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

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<th>Research area</th>
<th>Specific disease/condition</th>
<th>Contact information (name, phone number, and e-mail address)</th>
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<tr>
<td>Asthma and pulmonary disease</td>
<td>Chronic obstructive pulmonary disease, asthma (adult)</td>
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<td>Pancreatic islet transplantation</td>
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</tr>
<tr>
<td>Gastroenterology</td>
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Spatial analysis of injury-related deaths in Dallas County using a geographic information system

Adil Abdalla, DVM, MS, Mark Gunst, MD, Vafa Ghaemmaghami, MD, Amy C. Gruszecki, DO, Jill Urban, MD, Robert C. Barber, PhD, Larry M. Gentiliello, MD, and Shahid Shafi, MD, MPH

This study applied a geographic information system (GIS) to identify clusters of injury-related deaths (IRDs) within a large urban county (26 cities; population, 2.4 million). All deaths due to injuries in Dallas County (Texas) in 2005 (N = 670) were studied, including the geographic location of the injury event. Out of 26 cities in Dallas County, IRDs were reported in 19 cities. Geospatial data were obtained from the local governments and entered into the GIS. Standardized mortality ratios (SMR, with 95% CI) were calculated for each city and the county using national age-adjusted rates. Dallas County had significantly more deaths due to homicides (SMR, 1.76; 95% CI, 1.54–1.98) and IRDs as a result of gunshots (SMR, 1.23; 95% CI, 1.09–1.37) than the US national rate. However, this increase was restricted to a single city (the city of Dallas) within the county, while the rest of the 25 cities in the county experienced IRD rates that were either similar to or better than the national rate, or experienced no IRDs. GIS mapping was able to depict high-risk geographic “hot spots” for IRDs. In conclusion, GIS spatial analysis identified geographic clusters of IRDs, which were restricted to only one of 26 cities in the county.

Geographic information systems (GIS) are computerized information management systems for analyzing and presenting geographic and spatial data. Over the past two decades, GIS have been used for multiple purposes, such as community policing, urban planning, environmental conservation, marketing research, disaster planning, and disease surveillance (1). However, its application in the field of injury prevention and control has been relatively limited, despite the emergence of several publications that have referred to the role of GIS in medical research and injury prevention. For example, Edelman focused on GIS utility in injury and trauma research (2), and Oppong and Denton implemented GIS to study the association between geographic distribution of HIV/AIDS and ethnic minorities in Dallas County from 1999 to 2002 (3). Other applications of GIS have included the identification of locations with a high frequency of motor vehicle collisions (MVCs) to minimize injuries and evaluate costs and outcomes of treatment (4), and the linking of burn injury incidence at a discrete geographic location to census data to determine potential socioeconomic risk factors (5).

Dallas County is the ninth largest urban county in the United States (6). It has a population of 2.4 million citizens; about half reside in the city of Dallas, and the other half reside in 25 other cities within the county (7). Crime reports for 2005 issued by the Federal Bureau of Investigation indicated a 2.4% increase in the murder rate per 100,000 inhabitants at the national level and a 2.7% increase in violent crimes in metropolitan counties with populations of 100,00 or more (8). Subsequently, The Dallas Morning News described the rate of injury-related deaths (IRDs) in Dallas County as one of the highest in the nation (9). From an injury prevention perspective, it is essential to determine the geographic distribution of these deaths. Such information may enable policy makers and stakeholders at county and city levels to develop local, community-based injury prevention programs to minimize the burden of injuries.

The objectives of this study were to analyze and present the geographic distribution and clustered zones of IRDs at the county and city levels using GIS, to determine the IRD rate in Dallas County and compare it with the national rate, to compare rates of IRDs among cities in Dallas County, and to identify zones with a high frequency of injuries.

MATERIALS AND METHODS

This is a population-based retrospective study of all IRDs in 2005 in Dallas County, a large urban county in Texas.

Data on injury-related deaths

Under Article 49.25 of the Texas Code of Criminal Procedure, the county medical examiner must be notified when any person dies an unnatural death or when the circumstances of death are unknown or lead to suspicion that the death was the result of unlawful means (10). Deaths that are the direct or indirect result of injury undergo a complete forensic post-mortem examination. This provides an opportunity to capture
all IRDs, including scene deaths, hospital deaths, and late deaths in Dallas County. Data collected by the county medical examiner’s office consist of information obtained from scene investigations, police reports, prehospital and hospital records, and autopsy and toxicology findings. Data obtained for the current study consisted of geographic location of the injury at the level of the street address, including city and zip code, as well as mechanism of injury and demographic characteristics such as age, sex, and race.

A total of 4318 deaths were reported to the county medical examiner in 2005. All were reviewed to identify deaths due to injuries. Victims of IRDs were excluded if they were not residents of the county or if they died outside county limits. The current study focused on six specific categories of IRDs based upon the most common mechanisms of injury and by intent: gunshot wound (GSW), MVC, motor-pedestrian collision (MPC), motorcycle crash (MCC), homicide, and suicide. The final study population consisted of 670 deaths, which constituted 16% of all deaths in the county. Some patients were classified in more than one IRD category. For example, patients who died after committing suicide with a handgun were included in both the suicide and GSW categories.

Data analysis

The standardized mortality ratio (SMR) is widely used by health professionals to compare the rates of health events among areas of differing population size (11). It is the ratio of observed deaths to expected deaths as a result of a specific cause. An SMR > 1 indicates that the observed incidence is more than expected, an SMR < 1 indicates that the observed incidence is less than expected, and an SMR equal to 1 indicates that the observed incidence is as expected.

Age adjustment (age standardization), an essential measure of adjustment that differentiates the SMR from the crude rate, is the key tool that controls for comparison among group sizes. Age adjustment can be performed using the direct or indirect method. The direct method is applied when the age-specific death rate is not the primary concern; the indirect method is applied when the age-specific death rate is the subject of interest. Age adjustment is used to compare the rate of IRDs among cities in Dallas County and the rate between Dallas County and the United States. This method assured minimum bias due to fluctuating differences in population size. The study utilized population data from the 2000 US Census and the national age-adjusted rates for 2004 to estimate the expected number of deaths for each category (per 100,000 population) of IRDs at the county and city levels. National death rates for each category (per 100,000 population) were obtained from the Centers for Disease Control and Prevention (12). A 95% confidence interval (CI) was calculated to adjust for cities with fewer IRDs. The following formulae were used to calculate the expected number of deaths and SMR with 95% CI for each of the six categories of IRDs for Dallas County and for each city within the county:

- **SMR = observed number of deaths (in a city)/expected number of deaths**
- **Expected number of deaths = city population size × national age-adjusted rate/100,000**
- **95% CI of SMR = SMR ± 1.96 × standard error**
- **Standard error = SMR/observed number of deaths**

The SMR was interpreted as equivalent to the national rate (represented with yellow in the figures and tables) if the 95% CI overlapped 1. The SMR was considered significantly better than the national rate (represented with green) if the point estimate was <1 and the 95% CI did not overlap 1. Conversely, the SMR was considered significantly worse than the national rate (represented with red) if the point estimate was >1 and the 95% CI did not overlap 1.

Geographic data and mapping

Geographic information on the county boundaries, cities, and road networks, as well as the population estimates of the county and cities (as of January 1, 2006), were obtained from the North Central Texas Council of Governments (13). The study utilized GIS for spatial mapping of IRDs in the county. GIS technologies use computerized referenced datasets to manage, analyze, and display geographic locations and associated attribute data. Data obtained from the medical examiner’s office were converted from an Excel spreadsheet into database format and imported into a geodatabase file. ArcGIS 9.2, GIS software from Environmental Systems Research Institute, was utilized to identify exact locations of each incident by a geocoding process of assigning address data to spatial locations. A point shapefile of all deaths was then created. Data were queued and processed by GIS software, joined with a spatial layer of all the cities within the county, and displayed on maps that reflected summation and pattern of distribution of IRDs by category. GIS spatial analysis and statistical tools were applied to obtain the density of IRDs per square mile (kernel density) and to identify the mean center of IRDs, as well as geographic distribution, by obtaining one standard deviation to encompass 68% of all IRDs. GIS applications were used to translate these calculations into visual analytic maps, with individual cities outlined as units of observation.

RESULTS

The study population is described in Table 1. A majority of IRDs occurred in young men of various ethnicities, due primarily to GSWs and secondarily to MVCs. At the county level, Dallas County experienced death rates higher than national rates due to GSW and homicide, but death rates were lower than the national levels for suicide, MVC, and MPC (Figure 1). Table 2 shows the number of deaths and SMRs with 95% CI for each city within the county by IRD categories. These data show that the city of Dallas had a significantly worse SMR due to GSWs, homicides, and MPCs than the national rates. The rest of the 25 cities in the county experienced IRD rates that were the same as or better than the national rates, or experienced no IRDs, as was the case in the cities of Balch Springs, Cockrell Hill, Combine, Sachse, Sunnyvale, and University Park. For example, in the category of deaths due to MVC, the cities of Dallas, Duncanville, Garland, Grand Prairie, Irving,
in the city of Dallas (Figure 3), where the density of IRDs was at a maximum of five incidents per square mile.

**DISCUSSION**

The findings of this study demonstrate that IRDs in Dallas County were predominantly homicides due to GSW. However, IRDs due to homicides have been reported, in most cases, as homicide and GSW. This may explain the similarity between homicide and GSW in frequency of incidences and density at a geographic location.

Homicides due to GSW were geographically restricted to a single city, the city of Dallas. IRD rates in the rest of the cities within the county were either the same as the national rates or better. GIS mapping allowed for a clear visual depiction of the geographic location of these deaths, enabling us to identify “hot spots” of these deaths. Such visual depictions greatly enhance the legibility of the data.

Injuries are a leading cause of death and disability and are the leading cause of death in the first four decades of life (14). Previous studies have shown that the vast majority of these deaths occur at the scene of the event due to nonsurvivable injuries (15). Hence, primary prevention of injuries remains the most important strategy to reduce the burden of IRDs on society (16). Injury prevention strategies may include a combination of engineering designs, environmental modifications, education, and enforcement of specific laws, such as speeding, seat belt usage, and drunk driving. In order to maximize their impact, these strategies need to be targeted toward the communities at highest risk of injuries. GIS technology provides a way to identify these target communities, as shown in this paper and previous published studies (2–5, 17).

Our findings suggest that in Dallas County, injury prevention efforts should be targeted toward the city of Dallas. In addition, these efforts should focus on reducing injuries due to GSW and MPC. By utilizing street-level geographic information of IRD by zip code, census tract, or block, GIS technology is also able to further localize specific neighborhoods within the city of Dallas that are most likely to benefit from prevention efforts. Such analyses may also help to determine the relationship between the frequency of IRDs and the time of occurrence (day of the week, time of the day). This information may be used to further customize injury prevention interventions toward the target population.

The maps generated suggest that GIS technology has important applications in injury prevention and control. From a scientific standpoint, GIS enabled us to pinpoint high-risk geographic locations on countywide maps, which may be studied to identify potential reasons for occurrence of those injuries. For example, there may be a higher rate of deaths due to MPC at a specific intersection if there are no pedestrian crossings or if the

### Table 1. Demography of injury-related deaths in Dallas County

<table>
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<tr>
<th>Demographic</th>
<th>GSW (n = 294)</th>
<th>Homicide (n = 249)</th>
<th>Suicide (n = 179)</th>
<th>MVC (n = 115)</th>
<th>MPC (n = 41)</th>
<th>MCC (n = 22)</th>
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<td>Age, years (mean ± SD)</td>
<td>34 ± 15</td>
<td>30 ± 14</td>
<td>41 ± 16</td>
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<td>Sex, male (%)</td>
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<td>81</td>
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GSW indicates gunshot wound; MCC, motorcycle crash; MPC, motor-pedestrian collision; MVC, motor vehicle collision; SMR, standardized mortality ratio.

Lancaster, and Mesquite had significantly better SMRs. There were significantly fewer deaths due to suicide in the cities of Carrollton, Dallas, Farmer’s Branch, Garland, Grand Prairie, and Irving. Some cities experienced significantly better SMRs in several categories. For example, the cities of Garland and Grand Prairie experienced better SMRs in deaths due to GSWs, homicide, suicide, and MVCs. These findings suggest that the primary reasons for the increased number of IRDs at the county level were GSWs and homicides in the city of Dallas. At the same time, the county had fewer deaths due to suicide, MVC, and MCC.

GSW mapping was used to depict this information visually, utilizing unique color codes for each city based upon its SMR (Figure 2). Further, GIS spatial analysis and statistical tools were applied to locate the geographic density of GSWs, homicides, and MPCs (kernel density) utilizing the mean center of IRD with one standard deviation encompassing 68% of deaths within each category. These were found to be clustered
Time allocated by the traffic lights for pedestrians is inadequate for safe crossing. A cluster of deaths due to GSW may be used to increase police patrols in specific neighborhoods. A rash of car crashes on particular streets may indicate the need for better lighting, speed limit enforcement, or checks for driving under the influence. Hence, from a policy perspective, GIS mapping may be used to identify target communities, set priorities for injury prevention interventions, and allocate appropriate resources to specific communities. The visual depiction of IRDs provided by these maps represents a powerful tool to educate policy makers and stakeholders at the local, state, regional, and national level.

### Table 2. Injury-related deaths in Dallas County

<table>
<thead>
<tr>
<th>City</th>
<th>Population</th>
<th>Deaths</th>
<th>GSW (Standardized mortality ratio, confidence interval)</th>
<th>Homicide</th>
<th>Suicide (Standardized mortality ratio, confidence interval)</th>
<th>MVC (Standardized mortality ratio, confidence interval)</th>
<th>MPC (Standardized mortality ratio, confidence interval)</th>
<th>MCC (Standardized mortality ratio, confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addison</td>
<td>15,100</td>
<td>3</td>
<td>0.67 (-0.64, 1.97)</td>
<td>0</td>
<td>1.82 (-0.24, 3.87)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Carrollton</td>
<td>50,467</td>
<td>9</td>
<td>0.20 (-0.19, 0.59)</td>
<td>0.68</td>
<td>0.36 (-0.14, 0.87)</td>
<td>0</td>
<td>1.24 (-1.19, 3.67)</td>
<td>2.98 (-1.15, 7.11)</td>
</tr>
<tr>
<td>Cedar Hill</td>
<td>43,050</td>
<td>4</td>
<td>0.93 (0.02, 1.85)</td>
<td>0.40</td>
<td>0.64 (-0.08, 1.36)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Coppell</td>
<td>39,200</td>
<td>4</td>
<td>0.77 (-0.10, 1.64)</td>
<td>0</td>
<td>0.70 (-0.09, 1.49)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dallas</td>
<td>1,272,850</td>
<td>485</td>
<td>1.71 (1.48, 1.93)</td>
<td>2.77</td>
<td>0.68 (0.54, 0.81)</td>
<td>0.42 (0.33, 0.52)</td>
<td>1.57 (1.03, 2.12)</td>
<td>0.89 (-0.44, 1.33)</td>
</tr>
<tr>
<td>DeSoto</td>
<td>46,950</td>
<td>5</td>
<td>0.64 (-0.08, 1.37)</td>
<td>0</td>
<td>0.78 (0.02, 1.54)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Duncanville</td>
<td>37,750</td>
<td>6</td>
<td>1.07 (0.02, 2.11)</td>
<td>0.90</td>
<td>0.48 (-0.19, 1.16)</td>
<td>0.36 (-0.14, 0.86)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Farmers Branch</td>
<td>27,950</td>
<td>5</td>
<td>1.44 (0.03, 2.85)</td>
<td>2.44</td>
<td>0.33 (-0.31, 0.97)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Garland</td>
<td>223,550</td>
<td>35</td>
<td>0.50 (0.20, 0.79)</td>
<td>0.46</td>
<td>0.57 (0.27, 0.87)</td>
<td>0.27 (0.10, 0.45)</td>
<td>0</td>
<td>0.67 (-0.26, 1.60)</td>
</tr>
<tr>
<td>Grand Prairie</td>
<td>156,000</td>
<td>15</td>
<td>0.32 (0.04, 0.61)</td>
<td>0.44</td>
<td>0.29 (0.04, 0.55)</td>
<td>0.17 (0.00, 0.35)</td>
<td>0.40 (0.38, 1.19)</td>
<td>0.48 (-0.46, 1.43)</td>
</tr>
<tr>
<td>Highland Park</td>
<td>8,700</td>
<td>1</td>
<td>1.06 (–1.32, 2.14)</td>
<td>11.36</td>
<td>3.05 (–2.93, 9.03)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hutchins</td>
<td>3,000</td>
<td>4</td>
<td>0.45 (0.15, 0.74)</td>
<td>0.42</td>
<td>0.45 (0.17, 0.73)</td>
<td>0.27 (0.08, 0.46)</td>
<td>0.92 (–0.12, 1.97)</td>
<td>0.37 (–0.36, 1.10)</td>
</tr>
<tr>
<td>Irving</td>
<td>202,750</td>
<td>31</td>
<td>2.11 (0.55, 3.66)</td>
<td>1.53</td>
<td>1.37 (0.17, 2.57)</td>
<td>0.20 (–0.20, 0.60)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lancaster</td>
<td>33,450</td>
<td>9</td>
<td>0.74 (0.28, 1.20)</td>
<td>1.00</td>
<td>0.74 (0.30, 1.18)</td>
<td>0.30 (0.06, 0.54)</td>
<td>1.38 (–0.18, 2.98)</td>
<td>0</td>
</tr>
<tr>
<td>Mesquite</td>
<td>136,100</td>
<td>31</td>
<td>1.03 (0.39, 1.67)</td>
<td>0.52</td>
<td>0.84 (0.29, 1.40)</td>
<td>0</td>
<td>0</td>
<td>0.77 (–0.74, 2.28)</td>
</tr>
<tr>
<td>Richardson</td>
<td>97,550</td>
<td>16</td>
<td>0.19 (–0.18, 0.56)</td>
<td>0</td>
<td>0.52 (–0.07, 1.10)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rowlett</td>
<td>53,100</td>
<td>3</td>
<td>3.25 (–3.12, 9.61)</td>
<td>5.50</td>
<td>2.95 (~2.83, 8.74)</td>
<td>2.20 (~2.11, 6.51)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Seagoville</td>
<td>12,550</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0.54 (0.0, 1.61)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Wilmer</td>
<td>3,100</td>
<td>3</td>
<td>1.23 (1.09, 1.37)</td>
<td>1.76</td>
<td>0.67 (0.57, 0.77)</td>
<td>0.32 (0.26, 0.37)</td>
<td>1.04 (0.72, 1.37)</td>
<td>0.69 (0.40, 0.98)</td>
</tr>
</tbody>
</table>

Yellow indicates the same as the national rate; green, significantly better than the national rate; red, significantly worse than the national rate; GSW, gunshot wound; MCC, motorcycle crash; MPC, motor-pedestrian collision; MVC, motor vehicle collision.
The study has a few limitations. Several cities had very few deaths due to injuries, resulting in potentially unstable estimates of SMRs with wide CIs. The study also did not include races other than black, white, and Hispanic in the analysis. However, races not included constituted only 4% of the county population. More detailed analysis of these data at the specific neighborhood level was not undertaken but may be necessary for devising injury prevention interventions. Such analysis is easily obtainable, as mentioned above. Although Dallas County residents who died outside the county were not captured, the primary purpose of the study was to locate high-risk areas within the county. Because of the complexity and resource intensity of IRD record retrieval arising from privacy concerns and confidentiality laws and regulations, the authors were unable to compare the incidence rate of IRDs of 2005 with that of previous years. Our study neither investigated date and time of IRD nor linked IRD rate to census attribute data. The population of the county and the cities was assumed to be constant over the study period. However, changes in population size are likely due to influx of new residents, or temporary changes during specific hours of the day or days of the week because of commuters. Finally, indirect adjustment was used based upon US national injury mortality rates. More accurate rates may be calculated using multivariate modeling.
However, we did not have the requisite data for undertaking multivariate risk adjustment.

In conclusion, Dallas County IRD rates due to GSW, homicide, and MPC were significantly higher than national rates. However, these deaths were restricted to the city of Dallas, while the rest of the cities in the county experienced IRD rates that were either the same as or better than national rates. GIS enabled us to visually depict specific geographic locations or “hot spots” of IRDs, which may be used to identify target communities for injury prevention interventions.

Acknowledgments

The authors would like to thank Dr. Ronald Briggs and Dr. Michael Tiefelsdorf in the Department of Geographic Information Systems, School of Economic, Political, and Policy Sciences at the University of Texas at Dallas for their invaluable help in this study. The authors also wish to thank Kelli R. Trungale, MLS, ELS, for editorial assistance.


Chronic vestibular dysfunction as an unappreciated cause of chronic nausea and vomiting

Tanya H. Evans, MD, and Lawrence R. Schiller, MD

In patients with chronic nausea and/or vomiting, gastroparesis is frequently diagnosed, often on the basis of abnormal gastric emptying scintigraphy (GES). When typical treatments fail, patients may be referred to a referral center. This retrospective study evaluated the diagnoses made in patients referred for chronic nausea and vomiting and appraised the GES utilized to assess these patients. Records of outpatients referred for chronic nausea and vomiting over a 3-year period were analyzed for previous evaluation and treatment, subsequent investigation, and response to treatment. Of 248 patients referred for chronic nausea and vomiting, 156 (63%) were referred with a suspected diagnosis of gastroparesis. Of 102 GES available for review, 95 were done with nonstandardized methods. Repeat standardized testing was normal in 27 of 36 patients (75%). Only 28 patients (11%) had confirmed gastroparesis. The most common specific diagnosis in the entire group was chronic vestibular dysfunction (CVD, 64 patients, 26%) made by abnormal modified Fukuda stepping test, nystagmus, or abnormal Romberg test. CVD patients did not typically report a history of an inner-ear disorder or vertigo. Eighty-nine percent of CVD patients were given trials of antivertiginous medications; of the 39 followed for a median of 5 months, improvement occurred in two thirds. Diagnosis of gastroparesis should not be based on a nonstandardized GES. In our referred patients, gastroparesis was infrequent, while CVD was much more likely. Treatment for CVD may mitigate the nausea and vomiting.
in conjunction with signs of altered vestibular dysfunction on physical examination. This included the presence of nystagmus, a positive Romberg test, or an abnormal modified Fukuda stepping test. We performed the modified Fukuda stepping test by having the patient march in place with eyes shut and ears occluded for 60 seconds. A turn of 90 degrees or more to the right or left was considered abnormal (see supplementary video online).

- Gastroesophageal reflux was defined by symptoms of heartburn and/or regurgitation in association with abnormal duration of reflux on pH-monitoring studies and/or improvement of symptoms with proton pump inhibitor therapy.
- Cyclic vomiting was defined on the basis of Rome III criteria as the presence of three or more discrete stereotypical episodes of vomiting in the prior year with absence of nausea and vomiting between episodes (4).
- Rumination syndrome also was based on Rome III criteria and was considered for those with persistent or recurrent regurgitation of ingested food not preceded by retching with subsequent remastication and swallowing (4).
- Postsurgical nausea and vomiting was characterized by symptoms of nausea and/or vomiting in the setting of prior gastric surgery and absence of delayed emptying.
- Medication-induced nausea and vomiting was distinguished by the resolution of nausea and/or vomiting with medication cessation or recurrence of symptoms upon rechallenge.

Numeric data were expressed as means or medians, and categorical data were expressed as proportions. Between-group comparisons were made using the chi-square or Fisher exact tests where appropriate.

RESULTS

Of 271 patients screened for inclusion, 23 were excluded: 8 had no record identifiable during the data collection period, and 15 were evaluated primarily for other complaints (6 for constipation, 4 for chronic diarrhea, 3 for abdominal pain, 1 for dysphagia, and 1 for allergies); none were pregnant or <18 years. A total of 248 patients were analyzed for the 3-year interval. Baseline characteristics are outlined in Table 1.

Prior prokinetic medications were tried in 85%.

Of the total cohort, 156 (63%) were referred with a suspected diagnosis of gastroparesis. Of these, 102 (65%) had gastric emptying scan reports available for review, of which 95 (93%) were done with methods other than the 4-hour international standard protocol. Ninety (95%) of these had been interpreted as abnormal. A review of each study protocol revealed that the most common deviation from the international standard was an examination duration less than the recommended 4 hours (found in 43 [45%]). Other deviations included the use of alternative meals (in 7 [7%]), concomitant administration of medications known to alter gastric motility (in 2 [2%]), concurrent symptoms of nausea or abdominal pain during the test (in 2 [2%]), or a combination of these aberrations (in 41 [43%]). Repeat testing using the international standard protocol was done in 36 patients who had a prior abnormal nonstandardized GES; 27 (75%) of these repeat studies were normal.

Table 1. Baseline characteristics in 248 patients referred for chronic nausea and vomiting

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>201 (81%)</td>
</tr>
<tr>
<td>Men</td>
<td>47 (19%)</td>
</tr>
<tr>
<td>Age in years (median, range)</td>
<td>42 (18–78)</td>
</tr>
<tr>
<td>Symptom duration in years (median, range)</td>
<td>2 (0.2–50)</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>196 (79%)</td>
</tr>
<tr>
<td>Nausea alone</td>
<td>52 (21%)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>145 (58%)</td>
</tr>
<tr>
<td>Prior hospitalization</td>
<td>98 (40%)</td>
</tr>
<tr>
<td>Risk factors for gastroparesis</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>63 (25%)</td>
</tr>
<tr>
<td>Prior gastric surgery</td>
<td>29 (12%)</td>
</tr>
<tr>
<td>Medications</td>
<td>91 (37%)</td>
</tr>
<tr>
<td>Prior evaluation</td>
<td></td>
</tr>
<tr>
<td>Endoscopy</td>
<td>196 (79%)</td>
</tr>
<tr>
<td>Abdominal imaging</td>
<td>135 (54%)</td>
</tr>
<tr>
<td>Neurologic imaging</td>
<td>34 (14%)</td>
</tr>
</tbody>
</table>

Suspected CVD was the most common specific diagnosis, found in 64 (26%). Findings of altered vestibular function that led to this diagnosis included abnormal modified Fukuda stepping test (in 36 [56%]), presence of nystagmus (in 17 [27%]), and abnormal Romberg test (in 1 [2%]). Ten patients (16%) had a combination of these findings. Forty-three of these patients with CVD (67%) were referred for suspected gastroparesis. Of these, 34 (79%) had previous GES available for review. Thirty-three (97%) were done with nonstandard methods, of which 29 (88%) had been interpreted as abnormal. When a standardized test was repeated in nine of these patients, it was normal in eight.

