined changes in HF hospitalization rates and 1-year mortality rates in the US in the years 1998 to 2007. They included only Medicare beneficiaries hospitalized during that time where the principal discharge diagnosis was HF. The adjusted HF hospitalization rates declined from 2845 per 100,000 person-years in 1998 to 2007 per 100,000 person years in 2008, a relative decline of 30%. The overall 1-year mortality rate declined slightly over that decade but remained high. This finding, of course, is good news. As the Framingham study has taught, approximately 90% of patients who eventually develop HF have preexisting systemic hypertension. Thus, if patients with hypertension were treated (and adequately), the number who develop HF would almost certainly decline.

OBESITY AND DIABETES MELLITUS IN HIGH-POVERTY URBAN AREAS VERSUS LOW-POVERTY AREAS

Ludwig and colleagues (7) from several US centers assigned 4498 women with children living in public housing in high-poverty urban areas (in which ≥40% of residents had incomes below the poverty threshold) to one of three groups: 1788 were assigned to receive housing vouchers, which were redeemable only if they moved to a low-poverty center tract (where <10% of the residents were poor) and received counseling on moving; 1312 were assigned to receive unrestricted, traditional vouchers with no special counseling on moving; and 1398 were assigned to a control group that was offered neither of these opportunities. The prevalence of a body-mass index (BMI) ≥35 kg/m², a BMI ≥40, and a glycated hemoglobin level of ≥6.5% were lower in the group receiving the low-poverty vouchers than in the control group, but not significantly different between the group receiving traditional vouchers and the control group. This study indicates that the opportunity to move from a neighborhood with a high level of poverty to one with a lower level of poverty was associated with a reduction in the prevalence of extreme obesity and diabetes mellitus. Better income is associated with better health.

INFANT MORTALITY

According to the World Health Organization and other groups in 2009, 3.3 million babies died around the world before they were 1 month old (8). Many apparently could have been saved by such simple techniques as ensuring that the mothers gave birth on clean surfaces, breastfed their babies, and kept them warm by holding them close. Among the 193 countries examined, the highest newborn death rate in the world is in Afghanistan, where one of every 19 babies dies before the first-month birthday. By comparison, one of every 233 newborns dies in the USA, 1 in 909 in Japan, 1 in 455 in France, 1 in 385 in Lithuania, and 1 in 345 in Cuba. The US is #41 worldwide in newborn death rates.

Some factors considered in explaining our high newborn death rate include the mother’s health before pregnancy. Maternal obesity, smoking, high blood pressure, and diabetes mellitus increase the chances that babies will not survive. African American babies have higher death rates than European American babies, no matter how rich or poor the mothers are. And the USA has an unusually high rate of premature births, which reduce a baby’s chance of survival. Possibly fertility treatments, common in the USA, lead to premature births and therefore higher newborn death rates.

SUICIDAL BEHAVIOR IN THE USA

The Centers for Disease Control and Prevention (CDC) in October 2011 presented its results from a study of >90,000 adults in 2008 and 2009 (9). The participants did not include homeless people, those in the military, or those hospitalized with psychiatric problems. An estimated 1 million adults in the USA per year reported making a suicide attempt in 2008 and 2009; 36,035 committed suicide in 2008. Suicide is the tenth leading cause of death in the US. An estimated 666,000 people visited US hospital emergency rooms in 2008 for self-inflicted violence. More adults in the Midwest and West have suicidal thoughts than those in the rest of the country. In the US in 2008, 8.3 million people had suicidal thoughts (3.7% of the population), 2.2 million people made suicidal plans (1% of the population), and 1 million people attempted suicide (0.5% of the population). According to the CDC, 0.8% to 1.5% of
adults in Texas in 2008 and 2009 attempted suicide. The state with the highest rate of suicidal thoughts was Utah (6.8%), and the state with the lowest was Georgia (2.1%). Actual suicide attempts were highest in Rhode Island (1.5%) and lowest in Delaware and Georgia (0.1%).

MULTIVITAMINS AND DIETARY SUPPLEMENTS

Two articles published in prominent medical journals in October 2011 suggest that multivitamins and many other dietary supplements often do not have health benefits and indeed in some cases may cause harm (10). Some nutrition researchers say taking vitamins is a waste of money for those without a specific nutrient deficiency or chronic illness. It appears from a number of studies that supplements do not make healthy people healthier. Vitamins B6 and B12, for example, are often touted as being good for the heart, but several studies have found that they do not lower the risk of cardiovascular disease. Vitamin C has not been shown in many studies to lower a person’s risk of getting a cold. Calcium, while important to bone health, does not lower the risk of heart disease or cancer and may increase the risk of kidney stones. Researchers and nutritionists still recommend dietary supplements for the malnourished and people with certain nutrient deficiencies or medical conditions. Folic acid, the supplement of folate, reduces the likelihood of a common birth defect when taken by pregnant women. It appears that a “balanced diet” is the best way to get needed vitamins, particularly when the diet consists of plant-rich foods. Vitamin C is found in citrus such as oranges and limes; dairy products are heavy in calcium; almonds are heavy in vitamin E; leafy greens such as spinach are heavy in folate.

HIRING SMOKERS

I remember reading years ago a $1.00 biography of Ted Turner who founded CNN and was one of the great innovators of the 20th century. Early on at CNN, he interviewed all prospective employees and was said to ask each one, “Do you smoke cigarettes?” If the potential employee said “yes” he apparently would reply, “If you are so dumb as to smoke cigarettes, you are not smart enough to work here.”

Baylor Health Care System announced that starting on January 1, 2012, it will no longer hire smokers in its North Texas facilities (11). Baylor Dallas has for some time aggressively pushed a “stop smoking” program for its current employees, and those who smoke face a surcharge in their health insurance cost. A ban on hiring smokers is controversial, but it is the right move. Baylor Dallas is not alone in the “no-smokers” hiring policy. Memorial Hermann Hospital in Houston, Texas, and the Cleveland Clinic in Cleveland, Ohio, already have done the same.

As we all know, tobacco use is the leading preventable cause of death in the USA. Dr. Donald Berwick, head of the Centers for Medicare and Medicaid Services, emphasized that persuading people to stop smoking is a top priority of a federal campaign to empower Americans to make lifestyle changes to prevent certain diseases.

ONE SPERM DONOR AND 150 CHILDREN

Jacqueline Mroz of The New York Times described a woman who used a sperm donor to conceive a baby 7 years earlier and hoped that one day her son would get to know some of his half-siblings (12). She searched a web-based registry for other children fathered by the same donor and helped to create an online group to track them. Over the years, she watched the number of children in her son’s group grow and grow and grow. Today there are 150 children, all conceived from the same sperm donor, in this group of half-siblings, and more are on the way.

As more women choose to have babies on their own and as the number of children born through artificial insemination increases, large groups of donor siblings are starting to appear. Although so far 150 is the largest, many others now comprise 50 or more half-siblings cropping up on websites and in chat groups where sperm donors are tagged with unique identifying numbers.

Now there is growing concern among parents, donors, and medical experts about potential negative consequences of having so many children fathered by the same donor, including the possibility that genes for rare diseases could be spread more widely through the population. Of course, accidental incest between half-sisters and half-brothers, who often live close to one another, obviously could occur.

Fertility clinics and sperm banks apparently earn huge profits by allowing lots of children to be conceived with sperm from popular donors. Families want more information on the health of donors and the children conceived with their sperm. Critics are calling on legal limits on the number of children conceived using the same donor sperm and a reexamination of the anonymity that cloaks many donors.

Other countries, including Britain, France, and Sweden, limit how many children a sperm donor can father. There is no such limit in the USA. There are only guidelines issued by the American Society for Reproductive Medicine, a professional group that recommends restricting conception by individual donors to 25 births per population of 800,000.