Compared with patients with other conditions, CVD patients more often presented with nausea alone and tended to have fewer hospitalizations, suggesting less severe symptoms (Table 3). Abdominal discomfort and dizziness were not distinguishing symptoms, and overt vertigo was reported only in a minority of CVD patients.
patients (6 [9%]). To assess for possible contributing conditions, various comorbidities were evaluated; only eight CVD patients reported a recognized history of an inner-ear disorder.

Antivertiginous medication trials were administered to 57 of 64 (89%) CVD patients. These typically included scopolamine, meclizine, or benzodiazepines alone or in combination.

Follow up was available for 39 of these patients for a median of 5 months. Symptomatic improvement was reported in 25 (64%), while 14 (36%) reported no change in symptoms.

**DISCUSSION**

This study has two main conclusions. First, despite the recommendations of experts to use a standardized protocol, most gastric emptying scans available for review were performed with nonstandardized methods. The most common deviation was duration less than the recommended 4-hour timeframe. Tougas et al (5) established a cut-off of >10% isotope retention at 4 hours after ingestion of a standard low-fat meal as indicative of delayed gastric emptying. Despite the validation of this cut-off as the international standard, many institutions still employ a variety of other protocols (6). When standardized exams were repeated at our institution, 75% were normal. Therefore, utilization of nonstandardized GES may lead to a misleading diagnosis of gastroparesis and should be abandoned.

Second, we found that CVD is a noteworthy consideration in patients with chronic nausea and vomiting, and treatments aimed at vestibular dysfunction may mitigate symptoms in some of those patients. CVD is classically characterized by symptoms of vertigo and postural instability but also may manifest with vegetative symptoms such as nausea and vomiting. Examination signs of CVD were found in 26% of our cohort. This is comparable to the 35% of adults over 40 years found to have CVD upon modified Romberg testing in the National Health and Nutrition Examination Survey (7). Although self-reported vertigo in population surveys has an estimated prevalence of 21% to 29% (8–10), the patients in our study presented with complaints of chronic nausea and vomiting and did not frequently report a history of vertigo or a known inner-ear disorder. The mechanisms whereby certain patients with CVD manifest symptoms are incompletely understood but may reflect impaired vestibular compensation to the initial underlying injury (11).

The suspected CVD diagnosis, in this study, was made most commonly on the basis of a positive modified Fukuda stepping examination. With visual, auditory, and proprioceptive inputs eliminated, patients must rely on their vestibular system to maintain orientation. Although the majority of normal subjects maintain orientation with 100 blindfolded steps in a quiet environment, Fukuda in his original experiments described a forward migration up to 1 meter and rotation up to 45 degrees from midline as normal (12). Patients with known vestibular lesions typically demonstrate >90-degree variations from midline (13). Therefore, to increase specificity for CVD, the 90-degree rotation was used as the cut-off in this study. Because advanced vestibular testing was not done as part of the evaluation of these patients, we cannot comment on the accuracy of the modified Fukuda test in this cohort of patients.

Therapy for CVD should ideally be targeted to the underlying lesion if identifiable, and affirmative physical examination signs should prompt referral for specialized confirmatory testing. Initial symptomatic improvement can occur with medications targeted at neurotransmitter targets within the vestibular system,

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic vestibular dysfunction</td>
<td>64 (26%)</td>
</tr>
<tr>
<td>Gastroparesis</td>
<td>28 (11%)</td>
</tr>
<tr>
<td>Cyclical vomiting syndrome</td>
<td>22 (9%)</td>
</tr>
<tr>
<td>Rumination syndrome</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Postsurgical</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Medication-induced</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Other miscellaneous</td>
<td>41 (17%)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>76 (31%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3. Characteristics of patients diagnosed with chronic vestibular dysfunction versus other diagnoses among 248 patients referred for chronic nausea and vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic vestibular dysfunction</td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Symptoms</td>
</tr>
<tr>
<td>Nausea alone vs. vomiting</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Vertigo</td>
</tr>
<tr>
<td>Prior hospitalization</td>
</tr>
<tr>
<td>Comorbidities</td>
</tr>
<tr>
<td>Inner ear disorder</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Prior gastric surgery</td>
</tr>
<tr>
<td>Depression/anxiety</td>
</tr>
<tr>
<td>Migraine</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Atherosclerosis</td>
</tr>
<tr>
<td>Thyroid disease</td>
</tr>
</tbody>
</table>
such as antihistamines, anticholinergics, and benzodiazepines. The fact that nausea and vomiting improved with treatments aimed at vestibular dysfunction in many of our patients with suspected CVD supports the notion that CVD may play an important role in the pathogenesis of chronic nausea and vomiting in at least some patients with otherwise idiopathic nausea and vomiting. Future prospective studies should determine the frequency of vestibular dysfunction presenting with chronic nausea and vomiting, the efficacy of therapies such as medications and vestibular rehabilitation, and long-term prognosis.

In addition to CVD, other diagnoses were elicited in our patients suspected of having gastroparesis. These diagnoses included cyclic vomiting, rumination syndrome, gastroesophageal reflux, and postsurgical and medication-induced nausea and vomiting. This reinforces the heterogeneity of potential causes for nausea and vomiting that must be considered in the differential diagnosis. The frequencies of these conditions in our cohort at a tertiary referral center may not be representative of the frequencies in the general community; nevertheless, these are important diagnostic considerations for frontline gastroenterologists, as specific therapies may be more effective than nonspecific symptomatic therapy.

There are limitations to this retrospective study. First, complete prior diagnostic information was not available for review in all patients. Second, patients were not studied prospectively with a uniform diagnostic protocol. Ideally, a prospective study would include standardized GES, advanced vestibular testing, a uniform treatment protocol, and scheduled follow-up. Thus, the data collected are incomplete. Nevertheless, we feel that there are lessons to be learned from our experience.

A review of current surgical treatment of patients with atrial fibrillation

Zachary J. Edgerton and James R. Edgerton, MD

Surgical therapy for patients with atrial fibrillation has undergone significant advances over the past 30 years. The Cox Maze III technique is currently the gold standard of care for these patients. However, Maze IV, a less complex procedure using alternative energy sources, is rapidly replacing the Cox Maze III in clinical practice. The use of alternative energy sources such as cryothermy and radiofrequency eliminates some of the “cut and sew” lesions of the Maze III, resulting in an easier and faster procedure with less morbidity. Video-assisted technology and hybrid procedures have further ushered in the future of surgical therapy. This article presents the latest surgical therapeutic options for patients with atrial fibrillation. The history of these procedures is presented, followed by a discussion of modern-era techniques, including concomitant ablation and standalone (also referred to as “lone”) procedures. Finally, the article explores breaking developments and future directions for the surgical treatment of patients with atrial fibrillation.

As the most common sustained cardiac arrhythmia (1), atrial fibrillation (AF) currently affects over 5 million Americans (2) and is projected to affect 12 million Americans by 2050 (1). Adults aged ≥40 years have an approximately 1 in 4 lifetime risk of developing AF (3). Problems associated with AF are threefold: rapid ventricular response, resulting in decreased cardiac output and occasionally tachycardia-mediated cardiomyopathy; loss of the atrial transport function, which variably may result in decreased cardiac output; and stasis with clot formation and thromboembolism. AF is a known risk factor for stroke, heart failure, and premature death (4). In fact, AF confers a 5-fold increase in the risk of stroke (5, 6), causing 15% of the strokes in the United States (7). A study of over 4600 patients revealed an increased mortality risk within the first 4 months of an AF diagnosis compared with the general population (hazard ratio, 9.62; \( P < 0.0001 \)) (4). This condition, therefore, has warranted much research over the past few decades. Procedural development has focused on less invasive techniques with lower morbidity.

This article highlights the current surgical therapy options for patients with AF. The history of surgery for AF is presented, followed by a discussion of modern-era techniques, including concomitant ablation procedures and standalone (also referred to as “lone”) surgical therapy. Finally, the article explores hybrid techniques and future directions for the surgical treatment of patients with AF.

THE EVOLUTION OF SURGICAL TREATMENT FOR ATRIAL FIBRILLATION

The first major surgical breakthrough in AF therapy was observed in 1980, when the left atrial isolation technique was reported (8). With AF isolated in the left atrium, the rest of the heart could be restored to normal sinus rhythm (NSR) as a result of this surgery. However, reduced cardiac output and the risk of systemic thromboemboli persisted because of the remaining AF. Two years later, Scheinman and colleagues developed His bundle ablation to control the irregular rapid ventricular response attendant to AF (9). Patients undergoing this procedure required a permanent ventricular pacemaker. The surgery conferred an improvement only in the AF-related irregular and rapid heart rate. It did not manage the loss of the atrial kick or the risk for the development of thromboemboli (8).

The Guiraudon corridor technique, an open-heart surgery that regulated the heart rate and reduced the need for a permanent pacemaker, was pioneered in 1985 (8). Despite such advances, neither side of the heart was in atrioventricular synchrony, thromboembolism risk remained high, and both atria remained in fibrillation after the surgery. The aforementioned His bundle ablation procedure yielded comparable physiologic outcomes without requiring open-heart surgery.

The following year, an atrial transection procedure, involving pulmonary vein isolation (PVI) and incisions in the atria, was performed on a patient for the first time (8, 10). With this patient’s heart having remained in NSR for 5 months, Cox et al established that AF could be corrected with surgical alteration of the atria.

Cox and colleagues went on to formulate the cut-and-sew maze technique (11). First performed on a patient in 1987 (11),
this Cox maze technique comprises several atrial incisions that form a set of scars that obstruct all potential points of reentry (12). Although efficacious, this Maze I procedure resulted in occasional left atrial dysfunction and the frequent inability to generate adequate sinus tachycardia in response to maximal exercise (8). Maze II, the next step in the evolution of the cut-and-sew procedure, excluded the sinus node incision in the high lateral left atrium dome transverse atriotomy was relocated to the right atrium. Also, in order to enhance intraatrial conduction, the left atrium dome transverse atriotomy was relocated to the posterior. Complete transection of the superior vena cava was required as a result of such modification, however.

The cut-and-sew maze technique then continued to progress. Maze III placed the septal incision posterior to the superior vena cava orifice, enabling enhanced exposure of the left atrium (8). This procedure enhanced long-term atrial transport and sinus node function, diminished the need for a pacemaker, lessened the recurrence of arrhythmia, and increased the occurrence of postsurgery NSR, all while being more technically manageable than previous maze iterations.

In 1999, Cox et al modified Maze III into a minimally invasive approach using a 7-cm right submammary incision (11). At that time, two patients underwent the surgery without cardiopulmonary bypass. Cox and colleagues as well as the Cleveland Clinic and the Mayo Clinic have illustrated the safety and efficacy of Maze III, with mortality rates of ≤1.4%, a 1.2% long-term failure rate, 90.4% of the patients being in NSR 3 years after surgery, and 3.2% to 15% needing new pacemakers (11, 13–15). Maze III is currently the gold standard of surgical therapy for patients with AF (16).

From Maze III to Maze IV and Radiofrequency Ablation

The conventional Cox Maze III procedure entailed multiple atrial incisions, which were associated with increased morbidity and complexity. Thus, the procedure was not commonly implemented. Widespread acceptance occurred only after advances in enabling technology yielded multiple energy sources that could be utilized to create lines of transmural necrosis, thereby replacing surgical incisions. This modified technique, Maze IV, employed a connecting lesion rather than the initial box lesion and isolated pulmonary veins bilaterally (8). Damiano et al innovated much of this procedure using bipolar radiofrequency (AtriCure, Inc.; Cincinnati, OH) and revealed that when performed with alternative energy sources, its efficacy equaled that of the traditional cut-and-sew maze approach (17). This group demonstrated that a box lesion yielded greater overall freedom from AF recurrence than did a single connecting lesion at 1 month (87% vs. 69%; P = 0.015) and 3 months (96% vs. 85%; P = 0.028) (18). Also, antiarrhythmic drug usage was lower in the Maze IV box lesion group compared with the single connection lesion group at 3 months (35% vs. 58%; P = 0.018) and 6 months (15% vs. 44%; P = 0.002). Furthermore, Weimar and colleagues studied 112 patients who underwent the Maze III procedure and 100 patients who underwent the Maze IV procedure (19). Median cardiopulmonary bypass time was significantly reduced with Maze IV compared with Maze III (129 minutes vs. 163 minutes; P < 0.001), as was mean aortic cross-clamp time (39 minutes vs. 90 minutes; P < 0.001). Maze IV also produced significantly lower major complication rates (P = 0.003). Freedom from AF was comparable between the two groups (90% [95% CI, 81–95] for Maze IV vs. 96% [95% CI, 86–98] for Maze III).

The maze procedure has flourished as a result of the discovery of alternative energy sources. Several treatments utilizing these energy sources were developed after Haïssaguerre and colleagues’ landmark finding that pulmonary veins are the major source of the early potential factors that cause paroxysmal AF (recurrent AF ending spontaneously ≤7 days) and that they respond to radiofrequency ablation (8, 20). Besides bipolar and unipolar radiofrequency and cryoablation, other energy sources that have been integrated into maze with varying levels of success include laser, microwave, and high-frequency ultrasound energy. Laser energy has been discontinued due to its inability to produce transmural lesions (21). Also, high-intensity focused ultrasound has not met safety criteria for treatment of patients with AF (22). Microwave energy is unsuccessful in PVI or long-term prevention of AF, as determined by Pruitt and colleagues in 2007 (23); therefore, its clinical use was virtually abolished, and it was then withdrawn from the market. Only radiofrequency and cryoablation have proven to be effective, efficient, and safe.

One objective in the utilization of radiofrequency energy is to increase resistive heating and reduce conductive heating in order to deepen the lesion penetration. Conductive heating restricts penetration by creating surface char. Some surgical devices minimize this conductive heating by using saline irrigation to cool the surface. Other devices utilize bipolar directional “pens” wherein the energy flows between the two poles of the pen. These pens may be irrigated for cooling or not. The directional nature of these pens also allows the surgeon to create scar tissue without causing collateral damage (12). Bipolar radiofrequency is the most commonly used energy source for minimally invasive surgical AF ablation (24). A 99.5% overall procedural success rate (procedure completion without conversion to cardiopulmonary bypass or median sternotomy) was revealed in a review of minimally invasive surgical AF ablation series using totally thoroscopic bipolar radiofrequency (24). Conversely, unipolar radiofrequency energy may produce less reliable transmural lesions (12). One variant of unipolar radiofrequency energy attempts to increase tissue contact by utilizing suction-assisted attachment to the atrium to ensure ablation line continuity. However, in animal studies, this did not prove efficacious (25).

Another form of energy used in the surgical treatment of patients with AF, cryoablation, freezes tissue, creating a scar via a bimodal process of tissue necrosis (12). Cryoablation usually requires emptying the heart on cardiopulmonary bypass because the immense heat sink of circulating intracavitary blood can absorb the energy, rendering a complete freeze of the endocardial tissue difficult or even impossible. It is therefore ineffective on the full, beating heart. A study of 63 patients undergoing concomitant cardiac procedures including cryoablation for AF yielded an 88.5% rate of freedom from AF at 1 year (26). Cryothermy is also not directional and may allow for collateral damage if not used with care.
CONCOMITANT SURGICAL ABLATION

Studies have shown that patients who undergo surgery for cardiac conditions other than AF but who have preoperative AF are at high risk for late morbidity, stroke, and reduced survival (27–29). Quader et al found that, in patients with preoperative AF undergoing coronary artery bypass grafting (CABG), 10-year survival was reduced by 24% compared with patients without AF (27). Ngaage and colleagues studied patients undergoing aortic valve replacement and determined that patients with preoperative AF had a significantly higher probability of later rhythm-associated interventions ($P = 0.0002$), congestive heart failure ($P = 0.005$), and stroke ($P = 0.005$) than did patients without AF (28). In another study, these authors demonstrated that preoperative AF was associated with a higher operative mortality rate (2% vs. 0; $P = 0.05$) as well as increased late cardiac events and stroke (63% vs. 31%; $P < 0.0001$) (29).

In light of such data, surgical AF ablation that is performed concomitantly with at least one other previously planned cardiac surgery is recommended by the International Society of Minimally Invasive Cardiothoracic Surgery consensus panel (30). Concomitant surgical ablation reduces the risks of stroke and thromboemboli, improves ejection fraction, increases NSR incidence, and improves long-term survival and exercise tolerance for patients with persistent AF (lasting >7 days, or lasting <7 days but necessitating cardioversion) and permanent AF (ongoing, long-term, refractory AF). Also, the current Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society expert consensus statement on catheter and surgical ablation of AF calls for all patients with AF undergoing other cardiac procedures to be considered for ablation if the risks of adding this procedure are small, the procedure is executed by an experienced surgeon, and there is adequate probability of success (16).

Studies, including several randomized controlled trials, have demonstrated that concomitant radiofrequency AF ablation is successful in restoring and maintaining NSR (31–35). Doukas et al revealed rates of return of NSR of 44.4% for patients undergoing concomitant AF ablation compared with 4.5% for patients undergoing mitral valve surgery without AF ablation ($P < 0.001$) (33). However, they performed only left atrial lesions, not the full maze lesion set. Similarly, Abreu Filho and colleagues demonstrated that 79.4% of patients having concomitant AF ablation experienced a return of NSR compared with 26.9% of patients having mitral valve surgery and no AF ablation ($P = 0.001$) (32). Chevalier et al reported 12-month postoperative NSR rates of 57% for patients undergoing concomitant AF ablation and 4% for those who had only mitral valve surgery ($P = 0.004$) (34). Finally, von Oppell et al conducted a study in which 75% of the patients receiving mitral valve surgery plus AF ablation were in NSR at 12-month follow-up compared with 39% of the patients who had only mitral valve repair ($P = 0.03$) (35). Gammie et al conducted a retrospective review of over 67,000 patients in the Society of Thoracic Surgeons National Cardiac Database who underwent cardiac procedures between 2004 and 2006 (36). For the 6231 patients who underwent surgery for AF and mitral valve repair, the risks were not significantly different for death (odds ratio [OR], 1.00 [95% CI, 0.83, 1.20]; $P = 0.975$), any reoperation (OR, 0.98 [95% CI, 0.87, 1.12]; $P = 0.802$), renal failure/dialysis (OR, 1.03 [95% CI, 0.88, 1.21]; $P = 0.689$), postoperative length of stay ≥14 days (OR, 1.00 [95% CI, 0.88, 1.13]; $P = 0.949$), or prolonged ventilation (OR, 0.98 [95% CI, 0.88, 1.09]; $P = 0.715$) compared with patients who had mitral valve surgery and no surgery for AF. Adjusting for preoperative characteristics, patients undergoing mitral valve repair and concomitant AF ablation did not have a significantly increased mortality risk compared with patients undergoing only mitral valve surgery (OR, 1.00 [95% CI, 0.83, 1.20]).

STANDALONE SURGICAL THERAPY FOR ATRIAL FIBRILLATION

The minimally invasive standalone technique is a key nonpharmacologic therapeutic option in the modern era. According to Cox, the ideal surgery for AF “would be performed via a minimally invasive incision (or endoscopically or robotically), off bypass, in less than 1 hour, with hospital discharge planned for the next morning” (37). Surgeons have strived to meet this objective, attempting to reap the efficacy benefits of the Cox Maze III technique while preventing the related morbidity and complexity. The minimally invasive standalone maze procedure includes left atrial appendage (LAA) exclusion, PVI, and ablation of the ganglionic plexuses (GPs) and the ligament of Marshall, all combined into one surgery (38). For nonparoxysmal patients, linear lesions can also be added (39). This procedure can decrease the risk of emboli, enable extensive mapping of the GPs and ligament of Marshall, and help prevent catheter ablation–related adverse events. However, compared with medical therapy, minimal access surgery does have some risks: lengthier hospitalizations and recovery periods, the required use of general anesthesia, greater patient discomfort, and the bleeding risk associated with LAA excision.

CryoMaze is one variety of such minimal-access AF ablation. Although called minimal access, it does utilize cardiopulmonary bypass with retrograde perfusion and employ a groin incision for cardiopulmonary bypass as well as a minimal-access mini-thoracotomy incision, as described by Gammie and colleagues (40). Between July 2002 and November 2005, 119 patients underwent CryoMaze. Thirty-three patients had preoperative intermittent AF, and 28 (85%) were in NSR at late follow-up (>3 years). However, for the 58 patients with continuous AF, the results were less impressive, with 27 patients (47%) being in NSR ($P < 0.0001$). The overall rate of freedom from AF was 60% at late follow-up. There was one perioperative stroke, which was entirely resolved within 1 month, and there were no late strokes. Another study was conducted using CryoMaze, this time with the multiple–purse-string technique, wherein atriotomies are avoided via the placement of sutures on the left and right epicardial surfaces (41). A total of 12 patients underwent this procedure, either combined with CABG (n = 9), combined with aortic valve replacement (n = 2), or as a standalone surgery (n = 1). Five additional patients required a small left atrial atriotomy to ensure that the mitral valve isthmus lesion was complete. There were no cerebrovascular accidents/
transient ischemic attacks or perioperative mortalities. There was 1 late death, and 91% of the patients were free of AF or flutter at a mean follow-up of 13 ± 6 months.

Also influencing the progress of surgical therapy for patients with AF is video-assisted technology. Wolf et al pioneered this innovation, conducting a video-assisted bilateral PVI and LAA exclusion via minithoracotomy in 27 patients with AF (18 with paroxysmal AF, 4 with persistent AF, and 5 with permanent AF) whose condition was intolerant to or refractory to pharmacologic interventions (42). At a follow-up of >3 months, 21 patients (91.3%) had freedom from AF. There were no deaths or conversions to sternotomy or full thoracotomy. Yilmaz et al performed a study of video-assisted totally thorascopic PVI with GP ablation and LAA amputation, for which data on the first 30 patients are available (43). With a mean follow-up of 11.6 months, 77% of the patients were free of AF. The mean operation time was 137.4 ± 24.7 minutes, and the mean length of hospital stay was 5.1 ± 1.8 days. No cerebrovascular accidents, pacemaker placements, or deaths occurred. Additionally, Edgerton and colleagues conducted a study in which video-assisted technology was utilized for PVI and partial autonomic denervation for 74 patients with AF (44). At a follow-up of 6 months, overall, 92.9% of the patients were in NSR as determined by an electrocardiogram, and 74.2% of the patients with longer-term observation had no indications of AF. By AF type, 56.5% of the patients with persistent/longstanding persistent (LSP) AF and 83.7% of the patients with paroxysmal AF were free of detectable AF (AF episodes >15 seconds). Partial autonomic denervation combined with PVI is proposed to be an effective and safe surgical option for patients with AF.

Video-assisted technology has played a key role in another recent study of a novel minimally invasive surgical method: the totally thorascopic video-assisted PVI, GP ablation, and LAA exclusion, with perioperative electrophysiologic confirmation (45). Krul et al utilized bipolar radiofrequency to treat 31 patients (16 with paroxysmal AF, 13 with persistent AF, and 2 with LSP AF). Eighty-six percent of the patients were free of AF recurrence, atrial flutter, and atrial tachycardia and were not using antiarrhythmic agents at 1-year follow-up. No deaths or thromboembolic events occurred. Therefore, this procedure could be a reliable, cost-effective new therapeutic choice for surgeons treating AF.

Pulmonary vein isolation alone, although effective for paroxysmal AF, is not sufficient treatment for patients with continuous AF, as seen by these preliminary results. Because of the substrate alterations that electrical remodeling brings about, this procedure as standalone therapy is insufficient for patients with persistent and LSP AF (46). The altered left atrial substrate beyond the PVs can initiate and sustain AF. Additional linear lesions are necessary in this group. The “Dallas lesion set” was developed to treat this group of patients. It is a set of linear lesions that replicates the left-sided Cox Maze III procedure and can be applied epically, on the full beating heart, with a totally thorascopic technique. The surgeon creates lesions at the roof line, the anterior line, and between the roof line and the LAA in this extended linear lesion set (47, 48). The Dallas lesion set was studied in 30 patients with persistent or LSP AF. The preliminary results are encouraging: 15 of 20 patients (75%) with LSP AF and 9 of 10 patients (90%) with persistent AF had freedom from AF at a follow-up of 6 months (39). PVI and GP ablation are more efficacious in paroxysmal AF (24, 49), but the Dallas lesion set can serve as a valuable surgical therapy option in persistent and LSP AF.

HYBRID PROCEDURES AND FUTURE DIRECTIONS

Hybrid procedures are further advancing the state of the art. A hybrid procedure combines epicardial and endocardial ablation, either staged or as a single procedure, through a partnership between the surgeon and electrophysiologist. Because data from recent studies are still incomplete, it has not yet been established whether the single or staged approach is most likely to produce favorable outcomes.

The nContact trial, performed by Horton, Hume, Natale, and colleagues, is one of the latest studies on the hybrid method. It included 57 patients with LSP AF and a large (≥5 cm) left atrium (50). Patients in group 1 (n = 22) underwent combined closed-chest epicardial monopolar radiofrequency ablation via a transabdominal transdiaphragmatic single port and catheter-based transseptal endocardial ablation. Patients in group 2 (n = 35) received manual catheter ablation alone. In group 1, there were 3 deaths (13.6%): one due to stroke, one due to left atrium-esophageal fistula, and one sudden death. No deaths were reported in group 2. The study demonstrated that this combined technique increases complication rates and does not improve outcomes in patients with a large atrium and LSP AF.