No one really knows how many children are born in the USA each year using sperm donors. Some estimates put the number at 30,000 to 60,000. Mothers of donor children are asked to report a child’s birth to the sperm bank voluntarily, but just 20% to 40% of them do so. Because of this dearth of records, many families turn to the registry’s website, www.donorsiblingregistry.com, for information about a child’s half-brothers or half-sisters. On the website, parents can register the birth of a child and find half-siblings by looking up a number assigned to a sperm donor. Many parents are shocked to learn just how many half-siblings a child has. It looks like there may be some legislation in this area in the near future.

ADOLPHE QUETELET AND BODY MASS INDEX

One of the first academics to seek correlations between measurement of body size (anthropometry) and social conditions was Belgian-born Lambert Adolphe Jacques Quetelet (1796–1874) (13) (Figure). A prodigy in mathematics, he also studied sculpture and painting, published poetry, and coauthored
a libretto. Quetelet founded the first astronomical observatory in Belgium in 1826. But soon he turned his attention from the stars to the study of the human form. When recruited to design a national census of the Netherlands, Quetelet— Influenced by seminal thinkers in probability theory, including Joseph Fourier and Siméon Poisson—established the principle that a random sample from a representative diversified group could be used to estimate the characteristics of a total population. Over the ensuing decades, Quetelet contended that “the study of man” could be aided by the study of averages of physical characteristics, as well as rates of birth, marriage, and growth. These data, over time, might provide insights into social differences between regions and countries. In 1831 and 1832, he conducted what is believed to be the first study of newborns and children based on their heights and weights and then extended his survey to adults.

Three years later, Quetelet published his seminal work, A Treatise on Man and the Development of His Aptitudes. Part of the book identified the growth spurts following birth and puberty. Quetelet’s ultimate aim was to define the characteristics of the “average man,” and he initially looked to the familiar bell-shaped curve that had been used by scientists to describe natural phenomena. But he had problems fitting people’s heights and weights into such a normal distribution. Quetelet ultimately devised novel formulas to link height and weight and is credited with providing the calculations for what we currently term the body mass index, the ratio of weight in kilograms and height in meters squared (thus a measure of weight standardized by height), and key measures of growth and development.

With this metric in hand, Quetelet and other academics of his era gathered in Brussels in 1853 at the first International Statistical Congress. Among the many projects launched by the meeting was one to prepare a “uniform nomenclature of the phenomena.” These data could then be linked to body size and the risk of various diseases, as well as social variables like geography, migration, war, and famine. While keen to apply statistics to social science, Quetelet, who still performed exacting astronomical measurements, was alert to the dangers of overinterpreting numbers associated with factors that might contribute, like crime rates, suicide rates, and intellectual aptitude. Thus was born the BMI, which, in my view, should replace the respiratory rate as one of the “vital signs” of the physical examination.

EXTREME WEATHER IN 2011

From February’s “snowmageddon” to spring’s deadly tornadoes, from Hurricane Irene to Texas’ raging wildfires, 2011 was an extraordinarily bad year for weather (14). The director of the National Oceanic and Atmospheric Administration’s National Weather Service described 2011 as the first year since 1980 (when such measurements began) in which 10 separate weather events each caused more than $1 billion in damage. These figures are partly due to increased population density: the more people living in a particular area, the more property that can be damaged when a storm hits. Extreme conditions happen in places that usually do not experience them and are therefore less prepared. A hurricane on the Eastern seaboard can be expected to cause flooding in coastal North Carolina and New Jersey—but not in northern Vermont. The average global land temperature from January through July was among the warmest since recordkeeping began over 100 years ago. Warmer temperatures lead to more severe and frequent extreme weather events, like tornadoes, droughts, and floods.

CHILDHOOD ALTRUISM

A recent social science study, published in September 2011 in the online journal PLoS One, asked 136 children aged 3 and 4 years old to step one at a time into a playroom where each was handed six sets of colorful stickers (15). They were told that they could keep all of their stickers or give some or all to a child they didn’t know. The social scientist was attempting to determine if children are altruistic. About two thirds of the children chose to give one or more sets of stickers to an unknown recipient who had none. There were no significant differences in generosity between boys and girls. Among those who declined to share, many had something in common: a variation in a gene known as AVPR1A that regulates a hormone in the brain associated with social behaviors. Researchers found that this genetic variant was associated with a significant decrease in willingness to share. Of the 136 children invited to share some of their sets of stickers, two participants gave away their entire supply. Asked in a videotaped interview why he gave away all his stickers, one child responded: “That’s how you become happy.”

Of the 136 children in the Israeli study, the largest group gave away one sticker; the second largest group gave away none. Twenty-two children gave away more than one sticker. Thus, altruism in young children, as in adults, exists in near equal parts with selfishness.

Another study, also published in PLoS One in October 2011, found a sense of fairness and altruism in 15-month-old babies, tested in part on their willingness to share a favorite toy (15). While genetics may play a part in people’s willingness to share, environmental influences from home, school, and the world at large may play a larger role, according to social scientists. Even children too young to talk seem able to absorb and imitate acts of empathy and generosity. Positive reinforcement can help cultivate generous behavior. Upon witnessing generosity in a child, parents are advised to resist any impulse to bestow a gift and instead offer praise of the child’s character as well as his or her behavior. Generosity apparently can be habit-forming. Magnetic resonance imaging has shown that being generous and being described as generous can engage the so-called reward circuitry in the brain, prompting release of dopamine-like neurotransmitters that are associated with positive feelings.

According to Kevin Helliker, writing in The Wall Street Journal, most research to study the roots of generosity takes

Figure. Adolphe Quetelet.
place in adults. Studies have found that about 70% of adults choose to share when cash is used in the same exercise as that performed with the Israeli children. It is a common exercise used by researchers known as “the dictator game,” in which the participant, the dictator, has to decide how to split a thick sum of money between himself and a recipient who is unknown and therefore not likely to reciprocate.

Experiments with children typically are staged free of parents, siblings, and other acquaintances from whom the child might expect a reward of some kind. In a large study of British school children aged 4, 6, and 9, psychologist Joyce Benenson (16) found a strong correlation between socioeconomic status and willingness to give. Acts of generosity were less common among children in poverty, because as she says, “Poverty is linked with myriad differences in socialization practices, including less interaction with unfamiliar adults” and greater exposure to violence.

**LEFT-HANDEDNESS**

Only about 10% of Americans are left-handed, yet since the end of World War II, nearly half of American presidents have been lefties (Harry S Truman, George H. W. Bush, William J. Clinton, and Barack Obama). Is there something special about left-handed people? Rik Smits (17), a left-handed science writer, attempted to answer this and other questions in *The Puzzle of Left-Handedness.* He writes that lefties and righties don’t differ in personality, ability, creativity, or any other measurable characteristic. Smits debunks a number of myths about “handedness,” but what makes us righties or lefties has not been determined. *The Puzzle of Left-Handedness* offers some interesting comments on handedness, but Smits’ speculations ultimately leave one scratching his or her head—with either hand.

**PHARMA IN THE JUNGLE**

Not long ago my ex-wife (Carey Cansler Roberts) sent me the book *State of Wonder* by Ann Patchett (18). (The book reminded her of our trip together to the Amazon, Menaus, and the Rio Negro many years earlier.) The book is about an American drug company based in Minnesota that wanted to develop a fertility drug to allow women to get pregnant at any age. The stockholders were overjoyed at the possibility. Deep in the Amazon rainforest along the banks of the Rio Negro, the Lakashi tribe had been living quietly, procreating without fanfare well into their eighth decade. An elusive but brilliant scientist, Dr. Annick Swenson, had discovered that these women gnawed on the bark of a rare tree deep in the jungle and that the bark imparted fertile longevity.