More efficacious and lower-risk bilateral thorascopic hybrid approaches for AF are being investigated. Mahapatra and colleagues performed a study of sequential surgical epicardial ablation with subsequent endocardial evaluation and catheter mapping with targeted ablation during the same hospitalization compared with catheter ablation alone (51). Forty-five patients with persistent or LSP AF received either the sequential ablation (n = 15) or the catheter-alone ablation (n = 30). Of the patients who were treated by catheter ablation alone, 53.3% had freedom from AF and were not using antiarrhythmic agents compared with 86.7% of the patients who received sequential therapy (P = 0.04) at a mean follow-up of 20.7 ± 4.5 months. Although small, the study’s positive results are promising. Further study is needed.

CONCLUSION

In the past three decades, and particularly in the time since the initial maze procedure was carried out on a patient in 1987, surgical therapy for patients with AF has seen extensive advances. The Cox Maze III technique remains the mainstay of such therapy. However, with innovations in surgical AF ablation by means of alternative energy sources, namely cryothermy and radiofrequency, Maze IV is becoming a feasible, less complex option. Findings from randomized controlled trials (31–35) support the International Society of Minimally Invasive Cardiotoracic Surgery consensus panel recommendation that AF ablation be performed when a patient is already undergoing at
least one other cardiac procedure (30). Video-assisted technology as well as hybrid procedures that combine epicardial and endocardial ablation have brought the future into the present. Prospective, randomized, controlled trials with long-term follow-up are needed as minimal access surgical therapy for AF progresses into the future.

Acknowledgment

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References


Heat-related illnesses lead to almost 6000 hospital visits per year, or two emergency department visits per 100,000 visits. Heat-related illnesses are most high among men (72%) aged 15 to 19 years and are most often associated with athletic activities (1). Global climate change will continue to have an impact on heat stress in people, on animal survival, and on food availability. The World Health Organization has estimated that over the past 30 years, 150,000 lives have been lost annually due to global heat waves and climate change (2). Weather changes have a great impact on athletes and workers by slowing efficiency and decreasing productivity (3, 4). When heat waves occur, overall mortality is also affected among the old and the young, due to their increased risk of dying from cardiovascular, respiratory, cerebrovascular, and some cardiovascular diseases, such as ischemic heart disease, heart failure, and myocardial infarction (3).

Despite increasing temperatures and environmental levels of carbon dioxide, one third of metropolitan areas do not have heat stress response plans (5). Cases of heat stress are handled on a case-by-case basis rather than by being addressed collectively as a public health concern. The National Institute for Occupational Safety and Health initiated heat stress criteria in 1986 and amended them in 2008 regarding worker heat stress safety (6). Few people are aware of these criteria, of the risk factors associated with a predisposition to heat stress, or of the signs or symptoms to look for that represent risk factors for heat stress. The rules and standards proposed by the Occupational Safety and Health Administration for workplace heat stress are recommendations and still not enforceable (7).

Screening for heat stress susceptibility in workers and athletes is an issue in need of public health criteria with enforceable rules based on evidence-based research. Screening for heat stress risk factors should consider physical demand level; cardiovascular, pulmonary, and endocrine status; previous history of heat stress; age; diseases; and medications including illegal drug use. Such screening should be part of the recruitment of any person expected to work or play in extremely hot environmental conditions. Older people are at increased risk for cardiovascular and thermoregulatory instability. The aging American workforce, undiagnosed disease, poor hydration while working or playing, and global warming are all factors that contribute to the need to screen workers and athletes for the risk of heat stress (8).

This article first reviews some physiological aspects of temperature regulation and then provides a formula for heat stress testing, discusses guidelines for screening, and reviews accommodations for those susceptible to heat stress.

PHYSIOLOGY OF TEMPERATURE REGULATION

The human capacity to regulate temperature equilibrium depends on various factors that ultimately impact the body’s ability to maintain a steady core temperature (6). Each person’s ability to maintain a steady inner core temperature can be influenced by environmental factors, age, gender, cardiovascular health, and even the medications they take (9). The type of clothing barrier that individuals wear influences their ability to cool down core body temperature and adjust to extreme environmental heat as well (10). Excessive clothing barriers can be extremely important in cases of athletic heat exhaustion and heat stroke mortality.

Under normal physiological conditions, the human body can maintain a stable core temperature even when stressed by extreme environmental temperatures as long as proper hydration is continuously provided (11, 12). Skin temperature is several degrees cooler than core temperature. It is regulated by the constriction or dilation of subcutaneous blood vessels, the rate of sweating production, heart rate, and cardiac output. Cardiovascular fitness as well as environmental factors play an important role in coping with extreme environment. Tolerance to temperature homeostasis via dehydration is more robust when individuals are physically fit and young (12–14). However, this ability to adapt to heat declines with age, the presence of disease, and a poor level of fitness (15). Any condition that affects the ability to sweat will also affect a person’s ability to maintain a constant body temperature.

Regarding medications, any medication that has the potential to affect the cardiovascular system, sweating ability, vasodilation, volume depletion, electrolyte equilibrium, venous pooling and cardiac output, or core temperature via...
the central nervous system has the potential to increase the risk for heat stress and heat stroke. Most notable among these medications are those listed in Table 1 (16). The table also reflects the mechanism whereby these medications might impact thermoregulation. Any individual taking these medications is at greater risk for developing heat stress, irrespective of age, weight, or environmental factors. Older individuals are more sensitive to these effects and are more likely to be on some of these medications due to their increased risk for chronic disease.

**FORMULA TO MEASURE HEAT STRESS RISK**

A worthwhile risk assessment model for heat stress that combines both environmental factors and physiological risk factors has been posed in a simplified formula. The formula incorporates both environmental factors (environmental stress index, or ESI) and personal factors (personal stress index, or PSI) as follows:

- **ESI** = 0.63Ta – 0.03RH + 0.002SR + 0.0054 (Ta × RH) – 0.073(0.1 + SR)–1
- **PSI** = 5(T_re0 – T_rec) × (39.5 – T_re0)–1 + 5(HR_t – HR_0) × (180 – HR_0)–1

Variables represent ambient temperature (Ta), relative humidity (RH), and solar radiation (SR), which require only a few seconds to reach equilibrium. The ESI is the first stress index using direct measurements of solar radiation, heart rate (HR), and rectal temperature (T_re). T_re0 and HR_0 represent the initial T_re and HR, and T_rec and HRc are measurements taken at a specific time.

This method considers environmental variations in temperature, humidity, and radiation as well as the individual’s heart rate and aerobic tolerance and is therefore a good objective measure of risk for heat stress in individuals (17). Tachycardia accompanies volume depletion, and that is reflected by the heart rate in this formula. The formula can detect febrile states because it measures rectal temperature.

The PSI and ESI scales are integrated mathematically to reflect cardiovascular strain relative to environmental stress on a scale between 0 and 5. The higher the value, the higher the strain. This formula and coordination of work-rest cycles in training have been used to prevent the risk of future heat stress injuries in military recruits.

One limitation of this risk assessment is that it doesn’t account for certain disease states, such as cardiac or respiratory disease compromise. It does not measure stroke volume, cardiac output, central venous pressure, or pulmonary wedge pressures, which are the benchmark measurements of cardiovascular and pulmonary compromise in diseased individuals. For this reason, the sensitivity and specificity of this risk assessment formula to screen for heat stress–susceptible persons with severe cardiopulmonary disease is somewhat limited, and other measures suggested later in this article should complement this risk assessment instrument.

**RECOMMENDATIONS FOR SCREENING WORKERS AND ATHLETES**

Several types or workers are at risk for heat stress in the US since they work outdoors for long hours in the sun or are in direct contact with flames or hot equipment (6). These include firefighters, bakery workers, farmers, construction workers, miners, boiler room workers, factory workers, and workers in manufacturing. Athletes at risk for heat stress include football players, runners, soccer players, hockey players, triathlon competitors, weight lifters, swimmers, hulers, and hunters due to the accelerated cardiovascular state and outdoor nature of these activities.

In addition, certain individuals have higher risks, including those with reduced mental capacity, Alzheimer’s disease or dementia, trismy disorders, dysrhythmias, and congenital heart abnormalities. Persons with reduced mental capacity may not drink fluids on a regular basis, so they must be put on frequent rest cycles and be reminded to drink fluids in hot environments. Aging individuals face brittle vasoregulatory mechanisms. All these factors can be screened for during physical evaluations.

A person’s desired level of job activity or athletic activity (physical demand level) is very important to assess as part of the history. Great physical exertion in a hot environment results in more stress on the cardiopulmonary system. Therefore, heat stress screening should be more thorough in individuals who anticipate heavy exertion in hot environments. In such situations, additional objective tests may be needed to improve the sensitivity and specificity of the screening process.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Mechanism of action</th>
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<tbody>
<tr>
<td><strong>Legal</strong></td>
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<tr>
<td>Alcohol</td>
<td>HR decrease, volume depletion</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>HR increase, increase in sweating</td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>HR lability, abnormal sweating</td>
</tr>
<tr>
<td>Antihistamine</td>
<td>HR lability, abnormal sweating</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>HR lability</td>
</tr>
<tr>
<td>Benzodiazipine</td>
<td>HR lability, abnormal sweating</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>HR lability, venous pooling, abnormal sweating</td>
</tr>
<tr>
<td>Diuretic</td>
<td>Volume depletion, decreased vasodilation</td>
</tr>
<tr>
<td>Laxative</td>
<td>HR lability, abnormal vasodilation</td>
</tr>
<tr>
<td>Neuroleptic</td>
<td>HR lability</td>
</tr>
<tr>
<td>Phenothiazine</td>
<td>Electrolyte imbalance</td>
</tr>
<tr>
<td>Thyroid agonist</td>
<td>HR increase, increased sweating (improperly controlled)</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Electrolyte imbalance</td>
</tr>
<tr>
<td>Tricyclic antidepressant</td>
<td>Electrolyte imbalance</td>
</tr>
<tr>
<td><strong>Illegal</strong></td>
<td></td>
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<tr>
<td>Cocaine</td>
<td>HR increase, increased sweating</td>
</tr>
<tr>
<td>Phencyclidine (PCP)</td>
<td>Abnormal temperature regulation</td>
</tr>
<tr>
<td>Lysergic acid</td>
<td>HR lability</td>
</tr>
<tr>
<td>diethylamidine (LSD)</td>
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</table>

*Modified from Glazer, 2005 (16).

HR indicates heart rate.
The categories of physical demand of work or play are easy to understand if they are categorized into light (requiring 0 to 19 lb of exertion), medium light (requiring 20 to 30 lb of exertion), medium (requiring 31 to 40 lb of exertion), medium heavy (requiring 41 to 70 lb of exertion), and heavy (requiring 71 to 100 lb of exertion) physical demand categories. These categories correspond to sedentary administrative-type jobs, light cleaning jobs, heavy cleaning jobs, manufacturing jobs with lifting duties, and construction work, respectively. The athletic corollary would be casual walking, light jogging, sprinting, marathon running, and playing football/participating in a triathlon, respectively.

During screening, the medical history should focus on the health and resilience of the cardiovascular and pulmonary systems and the medication history. It is also important to assess whether the individual has had prior episodes of heat stress or heat stroke. Some specific aspects of the screening include obesity, fitness level, cardiac function, and diabetes, as discussed below. Table 2 summarizes the recommendations for heat stress screening based on physical demand level for individuals who are working or playing in a heat-stressed environment.

### Obesity

Recent studies indicate that approximately one-third of our children and adults fall into the overweight or obese category. A high body mass index (BMI) adds additional burden on the cardiopulmonary system (6, 7, 18). Thermoregulation of the core temperature can be more challenging if there is increased peripheral insulation. Obesity increases the core temperature and decreases a person’s ability to effectively cool down rapidly with the usual cardiovascular thermoregulatory mechanisms. In addition, obesity is an independent risk factor for increased cardiovascular disease (14).

The association seems to be independent of hormonal factors such as leptin. Therefore, screening for BMI is easy and reasonable to do and should be included as part of the screening protocol for persons who are about to engage in activities that expose them to heat, which will further stress the cardiovascular system. As recommended by the Federal Motor Carrier Safety Administration for truck drivers, a BMI >30 kg/m² should trigger a need for more frequent rest periods in a heat-stressed environment for various reasons. At this level, data correlate a high BMI with a risk for labile hypertension, higher mortality from sudden death, and sleep apnea (19). Such persons can work in the heat for very short periods of time with frequent break sessions for cooling until they decrease their BMI to a safer level.

### Fitness Level

Fitness level is an important part of the intake history because a sedentary individual is more likely to succumb to heat stress than an active one. If it is necessary to assess a person's cardiovascular resilience, a simple 3-minute step test and pulse recovery monitoring can easily be done. This test must be performed in a standardized manner using a 12-inch step. The participant steps up and down to a 96-beat-per-minute metronome beat for 3 continuous minutes. Pulse recovery from baseline after 3 minutes of rest is standardized according to the scoring in Table 3, which determines the individual's level of fitness. Fitness levels are not static and can be improved with gradual exercise. If individuals are not fit, their tolerance to heat will be inadequate, and they should not be exposed to long periods in the heat before they improve their fitness and cardiac conditioning.

### Cardiac Function

Cardiac screening tests, such as a stress echocardiogram or electrocardiogram, which are considered the gold standard for cost-effective screening (20), are recommended only in certain circumstances. If a person is going to be in a medium or heavier physical activity, it is advisable to screen that person for cardiac risk factors with objective tests before he or she is exposed to the stress of a hot environment, in order to mitigate the risk for adverse cardiac events. In addition, at age 35, the cardiopulmonary system of average adults begins a slow aging process that can be mitigated only with exercise and is unpredictably impacted by environmental and genetic factors. For this reason, those older than 35 years should be screened with basic cardiovascular screening tests if they have any cardiovascular risk factors or if they are going to be challenged by physical demands of medium-heavy levels or greater, as indicated in Table 2.

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**Table 2. Recommendations for heat stress screening for workers and athletes**

<table>
<thead>
<tr>
<th>Weight to be lifted or exerted (lb)</th>
<th>Physical demand level of work or activity</th>
<th>Components of screening needed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Medical questionnaire*</td>
</tr>
<tr>
<td>0–19 Light</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>20–30 Medium light</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>31–40 Medium</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>41–70 Medium heavy</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>71–100 Heavy</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Focused questionnaire to include cardiopulmonary function, fitness level, prior episodes of heat stress, and medications.

BP indicates blood pressure; BMI, body mass index; EKG, electrocardiogram.

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Diabetes as related to cardiac function

Diabetes is highly associated with ischemic heart disease and cerebrovascular accidents, events that can be provoked by heat stress (21). For this reason, those exposed to heat should be screened for diabetes, even if they are in a sedentary role. A urinalysis can be used for most screening. For individuals engaging in an activity above a medium physical demand level, the more sensitive serum glucose test is appropriate. A urinalysis positive for glucose also indicates the need for serum glucose testing. A serum glucose level >200 mg/dL indicates the need to stabilize the glucose before the individual is allowed into a heat-stressed environment, as he or she has an increased risk for negative cardiovascular events (22).

ACCOMMODATION OF HEAT STRESS–SUSCEPTIBLE PERSONS

The Americans with Disabilities Act Amendments Act of 2008 (ADAAA) requires employers to accommodate employees who have gone through a disabling disease process that makes them incapable of accomplishing their usual work due to medical disability (23). The expanding focus of the ADAAA places the burden on employers to accommodate workers after clearance from their personal physician. Guidelines from the Federal Motor Carrier Safety Administration, which appear in Table 4, specifically address recovery from cardiovascular and pulmonary instability and are applicable to a wide range of situations, including heat stress screening.

Rest/work cycles based on physical demand and temperature, as shown in Table 5, can also be applied. The threshold limit values (TLVs) in the table are based on the assumption that nearly all acclimatized, fully clothed workers with adequate water and salt intake should be able to function effectively under the given working conditions without exceeding a deep body temperature of 38°C (100.4°F). They are also based on the assumption that the Wet Bulb Globe Temperature (WBGT) of the resting place is the same as or very close to that of the workplace. Where the WBGT of the work area is different from that of the rest area, a time-weighted average should be used (24).

Table 3. Scoring on the 3-minute step test for men and women based on age*

<table>
<thead>
<tr>
<th>Variable</th>
<th>18–25</th>
<th>26–35</th>
<th>36–45</th>
<th>46–55</th>
<th>56–65</th>
<th>65+</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>50–76</td>
<td>51–76</td>
<td>49–76</td>
<td>56–82</td>
<td>60–77</td>
<td>59–81</td>
</tr>
<tr>
<td>Good</td>
<td>79–84</td>
<td>79–85</td>
<td>80–88</td>
<td>87–93</td>
<td>86–94</td>
<td>87–92</td>
</tr>
<tr>
<td>Average</td>
<td>95–100</td>
<td>96–102</td>
<td>100–105</td>
<td>103–111</td>
<td>103–109</td>
<td>104–110</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>52–81</td>
<td>58–80</td>
<td>51–84</td>
<td>63–91</td>
<td>60–92</td>
<td>70–92</td>
</tr>
<tr>
<td>Above average</td>
<td>96–102</td>
<td>95–101</td>
<td>100–104</td>
<td>104–110</td>
<td>106–111</td>
<td>104–111</td>
</tr>
</tbody>
</table>

*Scores are the age-adjusted standards based on guidelines published by the YMCA (http://www.exrx.net/Testing/ YMCAtesting.html). In the test, the participant steps up and down a 12-inch step to a 96-beat-per-minute metronome beat for 3 continuous minutes, and pulse recovery from baseline after 3 minutes of rest is recorded.

Table 4. Guidelines for truck driver certification that apply to heat stress screening*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>High blood pressure</td>
<td>Disqualify if blood pressure exceeds 160/100</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>Disqualify if serum glucose ≥200 mg/dL and refer to PCP</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Refer to PCP for possible alternative change of medications†</td>
</tr>
<tr>
<td>Disqualifying medications</td>
<td>Refer to PCP for possible alternative change of medications†</td>
</tr>
<tr>
<td>Body mass index</td>
<td>Refer for counseling if &gt;40 kg/m²</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
<td>Screen for sleep apnea</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Clear with benign arrhythmia after medication control and normal baseline stress echo biannually</td>
</tr>
<tr>
<td>Cardiac stent placement</td>
<td>Wait 2 months then clear with normal baseline stress echo and normal biannual echo; ejection fraction must be &gt;40%</td>
</tr>
<tr>
<td>Cardiac bypass</td>
<td>Wait 3 months then clear with normal baseline stress echo; repeat every 2 years; ejection fraction must be &gt;40%</td>
</tr>
</tbody>
</table>

†Disqualifying medications are specific for underlying cardiac or pulmonary diseases that may not be capable of substitution.
PCP indicates primary care physician; echo, echocardiogram.
CONCLUSION

In our increasingly warmer global climates, specific screening is needed for heat stress to prevent morbidity and mortality in the workplace and during sports activities. Most people who are screened using these simple tests and guidelines will avoid undesirable outcomes. The recommendations for screening individuals supereimpose existing tools and thus increase the sensitivity and specificity in identifying those at risk for heat stress. These methods also help accommodate individuals who might need to recover from an illness that temporarily affects cardiovascular fitness. Occasionally, there will be those with congenital problems such as Kawasaki's disease, which can cause unforeseen cardiac complications that remain undetected until the fatal cardiac arrhythmia occurs on a hot summer day on the athletic field. Yet, the goal of primary care providers is to prevent 99.9% of preventable illness. By using the screening tools recommended in this article, we can be better equipped to accomplish that goal.


Table 5. Work/rest regimen based on work load and temperature*

<table>
<thead>
<tr>
<th>Work/rest regimen each hour</th>
<th>Work load</th>
<th>Light</th>
<th>Moderate</th>
<th>Heavy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous work</td>
<td>30.0°C (86°F)</td>
<td>26.7°C (80°F)</td>
<td>25.0°C (77°F)</td>
<td></td>
</tr>
<tr>
<td>75% work, 25% rest</td>
<td>30.6°C (87°F)</td>
<td>28.0°C (82°F)</td>
<td>25.9°C (78°F)</td>
<td></td>
</tr>
<tr>
<td>50% work, 50% rest</td>
<td>31.4°C (89°F)</td>
<td>29.4°C (85°F)</td>
<td>27.9°C (82°F)</td>
<td></td>
</tr>
<tr>
<td>25% work, 75% rest</td>
<td>32.2°C (90°F)</td>
<td>31.1°C (88°F)</td>
<td>30.0°C (86°F)</td>
<td></td>
</tr>
</tbody>
</table>

*From American Conference of Governmental Industrial Hygienists (24).
Delayed takotsubo cardiomyopathy caused by excessive exogenous epinephrine administration after the treatment of angioedema

Gautam R. Patankar, MD, Michael S. Donsky, MD, and Jeffrey M. Schussler, MD

We present a case of delayed takotsubo cardiomyopathy caused by accidental overadministration of exogenous epinephrine. This case highlights some of the prototypical features of takotsubo cardiomyopathy in an unusual clinical scenario.

CASE REPORT

A 44-year-old African American woman with previous hypertension, depression, and hyperlipidemia presented to an outside hospital with a 6-hour history of lower lip edema. Her medications included lisinopril 10 mg daily, which she had been taking for 1 year, and escitalopram 20 mg daily. She had no known drug allergies or previous operations. She had a 10 pack-year history of tobacco, but had quit 1 week prior to admission. Her family history was significant for coronary artery disease, hypertension, and diabetes mellitus.

Her initial blood pressure was 124/98 mm Hg, her pulse was 105 beats a minute and regular (Figure 1a), and her respiratory rate was 20 breaths a minute. She had edema of the lower lip, face, and oropharynx. Her lungs were clear to auscultation. She had normal heart sounds and no precordial murmur. Her white blood count was 13,900/mm^3; hemoglobin, 12,700 g/dL; and troponin, 0.83 mg/mL.

In the emergency department, the patient was given methylprednisolone sodium succinate 125 mg ×2 intravenously, dexamethasone 4 mg intravenously every 6 hours, and diphenhydramine. She was initially given epinephrine 0.3 mg subcutaneously. The patient’s lip edema did not abate, and the oropharyngeal edema worsened. A second dose of epinephrine was ordered, but the patient was incorrectly given 3 mg subcutaneously. Over the next 10 minutes, she became hypotensive and more tachycardic and developed pulmonary edema. She was transferred to the intensive care unit and started on norepinephrine bitartrate. During the next 24 hours, her blood pressure rose and she was weaned from norepinephrine. She was continued on dexamethasone 4 mg every 12 hours and diphenhydramine 25 mg intravenously every 6 hours. A transthoracic echocardiogram showed a left ventricular ejection fraction of 67% with no wall motion abnormalities.

On day 3, the patient’s dyspnea increased, and midsubternal chest pain appeared. An electrocardiogram now showed deep T-wave inversions in the precordial leads (Figure 1b). Her...
troponin level was now 3.97 ng/mL. She was transferred to Baylor University Medical Center at Dallas.

Cardiac catheterization showed “apical ballooning” without evidence of epicardial narrowing, a picture consistent with takotsubo cardiomyopathy (Figure 2). Her blood pressure remained stable, and she was ultimately discharged home on carvedilol 6.25 mg twice a day. A year later, the patient’s dyspnea is gone, her cardiomyopathy has resolved, and she has had no recurrence of chest pain.

DISCUSSION

Takotsubo cardiomyopathy (“broken heart syndrome”) is a clinical entity that mimics acute myocardial infarction in the setting of normal or near normal epicardial coronary arteries (1). Its exact mechanism is unknown, but these events appear to be temporally related to stressful situations where there are high levels of adrenergic stimulation (2). It is known that endogenous adrenergic stimulation (e.g., pheochromocytoma) can result in manifestations of this entity (3). A previous case occurring after administration of epinephrine has been reported (4).

Myocardial biopsies of takotsubo patients demonstrate contraction-band necrosis, a unique form of myocyte injury characterized by hypercontracted sarcomeres, dense eosinophilic transverse bands, and an interstitial mononuclear inflammatory response that is distinct from polymorphonuclear inflammation seen in the usual myocardial infarct (5). Follow-up studies of these patients show resolution of the contraction-band necrosis, which correlates with the resolution of symptoms in the patient (6).

The treatment of patients with takotsubo cardiomyopathy includes beta-blockers and angiotensin-converting enzyme inhibitors, and in most cases there is complete resolution of cardiac dysfunction (7). During the period of time when the cardiomyopathy is most severe, heart failure and arrhythmias can occur. Severe complications such as myocardial rupture and death have also been reported (8–10).

The exact time course between exposure to the stressful event, catecholamine surge, or exposure to exogenous catecholamines and the resultant end-organ damage is not well described. In our case, there was a lag time of at least 48 hours between exposure to the epinephrine and the resultant cardiomyopathy. No documented cases have demonstrated such a delayed time course. It is important to recognize the signs and symptoms of this entity, as the treatment is different from that of an acute ischemic event or myocarditis. In general, if the patient has no complications related to the acute cardiomyopathy, typically the cardiac dysfunction rapidly resolves with no further sequelae.

May-Thurner syndrome: a not so uncommon cause of a common condition

May-Thurner syndrome is a rarely diagnosed condition in which patients develop iliofemoral deep venous thrombosis (DVT) due to an anatomical variant in which the right common iliac artery overlies and compresses the left common iliac vein against the lumbar spine. This variant has been shown to be present in over 20% of the population; however, it is rarely considered in the differential diagnosis of DVT, particularly in patients with other risk factors. Systemic anticoagulation alone is insufficient treatment, and a more aggressive approach is necessary to prevent recurrent DVT. Herein, we present a patient with multiple risk factors for DVT. With a comprehensive diagnostic approach, she was found to have May-Thurner syndrome. Local infusion of thrombolytics as well as mechanical thrombectomy failed to resolve the thrombus. Subsequently the patient underwent successful stent placement in the area that was compressed followed by 6 months of chronic anticoagulation with warfarin. There has been no recurrence of DVT in the ensuing 18 months.

A 27-year-old African American woman presented with a 12-hour history of left lower extremity swelling associated with 7/10 dull throbbing pain. The patient stated that the pain began initially in her left foot and, within several hours, began to radiate to her left groin. These symptoms began 2 weeks after an 8-hour automobile ride from Houston to New Orleans. The patient had no prior medical history. Her only daily medication was an oral contraceptive, drospirenone/ethinyl estradiol. She had no significant family history. She smoked several cigarettes per month but denied any alcohol or drug use. On examination, the patient's vital signs were within normal limits. Her left lower extremity was warm, swollen, and erythematous from mid-calf to mid-thigh. Dorsalis pedis and posterior tibial pulses were normal, and reflexes, strength, and sensation were all normal. A complete blood count and basic metabolic profile were within normal limits. Her prothrombin time was 16.5 seconds, activated prothromboplastin time was 26.3 seconds, and international normalized ratio was 1.3. The patient had an elevated D-dimer at 24.3 mg/L.

Left lower extremity ultrasound revealed extensive iliofemoral deep venous thrombosis (DVT). Urgent lower extremity venography revealed extensive thrombus in the left femoral, popliteal, and iliac veins (Figure 1). A 5 French Cragg-McNamara catheter was inserted in the left femoral vein, through which an 18-hour infusion of 1 mg/hr tissue plasminogen activator (tPA) was initiated. Following the tPA infusion, the patient was started on a heparin drip, which was titrated to an activated prothromboplastin time of 50 to 70 seconds. Repeat venography 2 days later revealed residual thrombus and stenosis (Figure 2). A mechanical thrombectomy was performed using a Trellis device (Figure 3) with the simultaneous infusion of an additional 5 mg of tPA, after which some resolution of the thrombus was noted; however, stenosis was still present (Figure 4). The stenosis within the left common iliac vein was then dilated with a 10 × 40 mm balloon, and a 14 × 40 mm stent was placed across the stenotic area (Figure 5). While the right common iliac artery was not directly visualized, this patient was proven to have May-Thurner syndrome (MTS) based on the proximal location of her DVT, the stenosis in the left common iliac vein.
in an area directly overlying the lumbar spine, and the appearance of residual thrombus and stenosis following thrombolytic administration and thrombectomy.

Following placement of the stent, the patient was started on 5 mg of daily warfarin, for which she was bridged with twice-a-day injections of 1 mg/kg enoxaparin for 5 days. The patient discontinued the warfarin after 6 months when a hypercoagulability workup, consisting of tests for Factor V Leiden, prothrombin gene mutation, homocysteine level, and antithrombin III level, was negative. Eighteen months postoperatively, the patient has had no recurrence of DVT.

DISCUSSION

MTS was first described in 1957 when it was noted that 22% of 430 cadavers on autopsy possessed an anatomical variant in which an overriding right common iliac artery caused compression of the left common iliac vein against the lumbar spine (1). More recently, a similar prevalence (22%–24%) of MTS was reported in a retrospective analysis of computed tomography scans (2). This compression is associated with intimal hyperplasia, which creates the potential for venous stasis and subsequent thrombosis (1). Despite the relatively high incidence of this anatomical variation, the clinical prevalence of MTS-related DVT is surprisingly low, reportedly occurring in only 2% to 3% of all lower extremity DVTs (3). It is thought that this low occurrence rate may be an underestimate of the actual prevalence due to missed diagnoses; the fact that there is a 55.9% predominance for left-sided DVT would seem to support this notion (4).

One reason for the apparent underdiagnosis of MTS may be the prevalence of other more easily recognized risk factors for DVT: DVT is more common in women, and 72% of women diagnosed with MTS are relatively young (aged 25–50) (3, 5). Additionally, these patients often have a history of oral contraceptive use, recent pregnancy, or recent prolonged travel. Accordingly, in a patient with identifiable risk factors, the diagnostic workup is often halted once the diagnosis of DVT is confirmed. Failure to correct the anatomical substrate of MTS could lead to DVT recurrence and additional complications, including pulmonary emboli, chronic venous stasis, and iliac vein rupture (28% of patients with iliac vein rupture have MTS) (6, 7).

The anatomical defect associated with MTS occurs high in the pelvis, an area that is not easily visualized by ultrasound (8). Accordingly, if MTS is suspected, contrast venography, magnetic resonance imaging, or intravascular ultrasound should be performed (9). Following thrombus removal, a computed tomographic angiogram or magnetic resonance venography should be obtained to assess the degree of stenosis and the hemodynamic effects of iliac vein compression (9).

It is generally accepted that long-term anticoagulation, while indicated, is not adequate to prevent long-term sequelae.
in MTS patients and that a more invasive therapeutic approach is indicated (5). Several historical innovative techniques have included creation of tissue slings, retropositioning of the over-riding vessel, and venovenous bypass (10–12). The mainstay of therapy has traditionally involved open repair of the affected vein; however, the standard of care has since evolved into a hybrid approach, involving the combination of thrombolytics and endovascular intervention. Both Moudgill et al and Suwanabol et al recommend catheter-directed thrombolysis combined with percutaneous mechanical thrombectomy (5, 9). It has also been suggested that an inferior vena cava filter be placed prior to lower extremity intervention in order to prevent further embolization during lytic therapy, especially in individuals with large clot burdens (5).

It is typically recommended that, following initial clot lysis, thrombolytic infusion should be continued for an additional 24 to 48 hours (9). Following completion of thrombolytics, an intravascular stent should be deployed in the area of iliac vein compression. Repeat imaging should be obtained to verify that the stent is positioned across the entire area of the compressed vein. Suwanabol et al recommend the use of large (12–14 mm) self-expanding stents, placed across the extent of the stenosis and extending into the inferior vena cava, if possible, to prevent migration (9). Stent placement has proven highly successful in MTS, with 2-year iliac vein patency rates reported between 95% and 100% (13). In our patient, we decided to discontinue warfarin therapy after 6 months for two reasons. First, we believed that the risks of chronic anticoagulation outweighed the benefits, since the underlying anatomical defect had been corrected by a stent. Second, the discontinuation of warfarin allowed us to test for hypercoagulability, which may have increased the risk for future DVT.

Angioedema from instant coffee

Kelly J. Larkin, MD, Toban Dvoretzky, BA, and Nicholas J. Solomos, MD

Acute allergic angioedema is an abrupt-onset, unpredictable inflammatory reaction of the skin and mucous membranes. Without treatment, the condition may resolve within hours; however, when swallowing or breathing is affected, emergent medical attention is required. We report an atypical presentation of this condition, with a unique dietary cause. A 50-year-old man with no relevant medical history emergently presented with acute angioedema of the lower lip, without urticaria. The inflammation spread to other facial structures but gradually dissipated after subcutaneous epinephrine was administered. Despite thorough questioning of the patient, the cause of the angioedema was not determined. Five days later, during tapered prednisone therapy, the angioedema recurred, and the patient acted to reverse the attack. Instant coffee was identified as the trigger. Beverages are very rarely reported as primary causes of angioedema. To our knowledge, this is the first report of an adult with angioedema triggered not by the caffeine in coffee, but by another characteristic of it.

We report the case of a man who presented at our emergency department (ED) with angioedema of the lower lip, without urticaria. Although the cause of the condition remained undetermined upon the patient’s discharge from emergency care, the offending agent was identified after a single recurrence 5 days later. We discuss the discovery of the trigger and review the relevant medical literature.

CASE REPORT

In October 2009, a 50-year-old man presented in the late morning at the employee health clinic of his employer (a hospital) with swelling of the left side of the lower lip, of 2 hours’ progressive duration. The painless inflammation was disfiguring and affected his speech. He was in good general health, was taking no medications besides daily aspirin and vitamins, and had no family history of similar inflammation. The only relevant episode in his personal medical history was a localized inflammatory reaction from a wasp sting to the hand in 2005. The patient speculated that he had bitten his lip earlier that morning, but he could not specifically remember having done so. He was given topical ice and 50 mg of oral diphenhydramine. After 45 minutes and no improvement, the clinic personnel recommended that he visit either his family physician or the ED of the hospital.

At the ED, the patient repeated his assumption that he had bitten his lip. Upon visual examination, the inflammation was inconsistent with abscess. The diagnosis was angioedema without urticaria. He was given an intramuscular injection of 125 mg of methylprednisolone.

Fifteen minutes later, the patient’s entire lower lip and the central portion of his tongue rapidly became asymmetrically inflamed. He was immediately given a subcutaneous injection of 0.03 mg of epinephrine, an intravenous catheter was inserted into his hand as a precaution, and he was given topical ice. He stoically declined an offer of admission to the hospital and remained under observation in the ED. During this time, his vital signs were within normal limits.

After approximately 2 hours, the inflammation began dissipating and was judged to be 25% improved. Preparations were made for the discharge examination. The ED staff thoroughly questioned the patient about his recent food intake, but no triggers were identified. Accordingly, the angioedema was attributed to an idiopathic but possibly histaminergic cause.

The patient was discharged after 4.5 hours of ED care with a prescription for a standard prednisone taper pack (beginning with two 40-mg doses). He was further instructed to take 25 mg of oral diphenhydramine on each of the next 2 evenings and then 10 mg of loratadine for 5 days, and to visit his family physician thereafter.

The patient later realized that he had not told the ED staff of his consumption that morning of a cup of instant coffee, from a newly opened jar. It had been his only intake of any foodstuff. Suspecting the coffee and challenging his reaction to it, he continued to drink single daily cups in usual amounts: 2 heaping teaspoons of coffee and 2 g of saccharine sweetener mixed into heated tap water. On the morning of the first 20-mg prednisone dose, and shortly after he had drunk a cup of the coffee, angioedema rapidly developed. The inflammation involved the left side of the lower lip and the left central portion...
of the tongue, abruptly spreading to the right side of the tongue but sparing the tip and the base. The patient took another 10 mg of prednisone. In an hour, the angioedema completely dissipated. He drank no more of the coffee thereafter.

After considerable discussion at the follow-up medical appointment, it was concluded that the coffee was the probable trigger. The family physician recommended against the patient’s drinking more of that coffee or any from another jar with the same production codes as the first. The patient complied and, through May 2012, had experienced no more angioedema after drinking coffee.

**Discussion**

In this patient’s case, the circumstantial evidence was strong that the coffee triggered the angioedema. The absence of angioedema in his family and personal medical histories eliminated inherited conditions from the differential diagnosis. The results of the oral challenge confirmed his personal suspicion of the culprit substance, and the absence of repeat attacks—for 2.5 years after the elimination of that trigger—excludes idiopathic causes and further supports the conclusions drawn at the time.

Acute angioedema presents with a rapid, unpredictable course that can pose merely a physical inconvenience or a life-threatening emergency for the patient (1). Clinically, challenges include accurate and timely diagnosis (2), determining whether conservative or aggressive treatment is appropriate (3), discerning the specific underlying cause or trigger of the condition (4), and counseling the patient in regard to recurrent episodes and measures for prevention and treatment. Zingale and colleagues have published a comprehensive flowchart to aid in the diagnosis of various types of angioedema that are unaccompanied by urticaria (5).

Our patient had no family history or previous personal history of angioedema. He was in good general health and had no known allergies to foodstuffs or environmental agents. Of medications that have been implicated in the immunologic triggering of angioedema, he was not taking penicillin (2), cephalosporin (2), angiotensin-converting enzyme inhibitors (5, 6), or bupropion (7), and he had never reacted adversely to aspirin (2, 8). In the absence of an identifiable environmental, dietary, or hereditary trigger, the ED personnel had to record the cause of this angioedema attack as idiopathic but possibly histaminergic (5) and trust that subsequent patient-physician interaction or the patient’s own insights would reveal the trigger.

Follow-up immunologic investigation might have revealed whether the angioedema was mediated by or associated with immunoglobulin E. In cases of suspected food allergy, the official practice guidelines of the American College of Allergy, Asthma, and Immunology (9) include medical testing and oral challenges as methods by which to pinpoint and eliminate triggers of angioedema.

According to the patient, the coffee (in crystal form) was an internationally distributed brand. Upon first opening, the jar and its seal were intact, and, according to the manufacturer’s code, the product would be fresh for nearly 2 more years. The patient had previously (but not recently) consumed this brand of coffee without incident. No family member experienced a reaction after drinking it. We speculate that our patient’s attacks were caused by an additive or change of formulation peculiar to that jar of coffee.

Beverages are very rarely reported as primary causes of angioedema. In adults, beer (10) and other alcoholic beverages (11) have been implicated. Our search for adult cases in the world medical literature revealed a single report that involved the drinking of coffee: a woman with chronic urticaria had an anaphylactic reaction from coffee and an analgesic in combination (8). Clinicians have implicated caffeine, in coffee and from other sources, as the trigger of urticaria or anaphylaxis in children (12, 13). Workers in coffee-processing plants have experienced airborne allergies from raw coffee (14). Our patient reported no inflammatory reaction to caffeine during a lifetime of its consumption in many forms. Accordingly, we believe that this is the first report of an adult with angioedema that was triggered not by the caffeine in coffee, but by some other characteristic of it.

**Acknowledgments**

The authors thank Jimmie E. Lewis, MD (Kelsey-Seybold Hospital Services, Houston) and Robert I. Schwartz, RN (Emergency Department, St. Luke’s Episcopal Hospital, Houston) for their care of the patient, and Prof. Dr. med. Johannes Ring (Klinik und Poliklinik für Dermatologie und Allergologie am Biederstein, Munich, Germany) for communications regarding the case of the adult with coffee-induced anaphylaxis (8).

Widespread tuberculosis including renal involvement

Gates Colbert, MD, Daniel Richey, DO, and John C. Schwartz, MD

Renal and urogenital disease is a prevalent finding of extrapulmonary *Mycobacterium tuberculosis*. Patients can present with unusual complaints not immediately suspicious for tuberculosis. We describe a 38-year-old man who presented with vomiting and an acute kidney injury. Imaging studies showed nodules throughout the lungs, retroperitoneum, abdominal viscera, and kidneys. Asymmetrical hydronephrosis was found on renal imaging. A classic beaded ureteral appearance (ureteritis cystica) was found during retrograde pyelography. The patient was screened and found to have a negative purified protein derivative skin test, negative acid-fast bacilli of sputum in three samples, and an indeterminate QuantiFERON Gold test. Evaluation of the urine for acid-fast bacilli was negative in four separate samples. A fifth urine sample for acid-fast bacilli was positive. A renal biopsy showed granulomatous interstitial nephritis with multiple areas of caseous necrosis. The patient was diagnosed with active tuberculosis and started on traditional four-drug antituberculous medical therapy. Kidney function remained marginal but did mildly improve with volume expansion and urinary drainage.

A 38-year-old Mexican man presented with progressive nausea and vomiting, explaining that he had had dry mouth, nausea, and nonbloody emesis for several weeks. He had noticed a 10-pound weight loss, but he was not anorectic. Urinary hesitancy was not immediately suspicious for tuberculosis. He denied fever, chills, cough, dizziness, syncope, chest pain, shortness of breath, swelling, rash, or leg weakness; he was not taking any medications and had no allergies; and he denied use of tobacco, alcohol, or street drugs. He had undergone a left-sided orchiectomy for a nonhealing abscess in Mexico over 20 years earlier. He was born in Mexico and moved to Houston as a young adult, living there 13 years before moving to Dallas several years ago. He worked in construction and described no recent travel, known sick contacts, or prior exposure to tuberculosis.

His initial vital signs were normal (temperature, 98.2°F; blood pressure, 124/87 mm Hg; heart rate, 105 beats per minute; respirations, 16 breaths per minute with 97% oxygen saturation), and his lung auscultation was clear. His abdomen was diffusely tender to palpation with no guarding or rigidity. The left testicle was missing with a well-healed scrotal scar and round soft right testicle. There was no skin rash or edema.

His pertinent laboratory results were as follows: white blood cell count, 14.4 K/μL, with 90% neutrophils, 2% lymphocytes, and no bands; hemoglobin, 11.4 g/dL; hematocrit, 34.1%; sodium, 125 mEq/L; potassium, 5.0 mEq/L; chloride, 80 mEq/L; bicarbonate, 19 mEq/L; anion gap, 26 mEq/L; blood urea nitrogen, 190 mg/dL; creatinine, 19.7 mg/dL; glucose, 151 mg/dL; total protein, 9.7 g/dL; albumin, 4.5 g/dL; and lactate, 1.3 mEq/L. Urinalysis results revealed a specific gravity of 1.015, pH of 6, 2+ protein, 2+ blood, 4 red blood cells per high-power field, 50 to 100 white blood cells per high-power field, and positive dipstick for leukocyte esterase and nitrite. In spot urine chemistries, the fractional excretion of sodium was 12.5%. Timed urine collection revealed a urinary volume of 2250 mL/day, a creatinine clearance of 6 mL/min, a urea clearance of 4 mL/min, and urine protein of 1.5 g/day.

Several imaging studies were completed. Renal sonography revealed a 13.0 × 7.0 cm right kidney with a 2.9 × 3.7 cm anechoic lesion in the superior pole and mild hydronephrosis, and a 13.4 × 8.5 cm left kidney with numerous echogenic lesions in the posterior pole up to 1.3 cm and severe hydronephrosis (Figure 1). No ureteral jets were visualized. Computed tomography (CT) of the abdomen and pelvis without contrast revealed multilocular renal cysts, 7.6 cm in the left kidney and 3.7 cm in the right kidney, multiple calcified retroperitoneal lymph nodes up to 13 mm in size, and calcific deposits in the prostate and both seminal vesicles. CT of the chest (Figure 2) revealed innumerable 1 to 2 mm nodules in both lungs, predominantly in the upper lobes. A chest radiograph revealed increased density in the medial left lung apex.

On Day 2, the patient’s renal function was unchanged. Because of difficulties placing the Foley catheter, urology was consulted. The catheter was placed with difficulty during cystoscopy because of a rigid “leadpipe” urethra. The bladder contained a large amount of white debris, which was adherent to the bladder mucosa but easily irrigated off the mucosa. The bladder debris was sent for bacterial, fungal, and mycobacterial culture.

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Retrograde pyelography revealed an irregular beaded appearance of both ureters consistent with ureteritis cystica (Figure 3). Bilateral ureteral stents were placed, and the Foley catheter was left in place. Renal biopsy was performed, which showed several areas of granulomatous interstitial nephritis with multiple areas of caseous necrosis (Figure 4). There was evidence of extensive tubular atrophy. Visualized glomeruli were normal with no glomerulosclerosis. Fungal and mycobacterial stains were negative. All initial tuberculosis tests were negative, including a purified protein derivative skin test, two sputum acid-fast bacilli tests, and three urine stains for acid-fast bacilli. In addition, a QuantiFERON TB Gold test was indeterminate.

At discharge, renal chemistries had stabilized with a blood urea nitrogen of 134 mg/dL and creatinine of 9.9 mg/dL. It was felt that the patient would likely need hemodialysis within the next several weeks or months. An arteriovenous fistula was placed in preparation for hemodialysis. His volume status was stable, with urine output matching oral fluid intake. He had no uremic symptoms.

DISCUSSION

Tuberculosis is the second most common cause of infectious disease–related mortality in the world behind HIV (1). Data from the World Health Organization in 2010 indicated that one third of the world population has been exposed to tuberculosis and has at least latent disease (2). The world incidence of active tuberculosis ranges from 30 to 340 cases (mean 140) per 100,000 population, with a total of 9.4 million cases. The world prevalence of active tuberculosis ranges from 40 to 500 (mean 165) per 100,000 population, with a total of 14 million cases. The annual mortality from tuberculosis ranges from 2 to 50 (mean 19) per 100,000 population, with a total death rate of 1.3 million. Tuberculosis in the USA is usually confined to patients with malignancy, immunosuppression, and HIV infection.

The offending microorganism is M. tuberculosis. The tuberculosis bacilli are inhaled into the lung, where they are locally contained by leukocytes and macrophages. Some organisms
cause active pulmonary disease, and others spread to distant locations as metastatic foci. Most patients with active tuberculosis present with pulmonary involvement. Extrapulmonary involvement occurs in only 20% of cases (3). After lymph node involvement, the most common site of extrapulmonary tuberculosis infection is the genitourinary system. Genitourinary tuberculosis accounts for 15% to 30% of all cases of extrapulmonary tuberculosis (4–9).

Renal infection with tuberculosis occurs by hematogenous spread of previously dormant organisms from a prior lung infection at the time of marginal cellular immunity (10). The tuberculosis organism has strict growth requirements, which makes the kidney, with its high oxygen tension, a prime site for new growth. The initial renal involvement is multiple cortical granulomas. As host defenses decline, the granulomas grow, coalesce, and ultimately result in caseous necrosis. An intense interstitial nephritis with severe calcification develops as the renal response to the now active infection. Contiguous spread of the infection may lead to ureteral and bladder involvement. Hematogenous-lymphatic spread can lead to involvement of the male (prostate-epididymis-testis) and female (uterus-fallopian tube) reproductive sites.

Renal involvement of tuberculosis often does not present with classic symptoms of fever, weight loss, or night sweats. Patients may present with usual lower urinary tract symptoms suggesting simple bacterial cystitis. Symptoms of renal colic are unusual. Initial urinalysis may show pyuria and hematuria, but no bacteria. Urine culture is often negative for usual bacterial organisms. Tuberculosis is one of the causes of sterile pyuria.

Often, renal imaging procedures will raise the suspicion of renal tuberculosis (11). Calyceal distortion and papillary necrosis may be seen on intravenous pyelogram studies. A markedly abnormal renal contour with multiple intrarenal calcifications on ultrasonography will suggest renal tuberculosis. Cystoscopy and retrograde pyelography can reveal a markedly abnormal urinary bladder and classic changes of ureteritis cystica. Hydronephrosis can be seen on any renal imaging procedure because of bladder or ureteral narrowing.

A definitive microbiologic diagnosis is made by isolating tuberculosis organisms from urine or tissue biopsy specimens. Acid-fast bacilli may be seen on microscopy of centrifuged urine. Renal histology reveals tubulointerstitial nephritis with granuloma formation, often with caseous necrosis (3, 12). Urine culture for acid-fast bacilli is the gold standard for diagnosis of renal tuberculosis; its specificity is 100%, but its sensitivity ranges from 30% to 90% depending on the number of samples tested (13–15). It may take 6 to 8 weeks before a positive urine culture becomes available.

Renal outcomes in renal tuberculosis are extremely variable. Diffuse renal scarring can lead to an autonephrectomy state with no function on the affected side. Spread of intrarenal infection to the renal pelvis can progress to pyonephrosis with a cement or “putty” kidney involving the entire renal pelvis. Urereal involvement can lead to diffuse ureteral strictures with subsequent urinary obstruction on that side. Bladder scarring can lead to urinary obstruction and compromise of renal function as well. Progression to end-stage renal disease is distinctly unusual. Tuberculosis causes <1% of all cases of end-stage renal disease.

Treatment of renal tuberculosis involves multidrug therapy. This has evolved over the years to the current four-drug regimen involving initial 2-month intensive treatment with rifampin, isoniazid, pyrazinamide, and ethambutol (3, 16). This is usually followed with a 4-month maintenance regimen involving rifampin and isoniazid. Urologic intervention may be indicated for unilateral disease because of pain or hemorrhage or for bladder augmentation (17, 18). Relief of ureteral obstruction by stenting or percutaneous nephrostomy may be indicated, especially if underlying parenchymal renal disease is mild and residual renal function is >15 mL/min, where escape from the dialysis requirement might occur.


In memoriam

R. GORDON HOSFORD, MD
Department of Internal Medicine, Baylor University Medical Center at Dallas

Dr. Gordon Hosford, 79, died on March 4, 2012, of throat cancer at Baylor Specialty Hospital in Dallas. He had been born at what is now Baylor University Medical Center at Dallas (BUMC) and practiced internal medicine there for 42 years. Dr. Hosford grew up in Fayetteville, Arkansas, where his father chaired the mathematics department at the University of Arkansas, and returned to Texas in 1949, when his father became vice president and later first provost at Southern Methodist University. He attended Highland Park High School and Southern Methodist University before attending medical school at Harvard University. His education was followed by a residency in internal medicine at Barnes Hospital in St. Louis, 2 years as an Air Force flight surgeon, and 2 years of postgraduate studies at Stanford Medical Center. He then practiced medicine in Dallas from 1963 until his retirement in 2005. Beyond his dedication to his patients, Dr. Hosford served in several leadership positions. He served on the board of directors and as president of the Dallas Heart Association and was a life board member and medical director of the Visiting Nurse Association.

COLEMAN G. JACOBSON, MD
Division of Dermatology, Department of Internal Medicine, Baylor University Medical Center at Dallas

Dr. Coleman Jacobson passed away on April 10, 2012, in Manchester, New Hampshire. He was born on April 18, 1921, in New Haven, Connecticut, and attended Iowa University. His education was interrupted by service in the Army Air Corps in World War II. He was a prisoner of war for almost 2 years in Germany after being shot down from a B24 bomber and earned an Air Medal and a Purple Heart for his service. In 1945 he returned from the war and attended medical school at the University of Iowa, graduating in 1949. After a residency in dermatology at the University of Pennsylvania, he founded the North Dallas Dermatology Clinic. In addition to serving on the medical staff at BUMC, he was a long-time professor of medicine at The University of Texas Southwestern Medical School, was chief of dermatology at Children’s Medical Center, and was a visiting professor of dermatology at Baylor University College of Dentistry. Throughout his career, Dr. Jacobson combined his love of world travel with service to third world countries, founding and supporting clinics and hospitals throughout Africa. Among his many accomplishments and honors, he received a lifetime achievement award from the American Academy of Dermatology in 2006; was president of the International Society of Dermatology, the Dallas Dermatology Society, the Texas Dermatological Society, and the Dermatology Foundation; and was a board member of the American Academy of Dermatology and chairman of the board of the Dermatology Foundation.

ROBERT GORDON LONG, MD
Department of Neurosurgery, Baylor University Medical Center at Dallas

R. Gordon Long, MD, a neurosurgeon at BUMC for 35 years, died on April 6, 2012. He was born in Nashville, Tennessee, on June 30, 1930, and received his medical degree from Vanderbilt University in 1955. After completing additional training and obtaining board certification in neurosurgery, Dr. Long joined the BUMC medical staff in 1964. He was chairman of the neurosurgery department from 1980 to 1990.