But Dr. Swenson took her own sweet time on the research, and the pharmaceutical company grew impatient—especially since she had eschewed all forms of contact. They did not even know exactly where she was. So the company sent a fellow scientist, Anders Eckman, to track her down and report on the state of drug development. Unfortunately, the Minnesotan did not do well in the Amazon, and within weeks Eckman was dead of a febrile illness.

Then, his lab partner, who became the heroine, was dispatched to the jungle. Marina Singh, a loner pharmacologist, had quit her obstetrics-gynecology residency after a horrendous medical error, oddly enough under the auspices of the department chair, none other than Dr. Annick Swenson. The senior physician, as a consequence, abandoned her junior physician at the time in the face of medicolegal calamity.

Marina suffered the various insults of the tropics during her hunt for the elusive Dr. Swenson: flotilla of insects, lost luggage, venomous snakes, psychogenic side-effects of antimalarial drugs, intermittent fevers, and generalized disorientation. The pharmacological drama shows that the bark of the magical tree turned out to confer immunity to malaria, in addition to providing fertile longevity. The scientists realized that the drug company would quickly pull the financial plug if it became aware that the goal of the scientists was to help the world’s poor fight mosquito-borne parasites, rather than to help wealthy Western women achieve pregnancy in their sixth and seventh decades. The industry wanted a blockbuster fertility drug, not a pennies-per-pill malarial agent. Hence, the secrecy of Dr. Swenson and her refusal to update the drug company and its anxious stockholders on her progress.

That the good Dr. Swenson had been nibbling the ambrosia bark herself and became pregnant and preeclamptic at the age of 72 years, and that her former underling, who quit midway through training, was the only available physician to perform the emergency C-section in the teeming Amazonian jungle, is not how most medical errors get worked out.

**PREGNANT MARATHON**

A few hours after completing the 26.2-mile Chicago marathon, Ms. Miller gave birth to a 7-pound, 13-ounce healthy baby. Ms. Miller is an experienced marathoner and was 38 weeks and 5 days pregnant during the marathon (19).

**THE IRONMAN WORLD CHAMPIONSHIP**

Thirty-eight-year-old Craig Alexander had won this event in 2008 and in 2009, and in 2011 he did it again (20). In 2011, he beat the previous record set in 1996 by approximately 1 minute. He completed the 2.4-mile ocean swim, the 112-mile bike ride, and the 26.2-mile marathon run in 8 hours, 3 minutes, 56 seconds. Britain’s Chrissie Wellington, 34 years old, won her fourth world title, finishing at 8:55:08. It is amazing what the human body is capable of.

Jacque Steinberg has written *You Are an Ironman* (21). The ironman and ironwoman triathlon must be completed within 17 hours. The ironman originally started in Hawaii with a field of 15. It now is an event held throughout the USA in which more than 50,000 athletes cross the finish line.

Jacque Steinberg’s book follows three men and three women, most in their 40s, who pay a nonrefundable $525 a year in advance to sign up for the 2009 Ironman Arizona. The reader follows the six as they put their normal routines on hold and adopt rigorous training regimens. One of the six was Leanne Johnson, who made a vow while cheering on her husband to his first ironman finish. Her husband, Scott, was born with cystic fibrosis and underwent a double-lung transplant before setting his sights on an ironman. It was now his wife’s turn, and the
30-year-old nurse drew the same support from her husband that she gave to him. Another of the six was a nurse with two teenagers who got the idea after overhearing two triathletes swap stories. Another was a former social worker and mother of five who took up running as an adult. Another was an English teacher inspired by the broadcast of the original ironman in Hawaii he had seen as a child.

HAPPILY MARRIED

Some people have considered it the top oxymoron. Lindsey Townsend (22), writing in the Dallas Morning News, had an interesting piece on marriage, a subject of which I am far from an expert. She states that “most of us still expect to be rocked by passion while nestled in security.” But she indicates that some of her friends who have been more or less happily married for years admit “after the second drink” that they resent the lack of passion in their lives. She calls that the “Raisin Bran syndrome”: “Even if you really like Raisin Bran, do you want to eat it every morning for the rest of your life?” She suggests that the real trouble starts when boredom leads to bad manners. “We stop behaving ourselves and all too often our beloved ends up getting the worst part of us, while we save the good stuff for strangers and friends.” She speaks of the pastor who was asked to give words of wisdom to a newlywed couple. He said, “After 50 years of counseling couples, it’s a bit humbling to admit that the best words of wisdom to a newlywed couple. He said, “After 50 years of counseling couples, it’s a bit humbling to admit that the best advice I have to offer is to be kind to each other.”

When I was at the National Institutes of Health for many years, I virtually always went into my office on Saturdays. The reason was peace and quiet. It was a time I could think out projects and manuscripts I was working on—how to package them, how to put a pink ribbon around them and get them through the editorial boards of various medical journals. Without that peaceful quiet think time, my publication list would be enormously shorter. Today, with e-mails, cell phones, car radios, and busy homes, it is more difficult for many to find sites where creativity comes alive.

THE 1% VERSUS THE 99%

Everyone likes a tax paid by someone else, so it is not surprising that 99% of us would rather the other 1% paid more taxes. As Scott Burns indicates, in 2009 the top 1% of all income tax returns in the USA with a positive-adjusted gross income pulled in a total of $1.3 trillion (25). Of that amount, 24% was paid in federal income taxes, or $318 billion. The top 1% received nearly 17% of all income and paid 37% of all federal income taxes. The bottom 75% of all taxpayers (annual income <$66,000) had a total of $2.75 trillion in income and paid $110 billion in income taxes, about 4.1% of income. The top 1% income people (those with adjusted gross incomes of $344,000 annually) paid 6 times as large a proportion of their income than the bottom 75%. The top 5% had household income of $155,000 or more; the top 10%, $112,000 or more; the top 25%, $66,000 or more; and the bottom 30%, <$32,000 annually. Those were figures for 2009.

Can people in the top 1% pay more? Of course, but how much of their $1.3 trillion can we take? Only $1 trillion is left because the top 1% already pay $318 billion in taxes. Since the official federal deficit is estimated at $1.3 trillion for the 2011 fiscal year, even if the top 1% paid 100% of their income in taxes, the federal budget would not be balanced. As Scott Burns indicates, “The 1% vs. the 99% is a powerful side byte for a political debate, but it is deeply trashy economics.”

JOBS, HOPE, AND CASH

Peggy Noonan (26), writing in The Wall Street Journal, starts a recent column this way: “Ten years ago, Steve Jobs was alive, Bob Hope was alive, Johnny Cash was alive. Now we are out of jobs, out of hope and out of cash.” She stated that she heard that from a Transportation Security Administration agent in New York. The agent’s joke, she indicated, was a good summation of the current moment and the public mood.

VIRTUES OF SOLITUDE

Diana Senechal’s fourth book, Republic of Noise: The Laws of Solitude in Schools and Culture, will be published in January 2012 (24). She is a former teacher in the New York Public Schools. She takes schools to task for a tight focus on rapid activity and instant results. She argues that schools need to make room for the things of solitude, such as literature, science, art, friendship, and matters of conscience. I am reminded of Johann von Goethe’s comment: “Talents are best nurtured in solitude; character is best formed in the stormy billows of the world.” Carl Sandberg said, “One of the greatest necessities in America is to discover creative solitude.” Henry-Marie Beyle stated, “One can acquire everything in solitude but character.”
SEVEN BILLION PEOPLE

The world’s population hit 7 billion in October 2011 (27, 28). The world’s population reached 1 billion in 1804; 2 billion in 1927; 3 billion in 1959; 4 billion in 1974; 5 billion in 1987; 6 billion in 1998; and now 7 billion in 2011. The United Nations projects that the world population will reach 8 billion by 2025 and 10 billion by 2083. The numbers, of course, could be much higher or lower depending on such factors as access to birth control, infant mortality rates, and average life expectancy, which has risen from 48 years in 1950 to 69 worldwide today.