BEN SCHNITZER, MD
Department of Urology, Baylor University Medical Center at Dallas

Ben Schnitzer, MD, died peacefully on March 29, 2012, at the age of 78. A lifetime resident of Dallas, Dr. Schnitzer graduated from Forest Avenue High School in 1950 at the age of 16 and received a scholarship to attend Southern Methodist University. He graduated from The University of Texas Southwestern Medical School and completed his residency at Parkland Hospital, where he was present in the emergency room when President Kennedy was admitted in November 1963. He then served in the US Navy for 2 years before beginning his 47-year practice of urology at BUMC. Dr. Schnitzer served on the board of directors of BUMC and as chief of urology from 1986 to 1996. He was the primary investigator for a number of innovative urological technologies and spearheaded patient education and screening activities in prostate cancer. In addition, Dr. Schnitzer was a clinical professor of urology at UT Southwestern Medical School.
Vertebral artery thrombosis and subsequent stroke following attempted internal jugular central venous catheterization

Michael J. Van Vrancken, MD, MPH, and Joseph Guileyardo, MD

Complications arising from internal jugular venous catheterization are uncommon. Injury to the carotid artery is reported as one of the more common injuries. Vertebral artery injuries are rare and include pseudoaneurysm formation, arteriovenous fistulas, lacerations, and dissection with thrombus formation. Occasionally, such injuries initially go unnoticed and have the potential to cause catastrophic outcomes, leaving clinicians and families wondering what transpired. A thorough autopsy can not only help discern the cause of death, but also help to bring closure to the family. Here we present a case of an unexpected death 3 days following surgery for idiopathic scoliosis in a 17-year-old male. During the surgical procedure, a right internal jugular venous catheterization was attempted but aborted after several failed tries. Twenty-four hours after the procedure, the patient became obtunded and progressed to brain death. At autopsy, he was found to have a right transmural vertebral artery puncture wound with thrombosis leading to a massive posterior circulatory stroke.

Since its initial description in 1952 (1), central venous catheterization has been frequently performed, with millions of days of patient exposure to central vascular catheters in the United States each year (2). Although the procedure is common and relatively safe, several complications have been described, with a prevalence ranging from 5% to 19% depending on the definition used (3, 4). In particular, internal jugular vein (IJV) catheter insertion is prone to several unique complications, some of which can, albeit rarely, prove to be fatal. Presented here is a case of vertebral artery thrombosis with subsequent stroke and death following attempted IJV catheterization.

CASE STUDY

A 17-year-old young man with a history of idiopathic scoliosis, essential hypertension, and a patent ductus arteriosus (surgically repaired at 1 month of age) was admitted for instrumented posterior spinal fusion from T2 to L1 for treatment of his scoliosis. Intraoperatively, right IJV catheterization was attempted for vascular access. After failed attempts, central line placement was obtained through right subclavian vein catheterization. The remainder of the operative procedure was uncomplicated, and the patient was subsequently admitted to the intensive care unit for postsurgical care. Initial postoperative neurological examination showed no focal motor or sensory deficits.

Approximately 24 hours postoperatively, the patient began showing decreased mental status, progressing to an obtunded state and requiring respiratory support. A computed tomography scan showed large right occipital and bilateral cerebellar ischemic changes with mild hydrocephalus and cerebral edema. A ventriculostomy was placed to relieve elevated intracerebral pressure.

On day 3, a two-dimensional echocardiogram showed no cardiac abnormalities. A magnetic resonance imaging study showed normal blood flow in the subclavian and common carotid arteries. There was symmetric bilateral tapering of blood flow into the internal carotid arteries with apparent cessation of intracranial blood flow secondary to severe cerebral edema. The patient died on postoperative day 3.

At autopsy, external examination found a 1- to 2-mm, well-defined, circular perforation at the right anterolateral aspect of the neck consistent with attempted IJV vascular catheter placement surrounded by a few smaller puncture marks. Within the adjacent neck tissues, there was a moderate amount of hemorrhage within perivascular soft tissue along the right anterior aspect of the cervical spine. There was no gross evidence of thrombus within the right carotid, right jugular, or either vertebral artery at their entrances into the lower cervical spine or within the cranial vault, although a moderate amount of hemorrhage was noted around the right vertebral artery at its entrance into the lower cervical spine (Figure 1). The heart weighed 325 g. The brain showed cerebellar tonsillar herniation with moderate flattening of gyri and narrowing of sulci consistent with cerebral edema. There was extensive necrosis of the entire right cerebellar hemisphere, and the left cerebellar hemisphere also contained large areas of geographic necrosis. None of the cerebellar branches of the vertebrobasilar system, including the inferior and superior cerebellar arteries, contained thrombus.

Microscopically, sections of each intracranial vertebral artery near the base of the skull showed both vessels to be well formed from the Department of Pathology, Baylor University Medical Center at Dallas. Corresponding author: Joseph Guileyardo, MD, FCAP, 2911 Turtle Creek Boulevard, Suite 300, Dallas, Texas 75219 (e-mail: guileyardo@sbcglobal.net).
and to contain patent lumens. Sections of the right vertebral artery at its entrance into the lower cervical spine showed extensive perivascular hemorrhage. The arterial wall was focally punctured through the intimal, elastic, medial, and adventitial layers of the vessel. Within the vessel there was definite luminal thrombosis with adjacent reactive changes involving the endothelium. The thrombotic material also focally extended through the disrupted muscular layer. These findings were further accentuated using the Russell-Movat pentachrome stain (Figure 2).

Microscopic sections of brain contained scattered “red” neurons and apoptotic nuclei consistent with diffuse and acute anoxic/ischemic encephalopathy. Blood vessels within the leptomeninges overlying the area of necrosis in the occipital lobe and left cerebellar hemisphere contained thromboemboli with microscopic features similar to the thrombus identified within the right vertebral artery (Figure 3).

**DISCUSSION**

Most catheterization-related vertebral artery injuries have occurred during IJV catheterization, although injury to the carotid artery is generally more frequent (5–7). Several types of vertebral artery injuries have been described following IJV catheterization, including arteriovenous fistulas, lacerations, pseudoaneurysm formation (8), and dissection with thrombosis, with arteriovenous fistulas and pseudoaneurysm as the most common. Of note, only two cases of injury with thrombosis of the vertebral artery leading to massive posterior circulatory stroke following IJV catheterization have been reported (9, 10).

Typically, injury to the vertebral artery occurs during IJV catheterization when the needle is directed lateral to the IJV or extends too deep. The portion of vertebral artery most susceptible to injury is the V1 portion between its origin from the subclavian artery and the C6 transverse foramen (11). Patient signs and symptoms following injury are typically delayed, with most presenting with bruises or pulsating masses representing arteriovenous fistulas or pseudoaneurysm, respectively. In the two previously reported cases of vascular injury with thrombosis, patients presented with altered mental status followed by an obtunded state leading to coma, similar to the case presented here.

Iatrogenic injury to the vertebral artery can occur under other circumstances, including cervical spine surgery, chiropractic manipulation, diagnostic cerebral angiography, percutaneous nerve block, and radiation therapy (12); therefore, with this patient’s history of recent spine surgery, special consideration was also given to possible vertebral artery injury secondary to the operative procedure.

Most cases of vertebral artery injury during spine surgery have occurred during cervical spine procedures. The patient presented here underwent spinal fusion from T2 to L1, a procedure that is well below the level likely to cause vertebral artery injury, in our opinion. Furthermore, even with anterior cervical spine surgery, injury to the vertebral artery is rare, with an incidence of <1% (13). Although relatively safe, anterior cervical corpectomy has a slightly higher incidence of vertebral artery injury compared to other anterior cervical spine surgeries (such as standard anterior cervical discectomy and fusion) (13–15).

During posterior cervical spine surgery, most cases of vertebral artery injury occur during the C1–C2 transarticular screw procedure.
fixation procedure for atlantoaxial instability secondary to the proximity of the artery and the blind passage of a guiding wire or transarticular screw into the C1–C2 facet joint (16–19). Additionally, most surgical injuries to the vertebral artery involve lacerations. This is distinctly different from the puncture and thrombosis seen in the present case, which is more consistent with previous reports of injury due to IJV catheterization.

The circumstances surrounding pathologic evaluation of the cervical and thoracic spine following surgical intervention present special challenges at autopsy. Admittedly, for many pathologists, involvement in such an autopsy can prove overwhelming with laborious and meticulous dissections involving complex anatomy. Preparation and detailed knowledge of the regional anatomy are essential to reach accurate conclusions, and systematic and thorough evaluation of all neck and back compartments will allow for the most complete information (20). Such efforts are certainly justified, since potentially catastrophic complications demand a thorough explanation whenever possible.

Numb chin syndrome as the initial presentation of posttransplant lymphoproliferative disorder

Rajin Shahriar, BS, Chris T. Alexander, MD, Cody R. Quirk, MD, Latoya Keglovits, MD, and Michael Van Vrancken, MD, MPH

Numb chin syndrome is a sensory neuropathy caused by compromise of the mental nerve, the posterior branch of the inferior alveolar nerve, which leads to numbness or tingling in its respective distribution. There is no loss of motor function, as the inferior alveolar nerve contains no motor fibers. While associated with certain benign etiologies (1–3), the condition is increasingly reported as a manifestation of malignancy, including prostate adenocarcinoma (4, 5), lymphoma and leukemia (6–8), multiple myeloma (9), and breast cancer (10). While many of these malignancies are associated with other historical or physical signs or symptoms, numb chin often presents as the initial symptom (11–15), and awareness of this physical finding should raise suspicion for an underlying malignancy and may even contribute to earlier detection.

CASE PRESENTATION

A 67-year-old white man initially presented to the emergency department at Baylor University Medical Center at Dallas with a 3-day history of new-onset bitemporal headache and a 1-day history of right lower lip swelling and numbness of the mandibular area. A 12-point review of systems was otherwise unremarkable. Right lower lip erythema and anesthesia were confirmed on examination, although other sensory or motor deficits were not found. The patient’s gait was normal, cranial nerves were intact, and neck movements were normal. Notably, hepatosplenomegaly and lymphadenopathy were not evident on physical examination. Due to our patient’s initial presentation with neurologic symptoms in the context of immunosuppression, he was admitted to rule out an infectious etiology and to undergo a diagnostic workup.

Our patient’s past medical history included gastroesophageal reflux disease treated with Nissen fundoplication, hypothyroidism, systemic hypertension, and idiopathic pulmonary fibrosis diagnosed by video-assisted thoracotomy with lung biopsy at age 63, for which he underwent bilateral sequential lung transplantation at age 66 (in October 2011). Postoperatively, he developed bilateral pulmonary infiltrates and was treated with broad-spectrum antibiotics. Fiberoptic bronchoscopy revealed acute lung injury. He was treated with high-dose corticosteroids for presumed acute transplant rejection but subsequently experienced worsening pulmonary infiltrates, which required repeat workup. A repeat fiberoptic bronchoscopy with biopsy confirmed acute lung injury with organization and acute rejection. Another course of corticosteroids appeared to result in improvement. He was then treated with a 10-day course of antithymocyte globulin (Atgam) for presumed chronic rejection and also had a tracheostomy because of prolonged respiratory failure. After this intervention, he was gradually weaned off the ventilator, the tracheostomy was removed, and he was eventually discharged home with no pulmonary complaints. In addition to receiving treatment for this episode of acute rejection, our patient was kept on a baseline immunosuppressive regimen of tacrolimus and azathioprine.

A sister had died at age 75 from complications of chronic obstructive pulmonary disease, and the patient was a former 20 pack-year smoker, who quit in 1974. As the patient tested positive for Epstein Barr virus (EBV) prior to lung transplant, an EBV quantitative polymerase chain reaction (PCR) test was ordered and revealed viremia with 28,700 copies (normal <250). Given his risk of infection from his immunosuppressive therapy, a computed tomography (CT) scan of the head, cultures, lumbar puncture, and chest x-ray were ordered. The CT revealed only microvascular ischemic changes consistent with the patient’s age. The patient’s B12 level was 907 pg/mL (reference range, 211–911), and folate was 21.8 ng/mL (reference range, >5.4). The cerebrospinal fluid protein was 60 mg/dL, glucose was 131 mg/dL, and cultures for fungi, acid-fast bacilli, Cryptococcus, arbovirus panel, and West Nile were all negative. The cerebrospinal fluid antigen for Histoplasma was negative. In addition, blood and urine cultures, cytomegalovirus, and herpes PCR were negative. Magnetic resonance imaging revealed innumerable nonlytic lesions throughout all the osseous structures of the skull. A CT of the abdomen and pelvis demonstrated prominent paraaortic lymph nodes, multiple hypointensities in hepatic lesions, and innumerable sclerotic lesions throughout the axial skeleton. A bone scintigraphy scan showed two small foci of uptake in the bilateral frontal regions and cortical uptake in the lower extremities.

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At this junction, hematology/oncology was consulted. The patient’s lactate dehydrogenase was 814 IU/L (reference range, 85–245). Serum protein electrophoresis did not reveal any monoclonal peaks. The patient’s immunofixation profile was negative, and kappa and lambda chain quantification was unrevealing for gammopathy. A repeat EBV quantitative PCR revealed 601,000 copies of virus/mL. Bone marrow biopsy revealed a sheet-like plasmacytoid infiltrate composed of medium to large cells. Many cells had a large centrally placed nucleolus with a finely dispersed immature chromatin pattern consistent with a plasmablastic type morphology (Figure 1). These cells stained positive for CD138 (Figure 2) with patchy positivity for CD56. CD20 was diffusely negative. In situ hybridization showed strong EBV early RNA positivity, and in situ hybridization for kappa and lambda were negative. These findings were compatible with a diagnosis of a plasmablastic posttransplant lymphoproliferative disorder (PTLD). The patient received one dose of CHOP (cyclophosphamide, hydroxydaunorubicin, Oncovin, and prednisone). Due to increasing weakness from the therapy, the patient and the patient’s family decided to pursue palliative care, and the patient died soon afterwards.

**DISCUSSION**

Numbness in the distribution of the mental nerve, or so-called numb chin syndrome, can be associated with both benign and malignant etiologies. To our knowledge, this is the first described case of numb chin syndrome as an initial presentation of malignancy in a transplant patient. It is still unclear how specific this clinical sign is for malignancy, the exact mechanism of effect on the mental nerve, if this sign is associated with a worse prognosis of malignancy, or if identification of a malignancy based on diagnostic workup done because of this sign would affect survival (16, 17).

In general, PTLD is a somewhat common but serious and potentially fatal complication of organ transplantation. PTLD accounts for about 20% of all malignancies following solid organ transplantation (18, 19). These cancers involve mostly B-cell components, but may also involve T cells or rarely natural killer (NK) cells (20). The cause is related to concurrent immunosuppression and EBV viremia (21). The underlying hypothesis is derived from an EBV-associated protein (LMP-1) that, in turn, stimulates tumor necrosis factor growth factors, leading to cell proliferation and transformation. Our patient received antithymocyte globulin, which bound to his T cells, inducing cytokine release initially before destroying the original T cells (22). The subsequent cytokine release undoubtedly led to the growth of EBV-infected B cells, marrow proliferation, and his final diagnosis of plasmablastic lymphoma (Figure 3). While most patients who develop PTLD do not have a history of treatment with antithymocyte globulin, immunosuppression is a key pathogenic mechanism in the natural history of the disease, and it is highly probable that this contributed to his disease.

Plasmablastic lymphoma was first described in the late 1990s as an oral cavity lesion mainly seen in HIV-positive individuals (23). The disease usually develops from 35 to 55 years of age (24). This lymphoma has also been reported in HIV-negative patients, particularly those who have had immunosuppression. Since its original description, it has subsequently been described in the PTLD setting, albeit rarely. In 2003, the first case of plasmablastic lymphoma was recognized in a transplant patient; it presented as a cutaneous lesion (25). In 2008, plasmablastic lymphoma was classified by the World Health Organization as a subtype within the monomorphic category of PTLD. The histological findings of diffuse infiltrates, mitotic activity, and necrosis support the overlying description as a high-grade malignant lymphoma (26).

The incidence of PTLD depends on several factors, including which organ is transplanted, the EBV serostatus of both the donor and recipient, and the aggressiveness of the immunosuppression. The risk factors for development of this disorder can be further refined by the type of organ transplanted, time posttransplant, recipient age, and ethnicity (27, 28). Also, PTLD can develop at any point after the transplant, even as early as 2 months, but most cases occur within the first year of transplant. A French study of
lungs and heart transplant patients found that the median time for development of malignancy was >2 years. Typical presentations of PTLD include mononucleosis-type symptoms, palpable lymph nodes on exam, and symptoms of organ dysfunction. While our patient’s natural history of PTLD was not unusual, we felt his initial presentation of numb chin syndrome without any of the typical signs or symptoms of PTLD was noteworthy.

Left ventricular myxoma presenting with prolonged fever

V. Sudhakumari, MD, DM, Thattungal M. Anoop, MD, Joby K. Thomas, MD, DM, and Raju George, MD, DM

Left ventricular (LV) myxoma presenting with fever of unknown origin is rare, with only one reported case (1). Here we present a patient with LV myxoma initially presenting as prolonged fever. The fever disappeared after operative excision of the myxoma.

CASE REPORT

A 45-year-old man presented with low-grade fever of 1-month duration. An extensive investigation did not reveal the cause of the fever. There was no palpitations, breathlessness, chest pain, syncope, loss of vision, night sweats, cough, loss of weight, or loss of appetite. On examination, the patient was febrile. A precordial systolic murmur was detected at the apex. The spleen was not palpable.

Routine blood and urine examination revealed no abnormalities. Hepatic and renal function were normal, as was the chest radiograph, tuberculin test, brucella antigen test, ultrasonography of the abdomen, and blood cultures. In addition, rheumatoid factor, antinuclear factor, and antineutrophil cytoplasmic antibody results were negative, and retroviral antibody and surface antigen for hepatitis B were nonreactive. The bone marrow examination was also normal.

Electrocardiography showed sinus tachycardia and left ventricular hypertrophy with a strain pattern. Two-dimensional transthoracic echocardiography showed a mass measuring 3.7 × 2.3 cm arising from the LV apex, with a normally contracting adjacent myocardium (Figure 1). The LV ejection fraction was 68%. The morphology and function of cardiac valves were normal.

On cardiopulmonary bypass, a soft brownish mass was seen arising from the LV apex (Figure 2). The tumor was surgically removed, and histology confirmed the diagnosis of myxoma (Figure 3). The patient’s postoperative period was uneventful; he had a smooth recovery, with resolution of the fever, and was discharged on the 10th postoperative day in sinus rhythm.

DISCUSSION

The cause of the fever in our patient is unclear, but it disappeared after excision of the tumor. Overproduction of
interleukin-6 has been linked to the principal mediator of the acute-phase protein responsible for symptoms such as fever, anemia, and arthralgia experienced by patients with cardiac myxomas, and raised serum levels may become undetectable after resection of the neoplasm (2).


Figure 3. Histopathology of the excised mass showing myxomatous cells suggestive of myxoma.

Avocations

"Water lily." Photo © Rolando M. Solis, MD. Dr. Solis is an interventional cardiologist on the medical staff of Baylor Medical Center at Garland.
A case of dyspnea and periorbital rash

George C. Eldho, MBBS, B. Sebastian Gailin, DM, C. Mohan Mithun, MBBS, Thattungal M. Anoop, MD, and R. Sudha, DM

A 75-year-old woman presented with dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, and edema. Macroglossia, generalized petechiae, raccoon eyes sign, and peripheral neuropathy were present, and an echocardiogram showed cardiac dilatation and left ventricular systolic dysfunction. Rectal biopsy and immune fixation electrophoresis confirmed the diagnosis of AL amyloidosis.

Amyloidosis is a group of diseases caused by extracellular deposition of insoluble polymeric protein fibrils in tissues and organs. Symptoms vary widely depending upon the site of amyloid deposition. Cardiac involvement may occur, with or without clinical manifestations, as a part of systemic amyloidosis or as a localized phenomenon and is associated with a poor prognosis (1). We describe a case of a 75-year-old woman with primary amyloidosis presenting as full-blown cardiac failure and classical cutaneous manifestations. The diagnosis was established by rectal biopsy and immunofixation electrophoresis.

CASE REPORT

A 75-year-old woman presented with gradually progressive breathlessness and pedal edema for 3 years with acute worsening of symptoms. There was associated orthopnea and paroxysmal nocturnal dyspnea. Edema initially started in the lower limbs and later involved the whole body and face. She had a history of easy bruising and noticed spontaneous ecchymotic patches for a couple of years with no other significant bleeding manifestations. She also gave a history of enlargement of the tongue, which made chewing and talking difficult, and a swelling just below the jaw for 2 years. Her relatives had noticed discoloration around the eyes for 1 year. Apart from this, she had paraesthesia of extremities, which was worse in a cold climate, constipation, and urge incontinence. Her sleep was disturbed at night, and she had daytime somnolence and a history of snoring, which was suggestive of obstructive sleep apnea. She had had no significant illnesses in the past, and there was no similar illness among her family members.

On examination, the patient had significant pallor and pedal edema. Macroglossia, petechiae, and ecchymosis in the periorbital area (raccoon eyes) and the perioral region (Figure 1) and over the trunk and extremities were present. Her pulse rate was 110 beats/minute; blood pressure, 120/90 mm Hg; and respiratory rate, 24 breaths/minute. Her jugular venous pressure was also elevated. Respiratory system auscultation revealed bilateral crepitations and rhonchi. There was cardiomegaly, with an audible S3 and pansystolic murmur. The nervous system examination showed a sensorimotor type of peripheral neuropathy.

A routine blood examination showed mild anemia with normal cell counts and a normal erythrocyte sedimentation rate. Her hemoglobin was 10 g/dL. A peripheral smear showed normocytic normochromic anemia, and a bone marrow biopsy showed mild plasmacytosis with 12% plasma cells. She had mild hyponatremia, a mild increase in activated partial thromboplastin time and prothrombin time, and a moderately raised fasting level of low-density lipoprotein; other biochemical tests were within normal limits. Urine examination showed a trace of albumin without hematuria and pyuria. Urine protein excretion was 0.981 g/day. A Bence Jones protein test and free light chain
assay in urine were negative. Serum electrophoresis showed no M band, but serum immunofixation electrophoresis was positive for amyloid light chain. The serum kappa was 9.3 mg/L, and lambda was elevated with 76.5 mg/L. The immunoglobulin assay showed an IgG of 75 mg/dL, IgM of 33 mg/dL, and IgA of 40 mg/dL. Serum levels of N-terminal prohormone of brain natriuretic peptide were elevated at 16,000 pg/mL.

A chest x-ray showed bilateral mild pleural effusion. Echocardiographic evaluation showed concentric left ventricular (LV) hypertrophy with a granular speckling pattern (Figure 2), global LV hypokinesia, moderate LV systolic dysfunction (ejection fraction 37%), restrictive LV filling, moderate pulmonary arterial hypertension, and mild pericardial effusion. The patient’s rectal biopsy was positive for amyloid deposits by hematoxylin and eosin staining (Figure 3) and Congo red staining. The Congo red stain examined under polarized light showed apple green birefringence. Her electrocardiogram showed low voltage complexes with normal axis and rhythm.

Based on the clinical picture and the study results, a diagnosis of primary amyloidosis was made. Treatment was started for heart failure, and the patient improved with supportive measures. She was discharged, with treatment planned for amyloid, but unfortunately she died of progressive heart failure within a few weeks of the diagnosis.

**DISCUSSION**

In primary amyloidosis, the fibrillary protein is AL type. A few patients have some form of plasma cell dyscrasias or other form of lymphoproliferative disorders, but most do not. The disease progresses rapidly. Macroglossia is the pathognomonic feature of AL amyloidosis. Easy bruising due to deposition of amyloid and deficiency of factor X and cutaneous ecchymoses, especially if around the eyes, may be seen. The heart and kidneys are the most commonly affected organs. Mortality is high in patients with cardiac involvement (2). Increased atrial septal wall thickening and granular speckling in the myocardium are highly specific for differentiating cardiac amyloidosis from other causes of LV hypertrophy (3). With early diagnosis, there is better response to therapy and prolonged survival (4).

On November 15, 2011, a celebration was held for John S. Fordtran, MD (Figure 1), on the occasion of his 80th birthday. The event was initially suggested by Dr. Fordtran’s long-time colleague, Guenter Krejs, MD, who traveled to Dallas from Austria for the event. He was assisted by Charles Richardson, MD, and C. Richard Boland, MD.

The celebration began on the evening of November 14, with a dinner party held at the elegant Aldredge House on Swiss Avenue in Dallas for the out-of-town guests and some of John’s colleagues from his early academic career in Dallas. John’s career was recounted by a gathering of out-of-town guests and by his academic colleagues from the University of Texas Southwestern Medical School at Dallas (UTSW) (Figures 2–4). Among those present who provided reminiscences was Marvin H. Sleisenger, MD, Dr. Fordtran’s collaborator with the classic textbook *Gastrointestinal Disease*. Dr. Sleisenger traveled from San Francisco and was still spry and engaging at the age of 88. Other guests in attendance who spoke about John’s impact on their profession were his prior gastroenterology fellow, Michael Brown, MD, who won the Nobel Prize in

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Medicine or Physiology in 1985; Mike Emmett, MD, chair-
man of the Department of Internal Medicine at Baylor Uni-
versity Medical Center (BUMC); and Mr. Joel Allison, president
and CEO of the Baylor Health Care System. Other friends in
attendance were Donald Seldin, MD, past chairman of the
Department of Internal Medicine at UTSW who initially
recruited Dr. Fordtran to the faculty, who regaled the group
with some of the history and accomplishments that punctu-
ated John’s career; John’s good friend, Dan Foster, MD, who
succeeded Dr. Seldin as chairman of internal medicine at
UTSW; his long-time colleague and chief of the Division of
Gastroenterology at BUMC, Dan Polter, MD; John McWhorter,
president of BUMC; Boone Powell Jr., past president of BUMC
during Dr. Fordtran’s tenure as department chairman; and John
Dietschy, MD, who succeeded John as chief of gastroenterology
at UTSW. Other out-of-town guests present included Drs. Raj
Goyal (Boston), Edward Lee (Washington, DC), Pete Peterson
(Breckenridge, Colorado), and from Austria, Drs. Flori Fuerst,
Christine Kapral, and Heimo Wenzl, just to mention a few.

On the morning of November 15, Dr. Fordtran presented
at medical grand rounds in the Beasley Auditorium at BUMC.
He reviewed the evolution of the discovery of Whipple’s disease
and our current understanding of this disease. His introduction
was provided by Drs. Emmett and Boland and included a review
of his curriculum vitae.

It was recounted that Dr. Fordtran is a native of Stockdale,
Texas, near San Antonio, and was born in 1931. He attended
the University of Texas at Austin from 1949 to 1952 and then
Tulane Medical School from 1952 to 1956. He then came to
Dallas and was an intern and resident in internal medicine at
Parkland Memorial Hospital from 1956 to 1958. He had a
brief stint as a researcher at the National Institutes of Health
(NIH) in Bethesda, MD, from 1958 to 1959; he reports that
the experience was not ideal because he missed the involve-
ment in clinical medicine, although he was stimulated by the
academic atmosphere and spirit of inquiry that permeated the
institution. He then moved to the Indian Health Service, where
he served as chief of medicine on the Navajo Reservation at
Fort Defiance Hospital in Arizona for 16 months, during 1959
to 1960.

His next step was to become a research fellow under the
tutelage of Franz Ingelfinger, MD, in Boston from 1960 to
1962. There he began what would become a storied career as a
world-renowned gastrointestinal physiologist. He developed
the use of a nonabsorbable marker of gastrointestinal fluid volume,
which permitted him to measure a variety of key, previously
unexplored issues in the physiology of absorption and secretion
by the gut. His experience with Dr. Ingelfinger made John an
official “Fingerling.” John pointed out that his training was
largely directed by Don Seldin, who had big plans for John
back in Dallas.

In 1962, John returned to Dallas as an instructor in internal
medicine at UTSW and Parkland Memorial Hospital, under
the careful guidance of Dr. Seldin. He quickly rose through
the academic ranks, being named chief of gastroenterology in
1963 (Figures 5 and 6) and full professor of medicine in 1969,
an astonishing 7 years after his return to Dallas. He served
as associate editor of the Journal of Clinical Investigation from
1972 to 1977, was elected to the American Society for Clinical
Investigation (aka the “Young Turks”) in 1968 and became its
president in 1976, and was also elected to the Association of
American Physicians (aka the “Old Turks”) in 1972. He served
as the editor in chief of Gastroenterology from 1977 to 1981.
He had grants from the NIH throughout his active research
career and won a prestigious MERIT Award from the NIH in
1991. He published over 182 original articles from 1961 to
2010, which included 20 papers in the New England Journal of
Medicine, 38 in the Journal of Clinical Investigation, and 65 in
Gastroenterology, representing monumental accomplishments.
During his career, John served as chairman of the Department of Internal Medicine at BUMC from 1979 to 1996 and president of Baylor Research Institute from 1991 to 2000 (Figure 7). He received numerous awards from the American Gastroenterological Association (AGA). He was awarded the Distinguished Achievement Award for his research in 1971, the Fiterman Award for Clinical Research in 1990, the Distinguished Educator Award in 1991, the Julius Friedenwald Award for contributions to the field of gastroenterology (the AGA’s highest honor) in 1993, and the Janssen Award for Lifetime Achievement in Gastroenterology in 1999, making him almost certainly the most recognized and celebrated figure by the AGA. John has had international impact as well. He won the King Faisal International Prize in Medicine in 1984 and was elected fellow of the Royal College of Physicians in London in 1997. In addition, he won the Ralph Tompsett Award for Excellence in Medical Education at BUMC in 2007, arguably anointing him as the consummate clinician, researcher, and teacher in his field. Most would have been proud to have excelled in just one of these endeavors; John excelled in all he did.

Not to diminish the above-cited accomplishments, but most clinicians in the field of gastroenterology know him best for editorship of Sleisenger and Fordtran’s Gastrointestinal Disease, which had its inaugural edition in 1973 and is currently in its 9th edition (Figures 8 and 9). Most clinicians consider it the gold standard of gastroenterology textbooks.

The medical grand rounds presentation was attended by a large audience of colleagues, former students, residents, fellows, and friends. After his lecture, the group moved to the Davis Auditorium in the Roberts Tower for a series of case presentations and discussions that were a recreation of the clinical case conference that was developed by John at UTSW (Figure 10). Several colleagues made presentations of unusually challenging cases, which both instructed and regaled the audience.

The first to present was Edward Lee, MD, chief of pathology at Howard University College of Medicine in Washington, DC, who discussed a mysterious case of a giant ulcerated inflammatory mass in the cecum that occurred in the setting of Bechet’s syndrome. Guenter Krejs, MD, and Heimo Wenzl, MD, from Graz, Austria, presented a case of severe D-lactic acidosis in a patient with short bowel syndrome following complications of bariatric surgery, which was exacerbated by the ingestion of simple sugars. Glenn Davis, MD, from Little Rock, Arkansas, showed some previously censored slides of Dr. Fordtran examining a patient from the 1970s and then presented a vexing case of mesenteric fibrosis syndrome, challenging the group to suggest...
an ideal management plan. Mark Feldman, MD, chairman of medicine at Presbyterian Hospital, Dallas, presented a case of acute appendicitis that complicated chronic ulcerative colitis, an illness that required a nimble diagnosis to reach an optimal outcome. Jane-Claire Williams, MD, and C. Richard Boland, MD, from BUMC presented the case of a young woman with juvenile polyposis and chronic anemia, in which the genetic alteration causing the juvenile polyposis was also responsible for the diagnosis of hereditary hemorrhagic telangiectasia (also known as Rendu-Osler-Weber syndrome), which accounted for abnormalities on her x-rays and her family history of severe arteriovenous malformations. Finally, Reed Hogan Jr., MD, from Jackson, Mississippi, presented a complicated case of liquid caustic ingestion that led to multiple strictures. He acknowledged that he had presented this same case at the gastroenterology conference in Dallas 28 years earlier and marveled at how innovative endoscopic technologies at Baylor relieved the symptoms and avoided risky surgical treatments at that time.

All agreed that the conference was an excellent recreation of the lively clinical atmosphere associated with the conferences initiated by Dr. Fordtran in the 1970s.

The final piece of the celebration was a lunch in John’s honor, followed by a series of testimonials by his friends, professional colleagues, and former students, led by Dr. Krejs (Figures 11–13). An incomplete list of those who spoke were Drs. John Andersen, Rick Boland, George Bo-Linn, Roger Camp, Dan DeMarco, Mike Emmett, Mark Feldman, Raj Goyal, Kent Hamilton, Greg Hodges, Reed Hogan (Jr. and III), Ed Lee, Dan Norman, Elizabeth Odstrcil, Pete Peterson, Dan Polter, Charlie Richardson, Don Seldin, Larry Schiller, Mary Sleisenger, and Stu Spechler. John commented that among the most important aspects of the gathering was seeing some of his oldest friends—notably Drs. Seldin and Sleisenger—at his side together with all of his prior colleagues and trainees, noting the remarkable number of clinicians who had taken the lessons learned over the years to patients in Dallas and throughout Texas, the United States, and the world.

Finally, Dr. Fordtran closed in his characteristically humble fashion and thanked all those who had traveled from near and far to see him. He asked the group to reassemble in 10 years, on the occasion of his 90th birthday.
A Dallas doctor who spoke truth to power: three perspectives

John S. Fordtran, MD, Robert Prince, MD, and Donald W. Seldin, MD

DR. MICHAEL EMMETT: INTRODUCTION TO THE ELGIN WARE LECTURESHP

This internal medicine grand rounds is the first Elgin W. Ware Lectureship in Medical History (Figure 1). Dr. Elgin Ware, a long-time urologist at Baylor University Medical Center at Dallas and chief of urology from 1986 to 1987, has spent his entire life in Dallas: he graduated from Highland Park High School, Southern Methodist University, and the University of Texas Southwestern Medical School before completing an internship at Baylor Hospital and a urology residency at Parkland Hospital.

After completing his training, Elgin entered the practice of urology and quickly became a leader at the local, state, and national level. He was the president of the Dallas County Medical Society in 1976, has been a delegate of the Texas Medical Association (TMA) for many years, and served as a trustee of the TMA from 1980 to 1990. He was elected president of the American Association of Clinical Urologists in 1978. Beyond the hospital, he served as a member of the Highland Park School Board for 14 years, worked as a volunteer and then director of the Stewpot, a downtown Dallas soup kitchen, and initiated a medical clinic to provide care to the indigent.

Finally, Elgin has a profound interest in medical history. He chaired the History of Medicine Committee of the TMA from 1989 to 2001. In 1995, he established the Elgin W. Ware, Jr., TMA collection of prints and drawings at the Blanton Museum of Art on the University of Texas campus to educate the public about the profound connections between medicine, art, and print making from the renaissance to the present. He also coestablished, with Robert Mickey, the History of Medicine Photography Gallery at the TMA. Now Elgin has generously endowed a history of medicine lectureship at Baylor, which will teach future generations of Baylor physicians about the roots of their profession. We thank him for yet one more important contribution to our profession and our education.

The first Elgin W. Ware Lecture in Medical History is presented by Dr. John S. Fordtran. Dr. Fordtran is an internationally renowned gastroenterologist and physiologist. He also is deeply interested in the history of medicine in Dallas and Texas.

DR. JOHN FORDTRAN: A DALLAS DOCTOR WHO SPOKE TRUTH TO POWER

In the mid 20th century, Jim Crow laws were still in place in the United States. Jim Crow is a nickname for discrimination against African Americans by legal enforcement or traditional sanctions. The purpose of Jim Crow laws was to ensure that blacks and whites would not meet as equals. The laws were sanctioned by the Supreme Court in 1896, which called for “separate but equal” status. The term is derived from a blackface song-and-dance act, called “Jump Jim Crow,” which was first performed in 1828 (1).

Because of Jim Crow laws and sanctions, in 1948, black doctors in Dallas were not allowed to be on the medical staff

From the Division of Gastroenterology, Department of Internal Medicine, Baylor University Medical Center at Dallas (Fordtran); the Department of Obstetrics-Gynecology, St. Paul’s Hospital and The University of Texas Southwestern Medical School at Dallas (emeritus) (Prince); and the Department of Internal Medicine, The University of Texas Southwestern Medical School at Dallas (Seldin).

Presented at internal medicine grand rounds, Baylor University Medical Center at Dallas, March 20, 2012. An earlier version of this talk was presented at the University of Texas Southwestern Medical School Library on March 30, 2011, at an event related to Dallas medical history images from 1890 to 1975.

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of Parkland, St. Paul’s, Baylor, or Methodist Hospitals. As such, they were unable to provide modern hospital treatment for their patients, and they were excluded from hospital-sponsored educational programs. Black students were also excluded from Dallas colleges, Southwestern Medical College, and the Dallas Public Library.

This prohibition against black physicians was facilitated by organized medicine. The American Medical Association (AMA) had no restriction on black physicians, but it recognized only one organization from each state, and in Texas that was the Texas Medical Association (TMA), which was for white physicians only (2, 3). The Dallas County Medical Society (DCMS) followed the TMA policy of white only. Dallas public hospitals, in turn, required membership in the DCMS as a prerequisite to membership on their medical staffs. Thus, no black physicians in Dallas could have privileges or staff membership at public hospitals. It is interesting to note that not all county medical societies in Texas followed this policy. For example, in 1932 a black physician named Dr. C. Austin Whittier was admitted to the Bexar County Medical Society (4, 5).

The National Medical Association existed for black doctors, and there was a Texas chapter of that organization called the Lone Star State Medical, Dental, and Pharmaceutical Association. The state societies had county chapters. In Dallas County, the chapter was named the C. V. Roman County Medical Society, for the pioneering physician from Dallas who was the first from Texas to lead the National Medical Association. Since the AMA recognized only one medical society from each state (e.g., the TMA), the Lone Star Medical Society was not able to affiliate with the AMA (2, 3, 6). The only hospital in Dallas that black doctors could use was the Pinkston Clinic Hospital (7), which had 14 beds (Figure 2). In equipment, diagnostic facilities, and educational activities, it was not nearly equal to the major public hospitals in Dallas. Moreover, it did not have round-the-clock nursing staff, an impediment that markedly restricted surgical treatment.

Peaceful enforcement of the restriction of black doctors from public hospitals in Dallas involved a conspiracy between white hospital administrators and white businessmen. If a black doctor complained about lack of access to a particular hospital, he would receive a call from his bank related to possible problems with the mortgage on his home. The mortgage problem would escalate to the point where the black doctor would withdraw his application for staff membership. On one occasion, a black doctor’s wife was threatened by the mayor’s office by asking her if she was aware of what it could do to her husband’s medical practice (8).

The TMA’s exclusion of African American physicians

As shown in Table 1, from its beginning in 1853 (2) until 1893, the TMA constitution and bylaws had no restriction against African American physicians. This restriction was added in 1893, and it was not stated as “white only” but rather it was a specific exclusion of Negro physicians (9, 10).

The discussion that led to the change in TMA membership requirements was recorded and published in the Transactions of the Texas State Medical Association in 1893 (10, p. 55), and is paraphrased as follows:

- Dr. Charles M. Rosser of Dallas thought that Section No. 3 as read would exclude ladies and admit colored people. He suggested the words “white man or woman” instead of the word “man” in the section.
- Dr. Robert W. Knox of Houston asked what races were to be deemed “white” and what “black.”
- Dr. Rosser said it was well known what “white” meant, and that it was the intention to exclude Negroes.
- Dr. William Keiller of Galveston thought learning made all men akin and that color had nothing to do with it.
- Dr. Albert G. Clopton of Jefferson said that the gentleman had not been long enough in the South to appreciate the prejudice which exists in the minds of the Southern people against anything like social equality between the whites and Negroes. He moved to amend the section to read “Every regularly educated physician except Negroes eligible to membership in this body.”

The amendment was put and carried by almost a unanimous vote.

In 1903, during the reorganization of the TMA (2), the bylaws were changed to specifically state that members must be white (Table 1) (personal communication, Betsy Tyson, April 2012; 11, p. 12).

In 2008, the AMA officially apologized for past inequality against black doctors (12). The apology stated that the AMA’s history of allowing discrimination went back to its very beginnings. Its policies effectively allowed each state to decide whether to let black physicians become members, and nearly all southern state medical societies barred black doctors from joining. It wasn’t until 1968 that the AMA threatened to expel organizations with racially exclusionary policies (12). This apology was noted in the Dallas Morning News on July 10, 2008, and the response suggested that African American physicians still do not enjoy full equality in Dallas medicine (13).
Responses of white doctors to the policy

As far as I could tell, none of the white doctors I knew in the 1940s and 1950s thought the policy was wrong, and I did not think it was wrong. However, if someone had objected to it, he or she would have probably been afraid to speak out in favor of African American doctors; that would have been equivalent to “touching the third rail” (personal communication, David Hitt, January 2011). Support of white-black equality could result in the loss of one’s medical practice with credentials in organized medicine and the US Navy. He often repeated the following aphorism: “On a lot of patients we can not make the correct diagnosis. Some we diagnose we cannot cure. But the correct diagnosis we should make.”

Tate Miller (Figure 3) was a native Texan from a small town with credentials in organized medicine and the US Navy. He was born in 1892 in Corsicana, Texas. He received his medical degree in 1915 from Vanderbilt, following which he was an intern at Parkland Hospital for 1 year. He then became a gastroenterologist by preceptorship with Dr. H. G. Walcott, the first gastroenterologist in Dallas. Dr. Miller practiced gastroenterology from 1916 to 1960, mainly in Dallas’ Medical Arts Building. From 1929 to 1943, he was a professor of clinical medicine at Baylor University College of Medicine while it was in Dallas. In addition, he served in the US Navy in both World War I and World War II (14, 15).

Tate Miller was active in Texas medical associations: he was president of DCMS in 1935 and president of the TMA in 1948. He was a gifted public speaker, known as the “Will Rogers of Texas Medicine,” according to the Dallas Morning News. One of his contemporaries noted that he was “plain famous for his fabulous jokes,” most of which he made up himself. It is also important to note that although Dr. Miller was a specialist, he often championed the cause of the general practitioners (15). “They built the medical profession, brought it to glory, and established in the minds and hearts of the public a place for their calling, above and beyond that held by any other calling” (16). He toured the state in the interest of better rural medical care. He often repeated the following aphorism: “On a lot of patients we can not make the correct diagnosis. Some we diagnose we cannot cure. But there is never a time in the practice of medicine that you can’t be kind to a sick man.”

Table 1. The Texas Medical Association constitution and bylaws: requirements for membership

<table>
<thead>
<tr>
<th>Year</th>
<th>Requirements for membership</th>
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<tbody>
<tr>
<td>1853</td>
<td>The association shall not be limited as to number, but shall be open to every gentleman of the medical profession, residing within the state, under the terms and conditions hereinafter to be exercised.</td>
</tr>
<tr>
<td>1892</td>
<td>Every regularly educated man within the limits of this state, who is a graduate of a regular medical college in good standing, and who adopts and conforms to the Code of Ethics of the American Medical Association, shall be eligible for membership in this body; provided they are members in good standing of their respective county or district medical societies. In all cases where there exists no county medical organization (and the qualifications for membership are perfect in every other respect), this fact shall not be a bar to membership.</td>
</tr>
<tr>
<td>1893</td>
<td>Every regularly educated physician within the limits of this state, who is a graduate of a regular medical college in good standing, and who adopts and conforms to the Code of Ethics of the American Medical Association, shall be eligible for membership in this body, except those of the Negro race.</td>
</tr>
<tr>
<td>1903</td>
<td>Each county society shall judge of the qualification of its own members, but as such societies are the only portals to this Association and to the American Medical Association, every reputable white and legally registered physician who is practicing, or who will agree to practice, non-sectarian medicine shall be entitled to membership.</td>
</tr>
</tbody>
</table>

The legislative body of the TMA is the House of Delegates. In 1949, each county in Texas was entitled to one delegate for each 100 members or fraction thereof (2, p. 234). Since a county with 4 physician members and a county with 99 physician members would each have one delegate, there would have been a predominance of general practitioners from rural areas in the House of Delegates in 1949. These men would have had respect and admiration for Tate Miller.

One of the customs of the TMA was for the retiring president to address the House of Delegates, and in 1949 Dr. Tate Miller spoke to the delegates at the annual TMA meeting (17), which that year was held in San Antonio (2). After brief comments about organizational issues and plans for future meetings, he broached a subject that must have surprised, if not shocked, the delegates.

I have been advised not to discuss this problem, but I feel it is a good thing to do. We have in Texas the Lone Star Medical Association made up of licensed Negro doctors, with whom our connection and cooperation have been poor. I urge the incoming president to form a friendly and able committee to work with . . . the Lone Star Medical Association to allow Negro doctors in Texas to enjoy the benefits of AMA membership, and to provide them with modern hospital facilities for the care of their patients.

The House of Delegates formed a Committee on Negro Medical Facilities; Dr. Tate Miller served as chairman, and other members included Dr. Truman Terrell of Fort Worth and Dr. Merton Minter of San Antonio.
One year later, in 1950, Miller gave a report from the Committee on Negro Medical Facilities to a reference committee (presumably a screening subcommittee of the House of Delegates). The report explained that “good Negro doctors tend not to come to Texas because it means giving up membership in the AMA,” and black doctors were “only asking for the right to improve the health of their people, and in the generosity of our professional conscience we cannot say no.” Miller therefore recommended that the TMA allow county medical societies to accept black doctors. To make this possible, he introduced a resolution to delete the word white from the requirements for membership in the TMA. When this resolution came before the House of Delegates in 1951, it was decided to give the matter further study, delaying a decision until 1952 (2, 18).

In 1952, the resolution to delete the word white from the requirement for TMA membership was tabled, and the House of Delegates instead recommended that the AMA recognize the Lone Star Medical Society in addition to the TMA. (This would allow Negro doctors in Texas to join the AMA, but it would not permit them to be on the medical staff of Texas hospitals.) The House of Delegates pledged cooperation with the Lone Star Medical Society and invited its members to attend scientific sessions of the TMA whenever “hotels and other places would allow” (2, 18).

In 1953, at the next TMA meeting, Miller again addressed the House of Delegates, with greater fervor and determination (6):

Two years ago a resolution to omit the word white as a requisite to membership in the TMA was introduced to you. One year ago after the required waiting period, during a moment of my enforced absence, a delaying and diverting resolution was introduced recommending to the AMA that they give recognition and extend favors to our Lone Star State Medical Association.

The AMA will not recognize two separate associations coming from the same state and the problem is handed back to us.

A motion was made and passed last year to table the recommendation that the word white be deleted, and it died on the table, so if it is desirable to consider it further, the resolution will have to be resubmitted and another year pass before it can be voted on.

Miller pleaded with the delegates: Membership in this organization “is open to all other races and creeds, friends and national enemies alike, whether they be white, yellow, brown or deep mahogany.” Membership “should be open to our American born, friendly, loyal Negro doctors.”

Following these remarks, Miller asked the delegates straight out whether they wanted his committee “to continue its efforts to remove the word white, or whether you prefer that it desist.” Then he said, “If you vote to continue I shall proudly carry that message to the Negroes. If you vote that we discontinue, I shall carry that message, but with shame and deep humiliation.” There was a delay of a year before the question could be considered again.

At the annual meeting in 1954, Dr. C. C. Boehler of El Paso introduced a resolution to strike the word white from membership requirements of the TMA (19). Tate Miller argued again in favor of the resolution, this time invoking Texas pride, Hippocrates, and the underlying rationale of organized medicine (3, 19):

In earlier years, I had an ambition to be present when Texas was the first to take a broadminded, realistic attitude [regarding discrimination against black doctors]. . . . My ambition now is to keep Texas from being the very last. There is no race or color exception in our oath of Hippocrates. It boils down to two simple questions. If organized medicine is a good thing that helps doctors take better care of sick folks, how can we in decency or charity withhold its benefits from other doctors? If organized medicine is not a good thing, why are we here?

After listening to Tate Miller, the delegates agreed that the committee should continue its work, and it concurred with the intent of the resolution. Constitutional changes required a layover of 1 year before final action, and the delegates voted in April 1955 by secret ballot—6 years after Miller originally raised the issue. Of the 154 members casting ballots, 102 voted favorably (76%) to delete white from the TMA’s constitution and bylaws (3). It is worth noting that the delegates decided to allow African American doctors to join the TMA even though there was tension between the TMA and the National Medical Association related to their opposite views on the need for the proposed forerunners of Medicaid and Medicare (2, 18).

The board of directors of the DCMS met on May 3, 1955, in the Medical Arts Building. It was announced that the bylaws of the TMA had been amended by eliminating the word white from membership requirements. The board of directors authorized a resolution to be presented to members of the DCMS, recommending and proposing a change in the bylaws of the DCMS to conform to the amended bylaws of the state association. On May 10, 1955, the DCMS met in regular session at Baylor Hospital. The following resolution was read by Dr. Glenn Carlson:

WHEREAS, the Constitution and By-Laws of the Texas Medical Association have been amended by eliminating the word white as a qualification for membership; and

WHEREAS, the Delegates from the Dallas County Medical Society to the Texas Medical Association were instructed to vote for the amendment which eliminated the word white from the qualifications for membership;

THEREFORE BE IT RESOLVED, that Chapter 1, Section 1, of the By-Laws of the Dallas Medical Society be amended by eliminating the word white from the following phrases: “every reputable and legally qualified white physician holding the degree of Doctor of Medicine”, and “except that white medical officers of the federal government.”

The DCMS met again in regular session on June 14, 1955, at Methodist Hospital. Dr. Carlson presented the above resolution again. On motion properly seconded, the amendment to the bylaws was unanimously adopted by the members present. These actions are documented in records maintained by the
DCMS. It is gratifying to note in the second clause of the resolution that in 1954 the DCMS had instructed its delegates to the TMA to vote in favor of removing the word white from the TMA constitution.

As a result of these actions by white doctors in Dallas and Texas, black doctors were eligible to join the DCMS, paving the way for their access to Dallas hospitals. Table 2 shows some of the other major national events that occurred between 1947 and 1964 in an effort to reverse segregation based on race.

**St. Paul’s Hospital**

From its founding in 1898, St. Paul’s Hospital (Figure 4) had three commitments: 1) to care for the sick and indigent of all classes, races, and creeds without prejudice; 2) to open its doors to all physicians; and 3) to maintain a “public medical staff” for the general public (20). In line with these commitments, on June 25, 1954—about 2 months after the tentative agreement of the TMA House of Delegates to remove the word white, but before the final vote and before the change in the DCMS bylaws—the *Dallas Morning News* published an article, “Negro MD’s to Practice in St. Paul’s” (Figure 5). The text of the article included the following statements, which are paraphrased here (21):

Saint Paul’s is not extending staff membership to the Negro doctors, but rather hospital privileges. But they will have both the privileges and the obligations of staff members. A check of Parkland, Baylor and Methodist indicated that privileges for Negro doctors had not come up for consideration.

Sister Mary Helen Neuhoff (Figure 7), who had been the CEO of St. Paul’s Hospital for only 1 year (22), made these decisions. Previous colleagues and family members described her to me as a talented administrator, strong-willed, perceptive, and with a majestic presence. She was reserved, formal, friendly, and a good listener. With her “hands-on” approach to patient care, she created a wonderful environment for practice and was concerned with the welfare of the underprivileged. She was gently persuasive and an “up-front person.” She left St. Paul’s Hospital in 1961 and died in 1992 (23).

Dr. John Goforth (1897–1985) was Sister Mary Helen’s confidant (Figure 7). A native of Beeville, a small town in South Texas not far from Stockdale, he went to Johns Hopkins Medical School and was a pathologist at St. Paul’s. He also had an office and a pathology laboratory in the Medical Arts Building, where he would have known Tate Miller. Like Miller, he served as president of DCMS. He was president of the medical staff at St. Paul’s from 1953 to 1955. He was prominent locally and nationally as a pathologist (24, 25).

As far as I can tell, Sister Mary Helen left no record of how or why she made the decision to allow black doctors to practice at St. Paul’s Hospital in 1954. The announcement of this event by the *Dallas Morning News* (21) was based in large part on an
interview with Sister Mary Helen, and it provides the only information I could find about the decision. Some of that report is paraphrased as follows:

The decision to extend hospital privileges to Negro MD's recently was approved unanimously by the hospital's medical staff. The details were worked out late Wednesday at a meeting of Sister Mary Helen, Dr. John Goforth (medical staff chief), and the five Negro doctors (21).