China remains the most populous nation with 1.34 billion people. In the past decade, it added 74 million, more than the population of France and Thailand. Nonetheless, its growth has slowed dramatically, and the population is projected to start shrinking in 2027 and by 2050 to be smaller than it is today. Three decades of strict family planning rules that limit urban families to one child and rural families to two helped China achieve a rapid decline in fertility.

India, with 1.2 billion people, is the second most populous country and is expected to overtake China around 2030 when its population will reach an estimated 1.6 billion. Nevertheless, India’s fertility rate, now 2.6 children per woman, should fall to 2.1 by 2025 and 1.8 by 2035. More than half of India’s population is under 25.

Europe is having the opposite problem. Spain used to give parents $2500 Euros (more than $3000) for every newborn child to encourage families to reverse the country’s low birth rate. But the checks stopped when Spain’s austerity measures took hold. Who will pay the bills to support the older ones in the years ahead is a bothersome question. In many European countries, birth rates are shrinking and populations are aging. Women have chosen to have their first child at later ages, and the difficulties in finding jobs and affordable housing are discouraging some couples from having any children. In 2010, for the fourth consecutive year, more Italians died than were born. Italy’s population, nonetheless, grew slightly to 60.6 million due to immigration, a highly charged issue across Europe now.

Unlike many countries in Europe, France’s population is growing slightly but steadily every year. It has one of the highest birth rates in the European Union, with around 2 children per woman. One reason is immigration to France by Africans with large family traditions, but it’s also due to family-friendly legislation. The government offers public preschools, subsidies to all families with >1 child, generous maternity leave, and tax exemptions for employers of nannies.

Like France, the USA has one of the highest population growth rates among industrialized nations. Our fertility rate is just below the replacement rate of 2.1 children per woman, but our population has been increasing by almost 1% annually due to immigration. With 312 million people, the US is the third most populous country after China and India.

Most of the population growth, of course, is coming from the developing nations, not from the developed nations. Since 1950, with projection to 2050, the developed nations are estimated to increase by 0.8 billion people and the undeveloped, by 1.3 billion. Thus, those with the least are having the most.

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In response to the earth’s reaching 7 billion people, a professor at Columbia University commented, “The consequences for humanity could be grim.” A New York Times columnist declared that “the earth is full” and that “we are eating into our future.” Another editorial mentioned “a human swarm that is over breeding.” We are overbreeding in a way that “prosperous, well-educated families” from the developed world do not.

Certainly this population growth has disproved Paul Ehrlich’s thesis in his 1968 The Population Bomb, which opened with this sentence: “The battle to feed all humanity is over. In the 1970s the world will undergo famines—hundreds of millions of people are going to starve to death in spite of any crash programs embarked upon now.” The book was wildly popular, but the mass starvation he predicted never materialized, and the people in India whom he thought could never feed themselves are now eating better than ever despite a population more than twice the size it was when The Population Bomb appeared.

Thomas Robert Malthus’ ominous warnings about a growing population’s outstripping the food supply were not borne out in his day (the late 1700s and early 1800s) or since. The predictions of Malthus proved to be wrong. The premise of his work, however—that there must be some limit to population growth—is hard to argue with. As William McGurn writes in The Wall Street Journal, “The main flaw in Malthus is . . . his premise. Malthusian fears about population follow from the Malthusian view that human beings are primarily mouths to be fed rather than minds to be unlocked. In this reasoning, when a pig is born in China, the national wealth is thought to go up, but when a Chinese baby is born the national wealth goes down” (28).

Matt Ridley, author of The Rational Optimist, suggests that human progress is driven when people connect with one another and exchange ideas as well as goods. In our own day, he believes, this interaction has been accelerated by the revolution in technology that has made distance largely irrelevant. That is one reason he takes a generally benevolent view of population growth. Matt Ridley goes on to say: “The mixing of ideas made possible by the Internet makes the drying up of innovations almost impossible to achieve, even if we wanted to, and the improvement in living standards almost inevitable” (28).

Maybe William McGurn is right: “Instead of looking for ways to reduce the number of people at the banquet of life, we would do better to look for ways to lay a better and more bounteous table” (28).

CHINA VS. USA

According to the World Bank, the size of China’s economy is $10.1 trillion and that of the USA, $14.6 trillion, both based on purchasing power parity (29). But China is narrowing the gap quickly. Over the past 10 years, the annual real growth of China’s GDP averaged 10.5% compared with 1.7% in the USA. The Chinese economy increased at an annual rate of 9.6% in the first half of 2011 versus a rate of <1% in the USA. Thomas Friedman, in a recent New York Times column, states: “We are the United States of Deferred Gratification. China is the People’s Republic of Deferred Maintenance. They save, invest, and build. We spend, borrow, and patch” (30).
The US’s reign as the largest world economic power began a little before 1890, when it supplanted the previous global giant, namely China, which had boasted the largest economy in the world from 1500 until nearly 1890. Yet during those 5 centuries when its economy was the world’s largest, China was never even close to being the world’s wealthiest country. Italy was almost twice as rich in 1500, the Netherlands almost 3 times as rich in 1700, and the UK 6 times as rich in 1870. Today, though the GDPs of the US and China are roughly equal, the average person in China lives on an income that can buy only 16% of the goods and services that the average person in the USA can buy, and it will take decades for that gap to close.

As Charles Kenny argues in Bloomberg Businessweek, second place is not all bad (29). In that position, the US probably would not have to be the world’s police. US military spending now accounts for more than two fifths of the world’s total, and it sucks up a larger percentage of GDP than the military spending of any other member of the Organization for Economic Co-operation and Development, which numbers 20 nations. And if the US is #2, it would probably be more popular around the world than it is presently. Our image abroad has improved enormously since 2007 and that of China has fallen. Nevertheless, the US still outperforms China on almost every conceivable quality-of-life indicator, including happiness polls, where China is in 70th place. The average American lives 5 years longer than the average Chinese, and our mortality rates for children <5 are less than half the Chinese levels. We have a democracy and elect the president. The same cannot be said of the leadership of the Communist Party of China. And certainly there are advantages to life, liberty, and the pursuit of happiness that we have in greater abundance.

IRAQ AND AFGHANISTAN

The Iraq War started in 2003 and ended in December 2011 (31, 32). It was not a victory and not a defeat; it was just over. A total of nearly 4500 troops died in the war. They come home to no parades or pleasant memorials. Whether Iraq will prove to be a democratic ally in the Middle East or retreat into sectarian violence, encouraged by neighboring Iran, remains to be seen.

An important lesson from the war is not about how it ended but about how it began—with the disastrously mistaken belief that the US could advance its interests by intervening militarily in the Middle East. Instead, the hubris bred hostility among Muslims and appears likely to make Iran the big winner in the Middle East. Instead, the hubris bred hostility among Muslims and appears likely to make Iran the big winner in the Middle East.

Although we are leaving Iraq, we are still trying nation-building in Afghanistan (33, 34). Three countries have tried before: Russia (then USSR) tried it three times, from 1839 to 1842, from 1878 to 1880, and in 1919. They failed each time and lost 28,000 troops. The British tried it three times, from 1839 to 1842, from 1878 to 1880, and in 1919. They failed each time and lost 28,000 troops. The British tried it three times, from 1839 to 1842, from 1878 to 1880, and in 1919. They failed each time and lost 28,000 troops. The British tried it three times, from 1839 to 1842, from 1878 to 1880, and in 1919. They failed each time and lost 28,000 troops.

Steve Jobs (1955–2011)

There is no question that Steve Jobs shook the world (35–44). He first redefined the personal computer, accelerating the decline of many of the first-generation computer companies that had focused on centralized mainframes. His 1984 advertisement for the first Macintosh (introduced that year) made other personal computers look Orwellian. With the Internet he became a broader disruptive force, first radically changing the music industry. His iPod (introduced in November 2001) let listeners buy one song at a time instead of the CDs planned by music publishers. And then there was the iPhone, which upended the mobile industry, and the iPad (introduced in April 2010), which defined the tablet.

But it was not always a straightforward line for Steve Jobs. He was the product of Joanne Schieble, a graduate student in speech therapy at the University of Wisconsin (now known as Joanne Simpson). His father was Syrian-born Abdul fattah Jandali, who was also at the University of Wisconsin working on his PhD in political science. (He was awarded his doctorate in 1956.) While a student in Madison, Wisconsin, he became romantically involved with Joanne, who became pregnant in 1954, but her father didn’t approve of the relationship with Mr. Jandali. Ms. Simpson went to San Francisco for a few months to get away while she was pregnant. She eventually put her son, Steve Jobs, up for adoption. Ms. Simpson returned to Madison and soon afterwards her father died, enabling her and Mr. Jandali to marry. After he graduated, they moved to Syria, where he became a diplomat, but a transitional government prevented that. Ms. Simpson was also unhappy in Syria, and they moved back to Green Bay, where she gave birth to their second child, Mona, who in 1993 published the novel The Lost Father. A few years later, Mr. Jandali and Ms. Simpson divorced, and she later remarried. Mr. Jandali was never involved in Mona’s life as she was growing up.

In 1955, Steve Jobs, as he stated in his commencement address at Stanford University in 2005, was adopted by Paul Jobs, a high school dropout who became a machinist, and Clara Jobs, who never graduated from college. He grew up in San Francisco. Jobs later had a relationship with his birth mother and sister but he never, despite opportunities, wanted to meet his biological father.

In 2006, widowed Mr. Jandali remarried, and he now lives in a gated Reno, Nevada, suburb. He apparently constantly reads books, usually on his iPad, and he has outlined several fiction and nonfiction books that he hopes to finish writing when he retires. He now manages a Reno casino in Boomtown.

Steve Jobs finished only one semester in college. After dropping out of Reed College in Portland, Oregon, Jobs traveled to India, shaved his head, wore local clothing, and became a Buddhist. The lessons of that philosophy stayed with him for the rest of his life.

In 1976, Jobs (age 21) and Stephen Wozniak founded Apple. Wozniak was a self-made engineer of brilliance. (In 1981, Wooz...
crashed his Beachcraft Bonanza and spent months recuperating; he returned to Apple only nominally thereafter. From then on, Jobs was “the man.”) No one quite knew what Jobs was. He was not an engineer or technologist, and he was no conventional businessman. He made himself up as he went along.

In 1979, Jobs led a group from Apple to visit Xerox. They emerged with the ideas that transformed the industry. At Xerox in the 1970s, a group of brilliant researchers invented the personal computer—they called it the Alto—complete with onscreen windows, menus, icons, graphics, and the mouse, all more or less what we know today. Allan Kay was foremost among these genius innovators. Kay built, in turn, on the 1960s inventions of Douglas Engelbart, who was the first to develop the mouse, the onscreen window, and the whole idea of computers that did more things than compute. Corporate Xerox was unimpressed with the Alto. It was expensive, and who needed a personal computer anyway? Xerox ushered in a group from Apple into their top-secret research arena in Palo Alto and allowed them to look and ask questions. Jobs led the Apple group and understood right away that the Xerox researchers had done something tremendous. They had made an easy-to-use computer that spoke pictures instead of numbers. Jobs saw that a cheap version of this elegant computer might be gigantically popular and hugely important. And he ran the project that rolled out the Apple Macintosh in 1984. That Mac was a milestone of modern history. The 1984 Mac had only 128,000 bytes of memory and a tiny 9-inch screen. It looked like an upright shoebox plus keyboard and mouse. But that was the beginning.

Two years later, in 1986, Jobs was fired from Apple, the company he started. Rather than become bitter or seek vengeance, Jobs came to recognize his firing as the best thing that ever happened to him. He maintained a cordial and respectful relationship with his former company. In the interim, he formed NeXT and Pixar. In 1997, Apple bought NeXT, and soon Jobs was CEO of Apple again.

Business historian John Steele Gordon described Jobs’ iPhone. In addition to its being a phone, “it’s an address book, a date book, a camera (both still and moving), a notebook, a clock that tells the time in any city in the world, a compass, a metric converter and a calculator. It takes dictation. You can send and receive written messages with it. It will tell you where you are and help you get where you need to go. It will keep track of your investments and tell you your net worth as of that second. You can deposit a check into your bank account with it while lying in bed. It will give you the latest news, via every major news organization. It’s a dictionary, an encyclopedia and a field guide to birds. It gives you the weather, both where you are and in any city in the world. It will tell you the phase of the moon, send you a bulletin when a new exoplanet has been discovered, tell you the sunrise and sunset times for any place on Earth, show you the cloud cover around the globe and tell you what that bright star in the sky is named” (44). It can do more than 350 things other than being a phone.

The iPhone and its larger brother, the iPad, are remaking the world before our eyes. Already, communications, journalism, publishing, the music business, and the movies will never be the same. “The iPhone and iPad are but the latest in a long series of innovations by Jobs that have fundamentally shaped the technical revolution made possible by the microprocessor, . . . a cheaply manufactured computer on a chip, . . . the most consequential invention since the steam engine about 250 years ago—and probably since agriculture, the invention that started humankind down the road to civilization itself some 10,000 years ago” (44).

As John Steel Gordon indicates, Jobs was not a magician; he is the Henry Ford of our time. Ford didn’t invent anything. Instead, he took something that had largely been invented by others and turned it into a world-transforming technology by making it accessible to the common man. Jobs didn’t invent the microprocessor any more than Ford invented the automobile. Indeed, he and his companies did not invent much of the technology that makes the iPhone and such so extraordinary. They put together the pieces invented elsewhere to produce something profoundly new that the public loved and could also afford.

Jobs along the way made Apple the second most valuable company in the world. Jobs owned 5.4 million shares of Apple and, according to the Forbes 400, was worth $7 billion, making him the 39th richest person in the world. (His fierce rival—Bill Gates—is #1, worth $59 billion.)

—William Clifford Roberts, MD
2 November 2011

8. In ranking of newborn deaths, ’we’re No. 41’ is USA’s shame. USA Today, October 4, 2011.
32. After nine years in Iraq, time for troops to come home. *USA Today*, October 24, 2011.
42. Razaque R. Steve Jobs put life and death in their place. *USA Today*, October 19, 2011.
ADVANCES IN SKIN AND WOUND CARE

The clinical relevance of treating chronic wounds with an enhanced near-physiological concentration of platelet-rich plasma gel


Objective: This study investigated clinical outcomes in chronic nonhealing wounds following the short-term use of an enhanced, near-physiological concentration of platelet-rich plasma (PRP) gel (AutoloGel System, Cytomedix, Inc, Gaithersburg, Maryland).

Design: Study design was a large, observational case series using a multicenter registry database (all wounds included), which compared different populations within the database.