No information is available on any background work that may have been needed to gain unanimous approval of the medical staff, what role was played by the Catholic Church or trustees of St. Paul's Hospital, or whether or not Sister Mary Helen knew or had talked to Tate Miller.

What did all this do for black doctors in Dallas?

First, based on the efforts of Tate Miller, Sister Mary Helen, John Goforth, and St. Paul's Hospital, black doctors received medical staff privileges at St. Paul's Hospital in 1954, and in 1956 they received full medical staff membership at St. Paul's (26). Second, black doctors were able to apply for and receive membership in the DCMS, the TMA, and the AMA. As a result of these two actions, black doctors were able to take much better care of their patients and to be part of continuing education programs at a major Dallas hospital. All of this occurred 8 to 10 years before passage of the Civil Rights Act in 1964. Dr. Emmett J. Conrad, an African American surgeon who came to Dallas in 1955, said that "Saint Paul opened its doors before the hospitals in Chicago, New York, San Francisco, and all the so-called bastions of liberty" (8). He also said, "I chose Dallas because it was the first place that gave me an opportunity to practice in a first-class hospital."

It should be noted that there were important limitations to what was provided to African American doctors through these efforts. First, St. Paul's Hospital remained segregated; black patients were isolated in one section of the hospital, and there were still separate water fountains, separate dining rooms, and separate waiting rooms. Second, the DCMS directory contained an asterisk by the names of black physicians so that their wives could be easily and automatically excluded from activities of the Wives' Auxiliary. Third, the black doctors were not protected from racial slurs from a minority of white doctors on the staff of St. Paul's Hospital (27). Finally, the medical staff and administration of other Dallas hospitals did not follow suit. In 1956, a Baylor Hospital source told the Dallas Morning News that no black physician had made application for membership. "But if they do apply, their applications will be handled in the same manner as those for white physicians" (26). At Baylor, an African American physician was not given privileges or staff membership until 1968. Methodist Hospital first gave privileges to a black doctor in 1962 (personal communication, Charles Tandy, April 2012). I was unable to find the date at which Parkland Hospital first gave staff membership to black doctors.

Motivations of St. Paul's and other hospitals

It is not entirely clear what made St. Paul's Hospital so progressive in providing black doctors access to its facilities.
There were personnel differences: different administrators and different medical staffs. Beyond that, the hospitals had different missions. As noted, St. Paul’s Hospital explicitly had a mission of serving “all races” (20). In addition, St. Paul’s had primarily general practitioners in solo practice; Baylor had mostly specialists and many group practices. There were obvious differences in religious affiliations.

Baylor’s delay in granting staff membership to black doctors may have been influenced by its partial moratorium on granting staff membership to all new applicants in the mid 1950s. Veterans from World War II were able to attend medical school in the late 1940s using support from the GI Bill, and this resulted in an influx of applicants for medical staff privileges at all public hospitals. Moreover, Truett Hospital at Baylor opened in 1950. It was the only air-conditioned hospital in the city, and it had the image of a “specialty” hospital. These features resulted in a further increase in applications for staff membership at Baylor. In 1954, even doctors on the teaching service could not get their patients into the hospital. The pressure to do something was enormous, and the two “solutions” were to build Hoblitzelle Hospital (which would take time) and to decrease demand by putting a moratorium on the addition of new physicians to the medical staff. In response to the desire of some prominent Baylor physicians to add partners, the moratorium was relaxed in 1955. New partners of attending physicians could join the staff in some departments (but not others). The partial moratorium was variably enforced after Hoblitzelle Hospital opened in 1959. In internal medicine, the moratorium was apparently still in force in 1966, when Dr. Dan Polter applied for privileges but was rejected (28).

It seems likely that Baylor’s policy of accepting new staff members only if they were to be partners of existing medical staff was one of the reasons that black doctors were not accepted prior to 1968. There is no way to know when black doctors would have been accepted at Baylor had this partial moratorium not existed. It is clear that St. Paul’s Hospital gave privileges to black doctors in 1954 despite “limited hospital beds,” indicating that it was also suffering from a hospital bed shortage when it accepted African American doctors. I do not know if shortage of beds delayed Methodist Hospital from welcoming African American doctors.

The bed shortage in Dallas in the 1950s may have been a double-edged sword in regard to allowing black doctors to use public hospitals. It could be used as a reason not to admit any new doctors to a hospital’s medical staff. But if a hospital administrator decided to give privileges to black doctors, disgruntled white doctors would not have the leverage of easily moving their practice to other hospitals in the city.

Some elements of Tate Miller’s unlikely success

Several factors contributed to Miller’s success. First, it took insight, empathy, and sensitivity for Miller to recognize that it was wrong to exclude black doctors from the medical staff of public hospitals; such exclusion had been the status quo for his entire life. Second, he banished fear. What he did was dangerous: he could have been physically hurt, and his family could have been ostracized. Third, he had credentials that made the delegates receptive to him—he was from a small Texas town and was in the navy—and he worked within the system of organized medicine. Fourth, general practitioners all across the state of Texas were indebted to Tate Miller for his visits, where he had spoken to them about the glory and the nobleness of the general practitioner in particular, and rural medicine in general. He was willing to ask for their help when he needed it.

Fifth, and probably most importantly, he argued mainly on the basis of quality medical care of African American people, rather than on general moral principles of right and wrong. He emphasized that black patients were not receiving quality medical care because their doctors did not have admitting privileges at public hospitals. He pointed out that most white doctors did not want black patients in their offices. Black doctors were therefore needed to take care of black patients, and white physicians should not allow a large segment of the city’s population to receive care from doctors who were excluded from the postgraduate benefits of organized medicine. Tate Miller therefore approached the issue based on undeniable medical concerns. Had he been a moral crusader, he probably would have gotten nowhere.

As was mentioned previously, Tate Miller told the TMA delegates in 1953 that he would carry their decision to the Negro doctors, but he never said which Negro doctors he was in contact with. Although it might be reasonable to assume he was referring to black doctors in Dallas, I found no evidence that that was the case. Perhaps he was corresponding with Dr. C. Austin Whittier, from San Antonio, who was president of the National Medical Association from 1948 to 1949 (19, 29, 30), the same year that Miller was president of the TMA. Articles in the National Medical Journal indicate that these two men were communicating with each other, and it would be just like Tate Miller to work through official channels of organized medicine, president to president.

As far as I can tell, after the TMA removed its restrictions on African American physicians, Tate Miller never again spoke about this issue. The underlying motives for his actions are unknown. However, a recent book by Dara Horn titled The Rescuer discusses individuals who step forward and take risks to help others (31). The book presented this story:

A guy in New York fell onto the subway tracks, and another man jumped down to rescue him. When he was asked why he did it, he said, “What else could I do? There was a train coming.” For most people, that would be a reason not to do it.

Rescuers actually don’t hesitate or agonize. They immediately recognize what the situation calls for. When they say that it is no big deal, we think they are being modest. They aren’t. They genuinely experienced it as no big deal.

I believe that Tate Miller considered what he did as no big deal. I think he perceived a serious problem, realized he was in a unique position to help, and was aware but unafraid of the substantial risks to his well-being. I think one of the
underlying forces causing him to act was his belief that all
good doctors were brothers and that this transcended any
differences between them.

While he didn’t consider what he did to be a big deal, it is
important to emphasize that no other white doctors in Dal-
las stood up. I certainly didn’t. Moreover, I think what Tate
Miller accomplished was monumental. He was a southern
white doctor who convinced an organization of southern
white doctors to dismantle a barrier that had long prevented
black physicians from using public hospitals to take care of
their patients. He did this 10 years before desegregation was
mandated by the federal government. I also think that the
lessons he taught 60 years ago are still important, because it
is very easy for doctors to close their eyes to conspiracies and
injustices in medicine as it is practiced and delivered today;

in doing so, they become part of the problem. I view Tate
Miller as brave, courageous, politically skillful, and highly
relevant to medicine today. This Dallas doctor spoke truth
to power, and to me he is a hero.

Other perspectives

Even though what Tate Miller did is well documented in
multiple primary sources and has been recounted on recent oc-
casions, during the last 2 years I could not find a single doctor
(black or white) who knew what he had done. This includes
many white doctors who were teaching and/or practicing
medicine or were in residency training in the late 1940s and
1950s and who knew and remember Tate Miller. Moreover,
when African Americans reminisce about how black doctors
got hospital privileges early on in Dallas, they rightly discuss
the important role played by St. Paul’s Hospital, but they
give little or no credit to Tate Miller (8, 27). This made me
pause and reconsider the exalted position into which I have
attempted to place him. Maybe what he did is of little sig-
nificance compared to the shame, humiliation, and repression
that were forced upon black doctors by white doctors for such a long
period of time. Possibly only black doctors who
endured such humiliation and disappoint-
ment, yet remained in Dallas to care for their
people, deserved to be called heroes in this
story. I therefore de-
cided to ask two other
physicians who were
in Dallas in the 1950s
to evaluate the signifi-
cance of these events.

The first is Dr. Rob-
ert Prince, author of A
History of Dallas from a
Different Perspective (7),

the front cover of which is shown in Figure 8. His great-grand-
parents were slaves in the Bear Creek area of Irving, Texas. He
was born at Pinkston Clinic Hospital in 1930, graduated from
Booker T. Washington High School, and received a bachelor’s
degree in chemistry from Wiley College in Marshall, Texas. He
then attended the University of California at Berkeley, where
he studied biochemistry. He served in the Korean War, after
which he attended Texas Southern University and was awarded
a master’s degree in organic chemistry. He then attended Meh-
arry Medical College in Nashville, where he was a member of
Alpha Omega Alpha. After receiving his medical degree from
Meharry, he completed an internship and residency in obstetrics
and gynecology at Hubbard Hospital in Nashville. He became
certified by the American Board of Obstetrics and Gynecol-
ogy, and he practiced obstetrics and gynecology in Dallas from

The second is Dr. Donald Seldin, who was born on October
24, 1920, in Coney Island. He grew up in Coney Island and
Brooklyn and attended New York University and Yale University
School of Medicine. He served in the US Army, during which in
1946 he provided expert medical testimony at the trial of Nazi
physicians at Dachau. In 1948 he returned to Yale as a member
of the Department of Medicine. In 1952 he became chairman of
the Department of Internal Medicine at Southwestern Medical
School in Dallas, at the age of 32. At Southwestern, he built
one of the greatest, if not the greatest, departments of internal
medicine in the United States. He was its chairman for 35 years
(32, 33). He is the most insightful person I have ever known
about human behavior.

DR. ROBERT PRINCE: PERSPECTIVE OF AN AFRICAN
AMERICAN PHYSICIAN

I considered Dr. Fordtran’s presentation both informative
and nostalgic. There is very little that I could add to this superb
work. I now will give my perspective of how these historic events
affected me and other African American doctors.

Dr. Tate Miller, Sister Mary Helen, and Dr. John Goforth
were courageous visionaries. Their decision to allow five African
American doctors to join the staff at St. Paul’s Hospital was
colossal.

At the turn of the 20th century, a few talented and well-trained
African American physicians came to Dallas; however, because of
the lack of hospital privileges and opportunities for continuing
medical education, most chose not to remain. Drs. Benjamin
Bluitt and C. V. Roman, the first African American physicians to
practice in Dallas, moved away after a few years of distinguished
service. They had made great civic contributions and improved
the standard of health care for the black community.

Dr. Bluitt built the first hospital for African Americans on
Commerce Street; my mother was born there in 1908. Dr. Bluitt
later moved to Chicago, and Dr. Roman returned to Nashville.
This loss of health care professionals created a massive void in
the isolated African American community. These pioneer physi-
cians would eventually be replaced during the early years of the
20th century. It would take another 50 years before health care
access changed for African American physicians.
The picture of Pinkston Clinic generated fond memories; I was born there. Dr. Pinkston was my family doctor, and he watched me receive my medical degree in Nashville. Drs. Shelton and Conrad invited me to join their multispecialty practice in South Dallas. I practiced with them for 7 years.

As I walked into this building today, an air of nostalgia enveloped my being. In a nanosecond, I was conveyed 70 years into another moment in time; the year was 1942. I remember seeing the Baylor medical students walking briskly across the campus. Their uniforms and their complexions were white. While I worked as a paperboy on the northeast corner of Gaston Avenue and Hall Street, I sat upon my bicycle and vowed that one day I would go to Baylor. My father encouraged me to pursue my dream. He pragmatically reminded me that Baylor was for whites only. My dad advised me to strive for academic excellence and prepare myself for a medical career. Then hopefully, the laws that prevented me from attending Texas’ colleges and universities would be rescinded and the door to academic freedom would open. Maybe one day I could use the public library. He often advised, “Prepare yourself for that day.” That day never came for me; I was 38 years old when Baylor integrated, in 1968.

Social justice moves at glacial speed. The wisdom of the majority at that time was that African Americans were not prepared to enter into the mainstream of the American waterway. To me, this ideology was about as cogent as a law saying that you could not go near the water until you learned to swim.

I completed medical school in 1960 and my residency in 1964. Because of the courage and resolute moral integrity of Dr. Tate Miller and others, I was allowed the join the Dallas County Medical Society and was admitted to the staffs of St. Paul's in 1964, Parkland in 1965, and Presbyterian in 1970.

The word about health care access quickly spread, and then well-trained and talented minorities began to come to Dallas. Today, we see access in all divisions of health care. The Goals for Dallas must include programs that continue to promote health care access at all levels; it is the right thing to do. Dallas has prospered greatly since the Texas Medical Association removed the white-only clause.

I came home to practice, to the land of my forefathers, who came here when Dallas was a spot on the prairie. Now, I am finally here at Baylor. This 70-year odyssey was arduous, but I am here now.

DR. DONALD SELDIN: REPAIRING BROKEN WINDOWS

Some of you may have seen the obituaries that were recently published in the New York Times and the Dallas Morning News announcing the death of James Q. Wilson, one of the great sociologists of the United States. Dr. Wilson was interested in many aspects of social behavior and focused particularly on issues of crime.

In the 1960s, the country was beset with a major wave of serious criminal acts. Murder, rape, and aggressive thefts were widespread. Police forces were concentrated on identifying and imprisoning the many perpetrators. At this time, a modest magazine article by James Q. Wilson appeared that changed the focus of police activities. Wilson entitled his article “Broken Windows.” The emphasis was on the disarray of various communities, which was the seedbed for the growth of criminal activity. He emphasized that it was of vital importance for police and other community leaders to focus on the chaos in small communities so that the grounds for the growth of major criminal acts would be removed.

In addition to emphasizing crusades against major criminal organizations (a necessary activity, to be sure), Wilson called attention to the importance of comparatively small public disturbances. He emphasized that a policeman assigned to a local community should remain there, become acquainted with the citizenry, and pay attention to minor transgressions. If a window was broken and left unrepaired, it could function as a stimulus to destroy other windows. Pretty soon, minor acts of disobedience would invade the community. Garbage would be littered everywhere, gangs would congregate, and street fights and drugs would dominate the scene. Wilson argued that correcting local public disarray would have the effect of restoring a sense of public order and communicate solidarity. Instead of focusing exclusively on top-down policies meant to correct major social disruptions, Wilson advocated a bottom-up approach in which relatively small violations of the public order were promptly corrected so that a sense of community could prevail.

Police organizations throughout the country were impacted by Wilson’s broken window emphasis and assigned police officers to specific neighborhoods to ensure a composed and civil atmosphere. The striking fall in major crimes that followed the adoption of this bottom-up approach was undoubtedly in part attributable to Wilson’s recommendations. The emphasis on broken windows bore great social fruit.

In Texas during the 1940s and 1950s, black physicians were prevented from pursuing patient care by various discriminating regulations. Access to patient beds was forbidden, and participation in white medical societies was prohibited. As a consequence, black physicians could not provide adequate care for their patients. Ultimately, in the 1960s, the civil rights movement approached the problem in a top-down manner.

In Dallas, Dr. Fordtran has pointed out that Drs. Tate Miller and John Goforth worked on behalf of black physicians on the basis of quality medical care and support of fellow physicians, rather than on general moral principles of right and wrong. In that respect, they were behaving in accordance with Wilson’s view of the critical importance of bottom-up activities. By correcting transgressions in local hospitals and local medical societies, the hostility toward what was perceived as a threat to a privileged medical community was markedly reduced.

Drs. Miller and Goforth had nothing personal to gain from their initiatives. Indeed, they were assuming a position that ran contrary to that of the medical establishment. To be sure, there were individuals who felt that any gesture in the direction of black assimilation was intolerable, so physicians like Drs. Miller and Goforth could be the object of personal attacks. However, by focusing on specific medical matters, such as access to beds and access to diagnostic and therapeutic procedures,
which were at the heart of the Hippocratic Oath, Drs. Miller and Goforth were able to persuade white colleagues of the justice of their approach without threatening deep-held and controversial social views. Through their actions, transgressions were partially corrected and hostility was gradually softened. White physicians were reassured that the extension of medical privileges to black physicians could only result in better medical care, warmer collegiality, and, obliquely, an affirmation of basic American rights. In a sense, Drs. Miller and Goforth, using the bottom-up method, had repaired the broken windows that had fractured good medical care in Dallas. When the US government, by a top-down approach, banned racial discrimination in all public places in 1964, it could look to a body of public support that stemmed from local initiatives of doctors like Miller and Goforth. The net effect was correction of severe medical injustice.

ACKNOWLEDGMENTS

Dr. P. L. Nixon from San Antonio gave a copy of his book on TMA history (see reference 2) to me and my wife Jewel as a wedding present in 1953. It was from this book that I first learned about Tate Miller’s work on behalf of African American doctors. I used this book extensively in preparing this talk and paper.

Drs. Robert Prince and Donald Seldin worked very hard to put these events in perspective, and their comments were mainly responsible for the warm reception and applause that were received when this story was told at Baylor grand rounds.

Thanks to John Fullinwider for inviting me to speak on any topic related to Dallas medical history at the UT Southwestern Medical Center Library in 2011. Many thanks also to all who allowed me to interview them: Herb Bailey, William (Doug) Crawford, Mike Darrouzet, Perry Gross, Arvel Haley, David Hitt, Pat Jenevine, John Kohler, William Larkin, Peter Louis, Mike Meierhofer, Charles Mitchell, Henry Neuhoff, Maurice C. Perry, Robert Prince, Arthur Shannon, Charles Tandy, Elgin Ware, and Myron Watkins. Dr. Peter Louis was especially helpful by arranging for me to meet with several African American doctors in his private office. From that meeting I was introduced to others whom I met in person or talked to by phone.

Betsy Tyson and Claire Duncan were wonderful hosts when I visited TMA offices in Austin and reviewed their exhibit, “Courage and Determination—A Portrait of Pioneering African-American Physicians in Texas.” They also helped me to review TMA records, and they conducted original research to answer several questions that arose during preparation of this talk and paper. Linda Doyle at the DCMS provided access to records of DCMS meetings and files on Tate Miller and John Goforth. Her assistance and friendly welcome are much appreciated.

Jason Cole searched records at the Dallas Public Library and by computer, and he also organized the bibliography. Martha Savage prepared many copies of the manuscript. Cindy Orticio worked diligently to help me convert the talk into a paper, and her editorial skills are much appreciated.

Betsy Tyson suggested the phrase for the title, “speaking truth to power,” and also provided two references on the origin of the phrase (34, 35).

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**Additional sources**

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Dr. Paul Grayburn (Figure 1) was born in Cincinnati, Ohio, on July 24, 1954. He graduated from Texas A&M University with a bachelor's degree in chemistry in 1976 and The University of Texas (UT) School of Medicine in Galveston, Texas, in 1981. After an internship and residency training in internal medicine at St. Paul Hospital (a UT Southwestern affiliate) in Dallas, he completed his cardiology and interventional cardiology training at the University of Kentucky Medical Center. He worked for 1 year as an instructor in medicine at the University of Kentucky Medical Center before returning to Dallas in 1988, where he practiced interventional cardiology and served as chief of cardiology at the Veterans Affairs Medical Center and was director of the echocardiography laboratories for UT Southwestern Medical Center. In September 2002, he came to Baylor University Medical Center at Dallas (BUMC) as the medical director of cardiology research.

Dr. Grayburn has coauthored >270 articles in medical journals and is author/editor of 9 book chapters. He has participated in several multicenter trials that have changed our understanding and management of cardiovascular diseases. Dr. Grayburn is an expert in echocardiography and valvular heart diseases. He has been a visiting professor and lecturer at numerous institutions in the United States and abroad. Dr. Grayburn is the epitome of what an academic physician should be: an outstanding clinician, teacher, researcher, and mentor.

Mina Benjamin, MD (hereafter, Benjamin): Today is March 21, 2012, and I am seated with Dr. Paul Grayburn at his office in the Baylor Heart and Vascular Hospital. Dr. Grayburn, thank you for the opportunity to have this conversation with you.

Paul Grayburn, MD (hereafter, Grayburn): My pleasure.

Benjamin: Dr. Grayburn, let me start with your move to BUMC in 2002. What prompted your move from UT Southwestern to BUMC?

Grayburn: There were many factors that influenced my decision. I had worked closely with Dr. Bill Roberts since 1997, when he appointed me associate editor of The American Journal of Cardiology. He asked me several times if I might be interested in coming to BUMC. He arranged meetings with Mike Emmert and Kevin Wheelan, and I eventually decided to make the move. A major consideration was the enormous patient volume in cardiology, which is a great asset to conducting clinical trials. Another factor was the high quality of the cardiologists here, many of whom I had known when they were residents or fellows at UT Southwestern. Finally, the Paul Thomas Chair in Cardiology Research and Education enabled me to have permanent funding for my research.

Benjamin: How has cardiovascular research grown since you came to BUMC?

Grayburn: It has grown exponentially in terms of the number of publications and the number and types of studies that have been done. This increase has been a team effort and not just the result of my coming to BUMC. Dr. Roberts had always done research here and continues to be productive. A lot of other people have played a big role. Dr. Cara East directs the Soltero Cardiovascular Research Institute, and she has done a fantastic job of bringing major drug and device trials to BUMC. All of our electrophysiology physicians are involved in major trials. These include studies of the left atrial appendage closure device, catheter ablation of atrial fibrillation, and resynchronization and defibrillator trials. There are also several important trials in the cardiac catheterization laboratory. Currently, Drs. Robert Stoler and Robert “Rick” Hebeler are doing percutaneous aortic valve replacement with the Medtronic core valve device. Dr. James Choi is doing an important renal sympathectomy trial, among others. Drs. Baron Hamman, Cara East, and Harold Urschel Jr. are doing stem cell work. The Cardiovascular Research Review Committee of the Baylor Foundation allocates research funding for various projects initiated by local investigators, including faculty, staff, fellows, nursing, and cardiac rehabilitation.

Benjamin: What made you choose to pursue your career in academia?

Grayburn: I believe that medicine is an academic pursuit because whether you are in pure private practice or in an...
academic setting, the field of medicine is always advancing. It is always necessary to keep abreast of modern advances and current standards of care. It is easier for me to do that when I am on the front lines actually participating in the cutting edge of new knowledge and new developments.

Benjamin: When did you publish your first paper?

Benjamin: What was it about?
Grayburn: It examined the improved accuracy of Doppler detection of aortic regurgitation compared to auscultation.

Benjamin: What was the first clinical trial you conducted?
Grayburn: As a cardiology fellow, I was involved in the early Thrombolysis in Myocardial Infarction (TIMI) trials as well as the early beta-blocker trials for acute myocardial infarction. My role was to enroll patients and do the cardiac catheterizations, but I was not listed as an author on any of the articles, since I was a mere fellow. Nevertheless, the experience was great and it stimulated my interest in clinical research.

Benjamin: You have done much work in contrast-enhanced echocardiography. What is the rationale behind using contrast material with echocardiography?
Grayburn: Many patients do not image well on echocardiography. Reasons are many and include obesity, chronic lung disease, or chest wall deformities. Often, a patient in the intensive care unit on a ventilator cannot be rolled over into the left lateral decubitus position, which is optimal for getting good images. Using a contrast agent gives us the ability to obtain better image quality and improve the ability to make the correct diagnosis.

Benjamin: What contrast material is used?
Grayburn: Currently, two ultrasound contrast agents are approved by the US Food and Drug Administration (FDA). Both of them are composed of perfluoropropane gas surrounded by a shell. Optison has a shell made of human serum albumin. Definity has a phospholipid shell.

Benjamin: How long does the procedure take? And how is that compared to conventional echocardiography?
Grayburn: Using a contrast agent may actually shorten the procedure because it is easier and faster for the sonographer to acquire images when they are of high quality. However, contrast injection requires an intravenous line. If the patient already has intravenous access, it is simple to inject a contrast agent. In an outpatient setting, one might have to obtain intravenous access first, and that may slow you down a few minutes.

Benjamin: Is there a difference in interobserver variability between contrast-enhanced echocardiography and conventional echo?
Grayburn: It has been shown that contrast improves observer variability and diagnostic accuracy for measuring left ventricular volume and ejection fraction by echocardiography.

Benjamin: How much more accurate is contrast-enhanced echocardiography than conventional echocardiography for measuring the left ventricular ejection fraction?
Grayburn: There are a lot of studies on this topic. To briefly summarize them, the 95% confidence intervals for left ventricular ejection fraction with an unenhanced echocardiogram are ±20%. That means that if the ejection fraction is 50%, you can be 95% confident that it is between 30% and 70%. The confidence intervals are ±10% after giving a contrast agent with standard two-dimensional echocardiography. The combination of three-dimensional echocardiography and contrast reduces the confidence intervals to ±5%.

Benjamin: What are the current recommendations of the American Society of Echocardiography regarding contrast-enhanced echocardiography?
Grayburn: Currently, both the American Society of Echocardiography and the Intersocietal Commission of Accreditation of Echocardiography Laboratories recommend that contrast be used in all patients in whom a diagnosis is unclear or when at least two contiguous endocardial borders cannot be clearly seen. It is estimated that 10% to 20% of transthoracic echocardiograms and up to 50% of stress echocardiograms should be done with contrast. Some centers use contrast routinely in every stress echocardiogram.