Setting: Thirty-nine centers contributed to the registry, including long-term acute-care centers, outpatient clinics, a durable medical equipment company, a home health agency, and a long-term-care center.

Patients: The target population included 285 chronic wounds (patient n = 200). Wound etiologies included diabetic, pressure, or venous ulcer; dehisced, surgical, or traumatic wound; and wounds of other etiologies.

Intervention: Therapeutic, PRP gel is produced from patient blood utilizing autologous platelets and plasma that contribute growth factors, cytokines, and chemokines, in a fibrin matrix.

Main measures: Area and volume of the wound and the linear total of undermining and sinus tracts/tunneling were calculated. Clinical relevance was determined by analyzing outcomes in wounds that responded to treatment.

Main results: A positive response occurred in 96.5% of wounds within 2.2 weeks with 2.8 treatments. In 86.3% of wounds, 47.5% area reduction occurred, and 90.5% of wounds had a 63.6% volume reduction. In 89.4% undermined and 85.7% of sinus tracts/tunneling wounds, 71.9% and 49.3% reductions in linear total were observed, respectively.

Conclusion: In chronic wounds recalcitrant to other treatments, utilization of PRP gel can restart the healing process. Rapid treatment response was observed in 275 of 285 wounds, and the magnitude of response was consistently high, with statistically significant outcomes reported for various subgroups.

AMERICAN JOURNAL OF MEDICAL QUALITY

National Priorities Partnership focus on eliminating overuse: applications to cardiac revascularization

Ballard DJ, Leonard BM


As one of several initiatives to transform health care delivery across the United States, the National Priorities Partnership has identified “eliminating overuse while ensuring the delivery of appropriate care” as a top priority. Cardiac revascularization procedures, including coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI), constitute one area of focus for reduction of overuse. Despite the multiyear development of clinical guidelines to define appropriate use of cardiac revascularization, substantial variability in the application of these procedures is observed. Concurrent data collection tools to support real-time clinical decision making regarding appropriateness are needed and can be used, along with financial incentives such as pay-for-performance programs and public reporting of performance information, to support more appropriate use of cardiac revascularization. Efforts to achieve more rational use of CABG and PCI should be made carefully and with the goal that patients receive the most appropriate and effective care.

AMERICAN JOURNAL OF TRANSPLANTATION

Limiting hepatitis C virus progression in liver transplant recipients using sirolimus-based immunosuppression


Hepatitis C virus (HCV) causes progressive liver fibrosis in liver transplant recipients and is the principal cause of long-term allograft failure. The antifibrotic effects of sirolimus are seen in animal models but have not been described in liver transplant recipients. We reviewed 1274 liver recipients from 2002 to 2010 and identified a cohort of HCV recipients exposed to sirolimus as primary immunosuppression (SRL cohort) and an HCV control group of recipients who had never received sirolimus. Yearly protocol biopsies were done recording fibrosis stage (METAVIR score) with biopsy compliance of >80% at both year 1 and 2. In an intent-to-treat analysis, the SRL cohort had significantly less advanced fibrosis (stage ≥2) compared to the HCV control group at year 1 (15.3% vs. 36.2%, P < 0.0001) and year 2 (30.1% vs. 50.5%, P = 0.001). Because sirolimus is sometimes discontinued for side effects, the SRL cohort was subgroup stratified for sirolimus duration, showing progressively less fibrosis with longer sirolimus duration. Multivariate analysis demonstrated sirolimus as an independent predictor of minimal fibrosis at year 1 and year 2. This is the first study among liver transplant recipients with recurrent HCV to describe the positive impact of sirolimus in respect of reduced fibrosis extent and rate of progression.

ANNALS OF THORACIC SURGERY

Bypass versus drug-eluting stents at three years in SYNTAX patients with diabetes mellitus or metabolic syndrome


Methods: Patients (n = 1,800) with left main or three-vessel disease or both were randomly allocated to treatment with a TAXUS Express² paclitaxel-eluting stent (PES) or CABG, and were included in predefined nondiabetic (n = 1,348) or diabetic subgroups (n = 452); 258 patients with diabetes also had metabolic syndrome.

Results: Among diabetic patients, the 3-year major adverse cardiac and cerebrovascular event (MACCE) rate (22.9% CABG, 37.0% PES; P = 0.002) and revascularization rate (12.9% CABG, 28.0% PES; P < 0.001) were higher after PES treatment. Diabetes increased MACCE rates among PES-treated patients, but had little impact on results after CABG. Compared with CABG, PES treatment yielded comparable MACCE in diabetic patients (30.5% versus 29.8%, P = 0.98) and nondiabetic patients (20.2% versus 20.3%, P = 0.99) with low Syntax Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) study scores of 22 or less. For patients with SYNTAX scores of 33 or greater, MACCE rates were lower with CABG (18.5% versus 45.9%, P < 0.001 diabetic; 19.8% versus 30.0%, P = 0.01 nondiabetic). Metabolic syndrome did not significantly predict MACCE or repeat revascularization.

Conclusions: These exploratory analyses suggest that among diabetic patients with complex left main or three-vessel disease, or both, 3-year MACCE is higher after PES compared with CABG. Although PES is a potential treatment option in patients with less complex lesions, CABG should be the revascularization option of choice for patients with more complex anatomic disease, especially with concurrent diabetes. Metabolic syndrome had little impact on 3-year outcomes.

CLINICAL CANCER RESEARCH
Colorectal cancers with microsatellite instability display unique miRNA profiles

Purpose: microRNAs (miRNA) are small noncoding transcripts that play an important role in carcinogenesis. miRNA expression profiles have been shown to discriminate between different types of cancers. The aim of this study was to analyze global miRNA signatures in various groups of colorectal cancers (CRC) based on the presence of microsatellite instability (MSI).

Experimental design: We analyzed genome-wide miRNA expression profiles in 54 CRC tissues (22 with Lynch syndrome, 13 with sporadic MSI due to MLH1 methylation, 19 without MSI [or microsatellite stable, MSS]) and 20 normal colonic tissues by miRNA microarrays. Using an independent set of MSI-positive samples (13 with Lynch syndrome and 20 with sporadic MSI), we developed a miRNA-based predictor to differentiate both types of MSI by quantitative reverse transcriptase PCR.

Results: We found that the expression of a subset of nine miRNAs significantly discriminated between tumor and normal colonic mucosa tissues (overall error rate = 0.04). More importantly, Lynch syndrome tumors displayed a unique miRNA profile compared with sporadic MSI tumors; miR-622, miR-1238, and miR-192 were the most differentially expressed miRNAs between these two groups. We developed a miRNA-based predictor capable of differentiating between types of MSI in an independent sample set.

Conclusions: CRC tissues show distinct miRNA expression profiles compared with normal colonic mucosa. The discovery of unique miRNA expression profiles that can successfully discriminate between Lynch syndrome, sporadic MSI, and sporadic MSS colorectal cancers provides novel insights into the role of miRNAs in colorectal carcinogenesis, which may contribute to the diagnosis, prognosis, and treatment of this disease.

GASTROENTEROLOGY AND HEPATOLOGY
IL-28B as a predictor of sustained virologic response in patients with chronic hepatitis C virus infection
Gonzalez SA, Keefe EB

Genome-wide association studies have recently identified single nucleotide polymorphisms in proximity to the interleukin-28B (IL-28B) gene that can predict sustained virologic response (SVR) in patients with chronic hepatitis C virus (HCV) infection who are undergoing therapy with pegylated interferon (IFN) a and ribavirin. IL-28B
encodes IFN-α3, a type III IFN involved in host antiviral immunity. Favorable variants of the 2 most widely studied IL-28B polymorphisms, rs12979860 and rs8099917, are strong pretreatment predictors of early viral clearance and SVR in patients with genotype 1 HCV infection. Variations in the distribution of IL-28B alleles may partly explain differences in SVR rates among ethnic groups. Further investigations have implicated IL-28B in the development of chronic HCV infection versus spontaneous resolution of acute infection and suggest that IL-28B may be a key factor involved in host immunity against HCV. Clinical trials of IFN-α as a therapeutic agent for chronic HCV infection are currently underway. The use of IL-28B polymorphisms as a predictive tool will have a major impact on treatment strategies for chronic HCV infection, particularly in the context of emerging therapies and direct-acting antiviral agents.

GLOBAl PUBLIC HEALTH

Health effects of an efficient vented stove in the highlands of Guatemala
Harris SA, Weeks JB, Chen JP, Layde P

In Guatemala, as in many places throughout the world, millions of indigenous people cook over non-ventilated indoor open fires. Indoor air pollution and accidental burns are well-known problems attributed to such fires. Efforts have been made to improve health outcomes by placing more efficient vented stoves in homes to decrease such exposure. The purpose of this study is to see if there are any measurable improvements in health outcomes after placement of such stoves within a community. Specifically, this study is designed to evaluate the health effects of placement of the ONIL stove, a rocket-style stove that has been shown to decrease household carbon monoxide (CO) levels and wood-fuel use. The ONIL stove was installed in more than 90% of the homes in Santa Avelina, Quiche, Guatemala between 2002 and 2006. The number of clinic visits per year for acute upper- and lower-respiratory illnesses in this village was compared for the years 2002 and 2006. Clinic visits for upper- and lower-respiratory illnesses combined decreased by 26%, and for acute lower respiratory solely, by 45% between 2002 and 2006. This study suggests that the placement of an improved vented stove may be associated with a corresponding decrease in acute respiratory illnesses.

INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY * BIOLOGY * PHYSICS

Survival outcomes in resected extrahepatic cholangiocarcinoma: effect of adjuvant radiotherapy in a Surveillance, Epidemiology, and End Results analysis
Vern-Gross TZ, Shiwani AT, Chen K, Lee CM, Tward JD, MacDonald OK, Crane CH, Talamonti MS, Munoz LL, Small W Jr

Purpose: The benefit of adjuvant radiotherapy (RT) after surgical resection for extrahepatic cholangiocarcinoma has not been clearly established. We analyzed survival outcomes of patients with resected extrahepatic cholangiocarcinoma and examined the effect of adjuvant RT.

Methods and materials: Data were obtained from the Surveillance, Epidemiology, and End Results (SEER) program between 1973 and 2003. The primary endpoint was the overall survival time. Cox regression analysis was used to perform univariate and multivariate analyses of the following clinical variables: age, year of diagnosis, histologic grade, localized (Stage T1–T2) vs. regional (Stage T3 or greater and/ or node positive) stage, gender, race, and the use of adjuvant RT after surgical resection.

Results: The records for 2,332 patients were obtained. Patients with previous malignancy, distant disease, incomplete or conflicting records, atypical histologic features, and those treated with preoperative/intra-operative RT were excluded. Of the remaining 1,491 patients eligible for analysis, 473 (32%) had undergone adjuvant RT. After a median follow-up of 27 months (among surviving patients), the median overall survival time for the entire cohort was 20 months. Patients with localized and regional disease had a median survival time of 33 and 18 months, respectively (P < .001). The addition of adjuvant RT was not associated with an improvement in overall or cause-specific survival for patients with local or regional disease.

Conclusion: Patients with localized disease had significantly better overall survival than those with regional disease. Adjuvant RT was not associated with an improvement in long-term overall survival in patients with resected extrahepatic bile duct cancer. Key data, including margin status and the use of combined chemotherpay, was not available through the SEER database.

INTERNATIONAL WOUND JOURNAL

Analysis of run-in and treatment data in a wound outcomes registry: clinical impact of topical platelet-rich plasma gel on healing trajectory
Carter MJ, Fylling CP, Li WW, de Leon J, Driver VR, Serena TE, Wilson J

Randomised controlled trials in chronic wounds typically exclude patients with comorbidities and confounding factors. Well-designed observational studies can provide complementary clinical evidence that randomised trials cannot address. This study determined if wound care registry outcomes could be an alternative data source and if the results would be robust and valid. Changes in wound area and depth were hypothesised to be different between run-in therapies and platelet-rich plasma (Autologel™, Cytomedix, Inc) treatment. From a treatment registry of 285 chronic wounds, 46 had run-in and post-treatment data. Seven chronic wound categories were identified. Mean wound age at study start was 52.4 days. General linear model repeated measures showed a credible and robust data set. Statistically significant differences for wound area and depth were observed between run-in and post-treatment period at multiple time points. Wound area and depth ≥50% reduction were analysed using Kaplan-Meier methods. During run-in, 15% of wound area improved compared to 28% post-treatment and 11% of wound depth improved during run-in compared to 39% post-treatment. Significant clinical outcomes indicated many previously nonresponsive wounds began actively healing in response to platelet-rich plasma therapy, indicating that registry data can be used as a complementary source of evidence.
Heuristic evaluation is a type of study that is useful for uncovering usability issues in a human-computer interface such as the electronic medical record (EMR). Findings can be very useful in overcoming usability problems to better realize the benefits of the EMR. Correction of the usability violations will improve the efficiency and effectiveness of EMRs. The authors discuss their use of heuristic evaluation to assess usability issues found in their nursing electronic documentation system.

**JOURNAL OF TRAUMA**

Blunt cerebrovascular injury is poorly predicted by modeling with other injuries: analysis of NTDB data

Cook A, Osler T, Gaudet M, Berne J, Norwood S


**Background:** Traumatic blunt cerebrovascular injury (BCVI) may portend catastrophic complications if untreated. Who should be screened for BCVI is controversial. The purpose of this study was to develop and validate a prediction score (pBCVI) to identify those at sufficient risk to warrant dedicated screening.

**Methods:** We conducted a cohort study using data for years 2002–2007 from the National Trauma Data Bank. Blunt trauma patients aged 16 years and older were randomly divided into two groups for score creation and validation. Final prediction model included age, sex, Trauma Mortality Prediction Model p(death), traumatic intracranial hemorrhage, cerebellar/brain stem injury, malar/maxillary fracture, mandible fracture, cervical spine fracture, cervical spinal cord injury, thoracic spinal cord injury, and chest Abbreviated Injury Scale ≥3. pBCVI was evaluated using receiver operating characteristic curve area and the Hosmer-Lemeshow statistic. The Youden Index estimated an optimal cut-point (J) of the pBCVI.

**Results:** The cohort numbered 1,398,310 patients, including 2,125 with BCVI. The overall incidence of BCVI was 0.15%. Cervical spine fracture had the strongest association with BCVI (odds ratio 4.82, *P* < 0.001). The receiver operating characteristic curve for pBCVI was 0.93 and the Hosmer-Lemeshow statistic was 206.3, *P* < 0.01. The optimal cut-point (J) of pBCVI was 0.0013 (sensitivity 0.91, specificity 0.82) and would miss 186 (8.8%) injuries in our cohort. To identify all BCVI using this model, an unrealistic 96% of the cohort would require screening.

**Conclusions:** A model based on a pattern of other injuries cannot be used as a stand-alone instrument to determine screening for BCVI. “Optimal” model cut-points are not ideal for all injuries. Clinical suspicion that integrates energy of mechanism and associated injuries remains essential to effectively screen for BCVI and minimize patient risk for a catastrophic missed injury.

**JAMA**

Association between biologic therapies for chronic plaque psoriasis and cardiovascular events: a meta-analysis of randomized controlled trials

Ryan C, Leonard CL, Krueger JG, Kimball AB, Strober BE, Gordon KB, Langley RG, de Lemos JA, Daoud Y, Blankenship D, Kazl S, Kaplan DH, Friedewald VE, Menter A


**Context:** Ustekinumab and briakinumab, monoclonal antibodies to the shared p40 subunit of interleukin (IL)-12 and IL-23, have shown efficacy in treating chronic plaque psoriasis (CPP). Preliminary reports of major adverse cardiovascular events (MACEs) in psoriasis patients receiving anti-IL-12/23 agents have prompted concern.

**Objective:** To evaluate a possible association between biologic therapies for CPP and MACEs via meta-analysis.

**Data sources:** Randomized controlled trials (RCTs) of anti-IL-12/23 (ustekinumab and briakinumab) agents and anti-tumor necrosis factor α (TNF-α) agents (adalimumab, etanercept, and infliximab) used in treating CPP were reviewed using the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and Ovid MEDLINE from database inception to May 2011. The results of registered unpublished completed studies were procured through abstract publications or poster presentations.

**Study selection:** Randomized, placebo-controlled, double-blind, monotherapy studies (with safety outcome data for MACE) of IL-12/23 antibodies and anti-TNF-α agents in adults. Studies of psoriatic arthritis were excluded.

**Data extraction:** Two investigators independently searched data while 6 investigators reviewed the abstracted data.

**Results:** A total of 22 RCTs comprising 10,183 patients met the predefined inclusion criteria. The primary outcome measure was MACE, a composite end point of myocardial infarction, cerebrovascular accident, or cardiovascular death during the placebo-controlled phase of treatment in patients receiving at least 1 dose of study agent or placebo. Absolute risk differences were used as an effect measure. There was no evidence of statistical heterogeneity across the studies using the I(2) statistic (I(2) = 0), allowing for combination of trial results using the Mantel-Haenszel fixed-effects method. During the placebo-controlled phases of the anti-IL-12/23 studies, 10 of 3179 patients receiving anti-IL-12/23 therapies experienced MACEs compared with zero events in 1474 patients receiving placebo (Mantel-Haenszel risk difference, 0.012 events/person-year; 95% CI, –0.001 to 0.026; *P* = .12). In the anti-TNF-α trials, only 1 of 3858 patients receiving anti-TNF-α agents experienced a MACE compared with 1 of 1812 patients receiving placebo (Mantel-Haenszel risk difference, –0.0005 events/person-year; 95% CI, –0.010 to 0.009; *P* = .94).

**Conclusions:** Compared with placebo, there was no significant difference in the rate of MACEs observed in patients receiving anti-IL-12/IL-23 antibodies or anti-TNF-α treatments. This study may have been underpowered to identify a significant difference.
**LIVER TRANSPLANTATION**

A randomized multicenter study comparing steroid-free and standard immunosuppression for liver transplant recipients with chronic hepatitis C


This randomized, prospective, multicenter trial compared the safety and efficacy of steroid-free immunosuppression to 2 standard immunosuppressive regimens in patients transplanted for hepatitis C virus (HCV) infection. Outcome measures were acute cellular rejection, severe recurrent HCV, and survival. Patients were randomized 1:1:2 to tacrolimus plus corticosteroids (Arm 1; n = 77); mycophenolate mofetil, tacrolimus, and corticosteroids (Arm 2; n = 72); or mycophenolate mofetil, tacrolimus, and daclizumab induction, with no corticosteroids (Arm 3; n = 146). A total of 295 HCV RNA-positive subjects were enrolled. At 2 years, there were no differences in acute cellular rejection, biochemical evidence of HCV recurrence, patient survival, or graft survival. Side effects of immunosuppression were not different, although there was a trend to less diabetes in the steroid-free group. Liver biopsy at years 1 and 2 revealed no differences in the proportion of Arms 1, 2, and 3 that had advanced HCV recurrence (grade ≥3 and/or stage ≥2; Year 1: 48.2%, 50.4%, 43.0%; Year 2: 68.5%, 75.9%, and 68.1%). While we found that steroid-free immunosuppression is safe and effective for liver transplant recipients with chronic HCV, there is no clear advantage to steroid sparing as compared to traditional immunosuppression.

**NEUROLOGY**

OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine

Lipton RB, Varon SF, Grosberg B, McAllister PJ, Freitag F, Aurora SK, Dodick DW, Silberstein SD, Diener HC, Degryse RE, Nolan ME, Turkel CC


Objective: To assess the effects of treatment with onabotulinumtoxinA (Botox, Allergan, Inc., Irvine, CA) on health-related quality of life (HRQoL) and headache impact in adults with chronic migraine (CM).

Methods: The Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) clinical program (PREEMPT 1 and 2) included a 24-week, double-blind phase (2 12-week cycles) followed by a 32-week, open-label phase (3 cycles). Thirty-one injections of 5U each (155 U of onabotulinumtoxinA or placebo) were administered to fixed sites. An additional 40 U could be administered “following the pain.” Prespecified analysis of headache impact (Headache Impact Test [HIT]-6) and HRQoL (Migraine-Specific Quality of Life Questionnaire v2.1 [MSQ]) assessments were performed. Because the studies were similar in design and did not notably differ in outcome, pooled results are presented here.

Results: A total of 1,384 subjects were included in the pooled analyses (onabotulinumtoxinA, n = 688; placebo, n = 696). Baseline mean total HIT-6 and MSQ v2.1 scores were comparable between groups; 93.1% were severely impacted based on HIT-6 scores ≥60. At 24 weeks, in comparison with placebo, onabotulinumtoxinA treatment significantly reduced HIT-6 scores and the proportion of patients with HIT-6 scores in the severe range at all timepoints including week 24 (P < 0.001). OnabotulinumtoxinA treatment significantly improved all domains of the MSQ v2.1 at 24 weeks (P < 0.001).

Conclusions: Treatment of CM with onabotulinumtoxinA is associated with significant and clinically meaningful reductions in headache impact and improvements in HRQoL.

**PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES**

Human tonsil B-cell lymphoma 6 (BCL6)-expressing CD4+ T-cell subset specialized for B-cell help outside germinal centers

Bentebibel SE, Schmitt N, Banchereau J, Ueno H


T follicular helper (Tfh) cells represent a Th subset engaged in the help of B-cell responses in germinal centers (GCs). Tfh cells abundantly express the transcription repressor B-cell lymphoma 6 (Bcl6), a factor that is necessary and sufficient for their development in vivo. Whether Tfh or Tfh-committed cells are involved in the help of B cells outside GCs remains unclear, particularly in humans. In this study, we identified a previously undefined BCL6-expressing CD4+ T-cell subset in human tonsils. This subset expressed IL-7 receptor and chemokine receptor 5 (CXCR5) and inducible costimulator (ICOS) at low levels (CXCR5hiICOSlo), and it was found exclusively outside GCs. CXCR5hiICOSlo CD4+ T cells secreted larger amounts of IL-21 and IL-10 than CXCR5hiICOShi GC-Tfh cells upon activation, and they induced proliferation and differentiation of naïve B cells into Ig-producing cells more efficiently than GC-Tfh cells. However, this subset lacked the capacity to help GC-B cells because of the induction of apoptosis of GC-B cells through the FAS/FAS-ligand interaction. CXCR5hiICOSlo CD4+ T cells expressed equivalent amounts of BCL6 transcript with CXCR5hiICOShi GC-Tfh cells, but they expressed less Bcl6 protein. Collectively, our study indicates that CXCR5hiICOSlo CD4+ T cells in human tonsils represent Tfh lineage-committed cells that provide help to naive and memory B cells outside GCs.
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