Benjamin: On October 10, 2007, the FDA announced a new black box warning for the perfluorocarbon-containing ultrasound contrast agents, contraindicating the use in patients with acute coronary syndrome, acute myocardial infarction, and worsening of clinically unstable heart failure. They recommended 30 minutes of recording vital signs in those patients undergoing transesophageal echocardiography (TEE). On what basis did the FDA post this warning? You called this warning "unjustified" in one of your published papers. On what basis did you formulate your conclusion?
Grayburn: The FDA based that warning on four reported deaths that occurred within 30 minutes of administration of the contrast agent Definity. However, careful independent review of the cases revealed that the deaths were attributed to the underlying disease process, and not to the contrast agent. So, the FDA modified the black box warning and removed the contraindications. The FDA convened a subsequent cardiology advisory panel, which recommended in a close vote that the black box warning be removed altogether.

Benjamin: Contrast-enhanced echocardiography has also been used to evaluate myocardial perfusion. What is the principle behind myocardial contrast echocardiography (MCE)?
Grayburn: Because the microbubbles are roughly half the size of a red blood cell, they pass freely through the coronary microcirculation, and this can be seen on ultrasound. So ultrasound contrast agents give you the ability to image myocardial perfusion without the risk of radiation and without the expense associated with nuclear scans.

Benjamin: Does MCE have an advantage over dobutamine stress echocardiography?
Grayburn: A contrast agent can certainly improve diagnostic accuracy and allow visualization of wall motion and perfusion simultaneously. That is a potential advantage over dobutamine stress echocardiography, which only evaluates wall motion. This also offers an advantage over nuclear testing in that the axial resolution of ultrasound is about 0.7 mm, which is 10 times better resolution than a nuclear scan. The improved resolution allows visualization of subendocardial perfusion defects, which cannot be identified by nuclear perfusion imaging.
**Benjamin:** What is the accuracy of MCE compared to coronary angiography in determining myocardial perfusion?

**Grayburn:** In 2006, Dijkmans et al published a metaanalysis of eight studies in which myocardial perfusion was performed by both MCE and nuclear techniques in patients undergoing coronary angiography. The diagnostic accuracy of MCE was statistically significantly better than that of nuclear imaging for detecting coronary artery disease.

**Benjamin:** What are the limitations of MCE?

**Grayburn:** The main limitation is that MCE requires good-quality echocardiographic images. Another practical limitation is that the contrast agents are not FDA approved for perfusion imaging, nor is there an MCE reimbursement code from the Center for Medicare and Medicaid Services. So, currently MCE is billed as an ordinary stress echocardiogram.

**Benjamin:** You have also done much work on the ultrasound-targeted microbubble destruction technique (UTMD). What is the rationale behind this technique?

**Grayburn:** The basis for UTMD is that ultrasound contrast agents undergo rapid inertial cavitation when exposed to high-energy ultrasound. The rapid collapse of the microbubbles, also called “bubble destruction,” can allow entry of genes, proteins, or drugs into surrounding cells by a process known as sonoporation. So my colleagues and I at UT Southwestern hypothesized that you could load microbubbles with genes or drugs, circulate them throughout the body, and then target delivery of those drugs or genes to a specific organ or tissue by ultrasound. This has now blossomed into a field for which more than 100 papers have been published.

**Benjamin:** What are the microbubbles made of?

**Grayburn:** The microbubbles have a shell made of phospholipids, albumin, or various polymers encapsulating a gas bubble of air, perfluorocarbon, or sulfur hexafluoride. The shells can be modified to carry genes, drugs, small interfering RNA (siRNA), or other molecular cargo, and there are different chemical methods for doing so.

**Benjamin:** How long do the microbubbles stay in the circulation?

**Grayburn:** In 15 minutes all the gas in the microbubbles is exhaled in expired air.

**Benjamin:** Are there side effects from destruction of the microbubbles by ultrasound waves?

**Grayburn:** Yes and no. In vitro experiments and animal experiments reveal dose-dependent side effects due to the fact that microbubble destruction creates very high local temperatures leading to damage to the cell membrane. This is both a blessing and a curse. By opening pores in the cell membrane, you can allow genes or drugs to enter the cells. But obviously if you do that too extensively, you could cause permanent damage to the cells. So like most drugs, there is a therapeutic window. If you give too high an ultrasound energy and too many bubbles, you can actually cause cell damage. If you don’t give enough, you don’t get the therapeutic benefits. The good news is that there is a safe and therapeutic window.

**Benjamin:** Are there other ultrasound parameters associated with side effects?

**Grayburn:** The two main variables are acoustic power and transmission frequency. Lower frequencies are associated with more effective microbubble destruction. Higher acoustic power is also more effective.

**Benjamin:** What kinds of substances have been delivered by UTMD?

**Grayburn:** In 2000, we published the first report of UTMD to deliver adenoviral gene vectors. Since that time, we and other investigators have delivered adenoviral gene therapy, plasmid gene therapy, drugs, proteins, antisense oligonucleotides, peptides, and siRNAs.

**Benjamin:** Are there any potential direct therapeutic effects of the technique without delivering a gene or drug?

**Grayburn:** Yes. When the microbubbles undergo inertial cavitation, the energy that is generated can actually permeabilize cell membranes. This has been shown to allow entry of chemotherapy into tumors in animal models. You can also use microbubbles in conjunction with high-intensity focused ultrasound to achieve cell death in certain soft-tissue tumors like prostate cancer and uterine fibroids.

**Benjamin:** Have the optimal parameters for delivery of these microbubbles to the target tissue been figured out yet?

**Grayburn:** No. In fact, I am currently working with ultrasound engineers at GE Global Research to try to develop instrumentation specifically designed for UTMD.

**Benjamin:** How useful is targeting the genes or drugs to specific desired locations in the human body?

**Grayburn:** It is very important because it potentially allows avoidance of the systemic side effects of gene therapy or chemotherapy.

**Benjamin:** Do all tissues show similar uptake rates with the technique?

**Grayburn:** No. There are two primary reasons for differing tissue sensitivity. One is tissue vascularity. Since the microbubbles are carried within the vascular space, hypovascular tissues or organs are difficult to target. Second, because ultrasound is needed to destroy the microbubbles, target tissues must be accessible by ultrasound. For example, the brain is difficult to target because it is encapsulated by the cranium, and ultrasound doesn’t penetrate bone well.

**Benjamin:** Has the UTMD technique been tested in humans yet?

**Grayburn:** No.

**Benjamin:** What kinds of genes have been targeted to the myocardium?

**Grayburn:** Multiple genes have been studied, including SERCA-2 for diastolic dysfunction, vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) for angiogenesis, and stem cell factor (SCF) to help enhance stem cell uptake into the myocardium.

**Benjamin:** You are also exploring novel therapies for diabetes mellitus using the UTMB technique. What gene do you use to target the pancreatic islets?

**Grayburn:** Several transcription factor genes are involved in embryogenesis of the endocrine pancreas. We have tested most of those genes in mouse and rat models and successfully
Benjamin: What is the quality of the new islets?
Grayburn: The new islets resemble fully formed adult islets under histological examination. Furthermore, with the new islets, blood sugar and C-peptide levels return to normal, as does the glucose tolerance test, so these appear to be completely normal islets.

Benjamin: How long does the restoration of the activity last in nonhuman animals?
Grayburn: In rats, the new islets persist for at least 6 months.

Benjamin: Have you also tried delivering VEGF genes to improve the survival of the transplanted islets?
Grayburn: Yes, we have taken islets from human donors, injected them into mouse liver, and then treated the recipient livers with VEGF. This improved the vascularity and survival of the implanted islet grafts and increased the percentage of mice who were cured of diabetes.

Benjamin: Do you have a rough estimate of a timeline for doing a human study using this technique?
Grayburn: We first need to complete our baboon pilot study and then work with the FDA on a plan to move to first-in-human trials.

Benjamin: Are there other projects in which you’re using the UTMD technique?
Grayburn: We just started a collaborative project with Drs. Carlos Becerra and Alan Miller in the new oncology center. They have some novel ideas about using microbubbles to treat pancreatic cancer.

Benjamin: Is the goal to target chemotherapeutic agents to the pancreas?
Grayburn: We have several broad ideas. One of those is to attach gemcitabine to the bubbles and target it directly to the pancreatic tumor rather than circulating it throughout the entire body. Second, we could use UTMD to disrupt the desmoplastic stroma, which tends to protect the tumor from chemotherapy. Third, we might be able to use the microbubbles to deliver therapy that might improve the immune response to the tumor.

Benjamin: Let me now shift to another field that you have been working on here at BUMC. Since 2005, you have been on the publications committee for the EVEREST study. What is the object of this study?
Grayburn: EVEREST II is a randomized trial published last year in the New England Journal of Medicine comparing the effectiveness of the MitraClip, which is a percutaneous device for repairing the mitral valve in mitral regurgitation (MR), to surgery. EVEREST II showed that the MitraClip is safer than surgery, as would be expected for a minimally invasive approach, but not quite as effective as surgery at eliminating MR. The MitraClip is currently being used in Europe and other countries primarily in patients who are considered high risk for surgery because of age, prior cardiovascular surgery, and other comorbidities. It is not approved in the US yet.

Benjamin: Is that technique indicated for all types of MR?
Grayburn: It is indicated both for degenerative MR, which is the most common type, and also for functional MR, which occurs secondary to left ventricular dysfunction. There are some patients in whom the MitraClip is not likely to be successful.

Benjamin: Could you describe the device used in the procedure and how it is introduced?
Grayburn: The device is a cobalt chromium clip with two arms, each of which is 8 mm in length. It has grippers that close the device around each of the mitral leaflets. It is designed to function like an Alfieri stitch, pinning the anterior and posterior mitral leaflets together at the site of the mitral regurgitation jet. It offers an advantage over the Alfieri stitch in that the design of the clip forces 8 mm of coaptation of the leaflet edges. It is placed by going up through the femoral vein into the right atrium, crossing the atrial septum with standard techniques, and then coming down upon the mitral valve from the left atrium.

Benjamin: How do you ensure the correct positioning of the clip?
Grayburn: Unlike most cardiac catheterization procedures, the MitraClip is placed under TEE guidance. I perform the TEE. The MitraClip device is deployed by an interventional cardiologist (Drs. Choi or Brown) and a surgeon (Drs. Mack or Hebele).

Benjamin: What are the potential complications of the procedure, and what are the rates of this complication?
Grayburn: The complication rate is low and depends on the nature of the patients being evaluated. In high-risk patients who have been declined for surgery because of extensive risk factors, the 30-day mortality rate is about 5% and the stroke rate is about 2%. The bleeding rate from primarily a groin bleed is about 10%. These complications occur less frequently in low-risk patients. The MitraClip is successful in reducing MR to mild or moderate in about 85% of the patients; another 15% do not have sufficient MR reduction.

Benjamin: How many patients have undergone the procedure so far?
Grayburn: We are doing these procedures at both the Baylor Heart and Vascular Hospital in Dallas and The Heart Hospital Baylor Plano. We have done about 30 procedures between the two institutions.

Benjamin: How many patients have undergone this procedure worldwide?
Grayburn: There are now over 5000 cases worldwide.

Benjamin: What about the long-term data on the patients who have the clip?
Grayburn: The first case was done in South America 9 years ago. The patient still has only mild MR, is feeling well, and has had no complications.
Benjamin: Since 2002 you have been on the committee for the Surgical Therapy for Ischemic Heart Disease trial, or STICH. What was the objective behind STICH?

Grayburn: The STICH trial is one of the most important cardiac surgery trials ever done. In the early days of bypass surgery, the CASS trial was done in patients who had mild stable angina, but patients with ejection fractions <35% were excluded. For all the years that we have done bypass surgery, no one has done a randomized controlled trial of patients who have heart failure and an ejection fraction <35% to understand whether revascularization would benefit them or not. That was the primary rationale of the STICH trial. To get into the trial, patients had to have heart failure symptoms, coronary artery disease amenable to coronary artery bypass grafting (CABG), and an ejection fraction ≤35%. This is the first major randomized trial to evaluate the role of revascularization in heart failure patients with ischemic cardiomyopathy.

Benjamin: What was the endpoint in this trial?

Grayburn: The major endpoint was all-cause mortality. The major secondary endpoint was cardiovascular mortality and heart failure hospitalization.

Benjamin: What was your role in the study?

Grayburn: I was director of the TEE substudy to evaluate the mechanism and severity of MR, which is common in ischemic cardiomyopathy. The first paper on MR in the STICH trial has just been accepted by Circulation.

Benjamin: What did the panel conclude at the end of the study?

Grayburn: The STICH trial has generated a bit of controversy. The primary endpoint of all-cause mortality trended in favor of bypass surgery, but it was not statistically significant. Therefore, some clinical trialists assert that STICH was a negative trial. A closer look at the data reveals more subtle findings. For example, there were many crossovers—patients who were assigned to CABG but never received it, or patients who were initially assigned to medical therapy but early on crossed over to CABG. When those patients were taken out of the analysis, the results were strongly in favor of CABG. The secondary endpoint, which was combined cardiovascular mortality and heart failure hospitalization, was dramatically improved by bypass surgery versus medical therapy. So I think the overall gestalt of the trial is that it favors revascularization with CABG for heart failure patients with ischemic cardiomyopathy, although this will remain controversial.

Benjamin: What about long-term follow up of the STICH patients?

Grayburn: Patients who were enrolled in STICH are being followed out to 10 years. This is called the STICH Extended Study (STICHES).

Benjamin: Dr. Grayburn, you have been invited to speak at many institutions, including Duke University Medical Center, The John Hopkins University Medical Center, Ohio State University, New York University, Massachusetts General Hospital, and the Mayo Clinic, among others. You have given >100 lectures since 2000. Which topics are you usually asked to lecture on?

Grayburn: I am usually asked to speak about valvular heart disease, UTMD, or cardiac imaging.

Benjamin: How many trips do you take a year for presentations or meetings?

Grayburn: Approximately 10 to 12 per year.

Benjamin: How would you describe your presentation technique?

Grayburn: I’m generally known as a good speaker. I don’t think there is any secret to it. You need to know the message you want to communicate to the audience, who the audience is, and then communicate in a succinct and concise manner. The other important thing to do is to make it clinically relevant, usually by linking the talk to a real patient’s story.

Benjamin: In your career thus far, what accomplishments are you most proud of?

Grayburn: I am most proud of innovative discovery. My colleagues and I were the first to describe the use of dobutamine echocardiography for elucidating the physiology of low-gradient aortic stenosis. We were the first to describe the use of dobutamine stress echo for myocardial viability. We wrote one of the first papers on myocardial perfusion imaging with ultrasound contrast agents. We pioneered the use of vena contracta measurement for quantification of MR. We were the first in the world to use UTMD for gene therapy.

Benjamin: You have received several awards throughout your career. Which one are you most proud of?

Grayburn: I think awards are overrated. If I had to pick one, it would be the National Institutes of Health K24 Award. It is a grant awarded for having a track record of mentoring junior faculty members. A number of my former trainees now hold faculty positions at famous institutions, and I am proud of them and their accomplishments.

Benjamin: How much time did you dedicate for teaching at that time?

Grayburn: The K24 award from the National Institutes of Health protected 50% of my time for teaching and mentoring.

Benjamin: What are your professional goals from here on?

Grayburn: I would like to advance UTMD to human studies. I would like to see the MitraClip approved by the FDA for human use, and I would like to help develop percutaneous mitral valve replacement.

Benjamin: Let me get to know a little bit about your work day and your personal life. What time do you usually get up? What time do you usually go to sleep?

Grayburn: I usually get up around 6:00 or 6:15 am and I go to bed early, usually after the evening news, about 10:30 pm.

Benjamin: Do you have a typical work day?

Grayburn: Some days I am doing procedures in the cath lab or seeing patients in the valvular heart disease clinic. Other days I am working in the animal lab or sitting at my desk writing papers or doing conference calls or going to meetings. There is a lot of variation, so there is no such thing as a typical day.

Benjamin: What do you do when you are not working on the weekends?
Grayburn: If I am not on call or at a meeting, I try to preserve weekends for my family. I have a wife, four kids, and three grandkids, and we enjoy spending time together.

Benjamin: How much vacation time do you take annually?

Grayburn: I typically take 2 to 3 weeks of vacation every year. I usually spend at least 1 week at a beach (Figure 2) and another snowboarding in Colorado.

Benjamin: When did you meet your wife? How long have you been married?

Grayburn: I met her when I was in medical school and we became best friends. We have been married for 32 years and have been blessed to have a really good relationship.

Benjamin: What do your four children do?

Grayburn: I have a daughter who does accounting for an oil and gas servicing company in Fort Worth. She and her husband have three kids. I have a daughter at Belmont University in Nashville, a son at Texas A&M, and a daughter who graduates from First Baptist Academy next year.

Benjamin: Do you have plans for retirement?

Grayburn: No. At some point, I might consider slowing down and focusing only on the things I am most interested in doing.

Benjamin: Is there someone or something that currently inspires you?

Grayburn: I think that I have really been blessed to have good mentors in my career. I did my cardiology fellowship at the University of Kentucky when Tony DeMaria was chief of cardiology. He is a very famous cardiologist and has been past president of the American College of Cardiology. He is the editor in chief of the *Journal of the American College of Cardiology*. He has been a mentor to me not only during my 3 years of fellowship, but throughout my career. After I left Kentucky, I was recruited to UT Southwestern by Jim Willerson, who has helped my career throughout the years. During my 15 years at UT Southwestern, David Hillis and Sandy Williams were mentors and role models to me. All of them have helped shape my career and inspire me to greater things. I have learned that having good mentors is really a key to success.

Benjamin: Thank you, Dr. Grayburn. Your fruitful career is quite inspiring.
Baylor Research Institute, Roche, French agencies establish strategic collaboration to develop therapeutic vaccines for chronic infectious diseases

Baylor Research Institute (BRI), Roche, the French National Agency for Research on AIDS and Viral Hepatitis (ANRS), and Inserm Transfert announced a long-term collaboration to develop therapeutic vaccines for chronic infections. The researchers will utilize a novel technology platform developed by Baylor Institute for Immunology Research (BIIR), a component of BRI, and ANRS and Inserm associated research units to identify and produce therapeutic vaccines that target dendritic cells, a critical component of the mammalian immune system.

“This targeted approach may be useful in a variety of areas of medical need. Our goal is to identify new and unique antibody constructs that will target specific dendritic cell subpopulations to drive and mount an immune response,” said Jean-Jacques Garaud, head of pharma research and early development at Roche.

The collaborating parties will identify and optimize potential lead candidates and then develop select molecules for clinical proof-of-concept. Each party brings unique strengths to the collaboration: BRI’s expertise in dendritic cell targeting and fusion protein biochemistry and ANRS and Inserm associated research units to identify and produce therapeutic vaccines that target dendritic cells, a critical component of the mammalian immune system.

“The concept of this vaccine program originated from more than 15 years of research in human dendritic cell biology and dendritic cell targeting at BIIR,” said Yong-Jun Liu, MD, PhD, vice president and chief scientific officer for BRI and director of BIIR. “We are extremely excited to work with the two world leaders in vaccine development and biologics research to move the basic research discovery toward the clinic.”

Baylor Dallas named a “Top 100 Hospital”

For the first time, Baylor University Medical Center at Dallas (BUMC) has been named among the Thomson Reuters 100 Top Hospitals award winners in the major teaching hospital category. Modern Healthcare magazine, a leading national publication covering the healthcare industry, published the list in its April 16 issue. The annual Thomson Reuters list measures hospitals across America on nine separate measures of performance related to patient care, clinical and hospital operations, financial performance, and quality of care in the community.

According to Thomson Reuters, “From a field of nearly 3,000 U.S. hospitals, these impressive winners clearly provide top-notch care and have achieved outstanding operational results.” BUMC’s quality initiatives were a major reason why BUMC made the 100 Top Hospitals list. Modern Healthcare’s feature story on BUMC focused on its efforts to reduce heart failure readmission rates from 29% to 7% in 9 months. For the past 3 years, the Baylor Heart Failure Program has had the lowest heart failure re-admission rate of any hospital in the country.

Baylor hospitals receive quality awards

Baylor Medical Center at Waxahachie was the 2012 recipient of the Texas Award for Performance Excellence (TAPE), given by the Quality Texas Foundation. Patterned after the Malcolm Baldrige National Quality Award criteria and process, TAPE is an annual recognition of Texas organizations that have achieved performance excellence and applied outstanding quality principles in their day-to-day operations. The Quality Texas Foundation cited several best practices that qualified Baylor Waxahachie to be its TAPE award recipient, particularly its shared leadership system that is well integrated throughout the organization; its process of identifying and creating service offerings to meet the requirements of its customer groups, enter new markets, and attract potential customers; and its cooperative relationships with local nursing homes that allow for continuity of care.

Baylor Medical Center at Garland and Baylor Regional Medical Center at Plano received the Texas Health Care Quality Improvement Silver Award from TMF Health Quality Institute, the Medicare quality improvement organization for Texas. The awards acknowledge hospitals for improving care related to acute myocardial infarction, heart failure, pneumonia, and surgical care, clinical areas designated as national health care priorities by the Center for Medicare and Medicaid Services and the Joint Commission. To earn the Silver Award, a hospital had to achieve or maintain

ACCOLADES

Alan Menter, MD, served as president of the Third World Psoriasis and Psoriatic Arthritis Conference, which was held in Sweden from June 27 to July 1, 2012, sponsored by the International Federation of Psoriasis Associations.

Yong-Jun Liu, MD, PhD, vice president and chief scientific officer of BRI and director of BIIR, received the Method to Extend Research in Time (MERIT) Award (R37), which extends the funding of his R01 grant, “Characterizing DExD/H box helicases as viral sensors in human dendritic cells,” for 3 to 5 additional years without peer review. The National Institute of Allergy and Infectious Diseases issues only 15 MERIT awards annually to investigators who show superior competence and have outstanding records of scientific achievement.

Karolina Palucka, MD, PhD, an investigator at BIIR and the Michael A. E. Ramsay Chair for Cancer Immunology Research, received the Career Award from a panel of her peers at the European Academy of Tumor Immunology Conference in Paris. Dr. Palucka’s work focuses on the development of therapeutic cancer vaccines. During her 15-year career with BIIR, she has designed and conducted more than a dozen clinical trials to test dendritic-cell–based vaccines to treat people who have cancer.

Michael Mack, MD, thoracic and cardiovascular surgeon at The Heart Hospital Baylor Plano, received the 2012 Presidential Citation Award from the American College of Cardiology. This award was established to recognize outstanding individuals making contributions to the cardiovascular profession.
Baylor Plano achieves Magnet recognition

Baylor Regional Medical Center at Plano achieved Magnet recognition as a reflection of its nursing professionalism, teamwork, and superiority in patient care. Magnet recognition is determined by the American Nurses Credentialing Center’s (ANCC) Magnet Recognition Program, which ensures that rigorous standards for nursing excellence are met. With this credential, Baylor Plano joins the Magnet community—a select group of 392 healthcare organizations out of nearly 6000 US healthcare organizations.

Baylor Plano was the fourth hospital in Baylor Health Care System (BHCS) to achieve Magnet status.

In addition, Baylor Medical Center at Waxahachie achieved the Pathway to Excellence designation from the ANCC. This designation identifies the elements of work environments where nurses can flourish. The designation substantiates the professional satisfaction of nurses at Baylor Waxahachie and identifies it as one of the best places to work.

Baylor McKinney participates in community health efforts

As the hospital prepared for its opening, Baylor Medical Center at McKinney collaborated with the city of McKinney, the McKinney Independent School District, and other nonprofit organizations to improve the community’s health through the McKinney Health Challenge—a major event supporting the city’s goal to become the most fit community in the country. A community-wide effort, the challenge took place over a 2-month period, from Relay for Life on April 27 through Baylor McKinney’s Open House on June 30.

“Our focus at Baylor McKinney is to take this healthy community and make it even healthier, and we are so pleased to work together with other community organizations to work towards this goal,” said Scott Peek, president, Baylor McKinney. “We’re bringing additional resources to the community, such as advanced imaging services and health screenings, which will promote prevention and wellness.”

RECENT GRANTS

- **Familial and early-onset colorectal cancer**
  Principal investigator: C. Richard Boland, MD
  Sponsor: National Institutes of Health
  Funding: $332,512
  Award period: 5/1/2012–4/30/2013
- **JC virus and human colorectal neoplasia**
  Principal investigator: C. Richard Boland, MD
  Sponsor: National Institutes of Health
  Funding: $267,374
  Award period: 2/1/2012–1/31/2013
- **North Texas Traumatic Brain Injury Model System: clinical and demographic data**
  Principal investigator: Rosemary Dubiel, MD
  Sponsor: University of Texas Southwestern Medical School/US Department of Education
  Funding: $233,107
  Award period: 10/1/2011–9/30/2012
- **New-onset post–coronary artery bypass grafting atrial fibrillation**
  Principal investigator: Giovanni Filardo, PhD
  Sponsor: National Institutes of Health
  Funding: $763,813
  Award period: 5/1/2012–4/30/2013
- **Randomized comparison of ductal preservation solutions for improving quantity and quality of isolated human islets**
  Principal investigator: Marlon Levy, MD
  Sponsor: National Institutes of Health
  Funding: $196,000
  Award period: 1/1/2012–12/31/2012
- **Targeting plasmacytoid dendritic cells to treat human myeloma**
  Principal investigator: Yong-Jun Liu, MD, PhD
  Sponsor: MD Anderson Cancer Center/National Institutes of Health
  Funding: $195,646
  Award period: 2/29/2012–1/31/2013
- **Characterizing DExD/H box helicases as viral sensors in human dendritic cells**
  Principal investigator: Yong-Jun Liu, MD, PhD
  Sponsor: National Institutes of Health
  Funding: $736,874
  Award period: 11/1/2011–4/30/2013
- **Understanding the early and late endosomal TLR9-mediated responses to viral DNA**
  Principal investigator: Yong-Jun Liu, MD, PhD
  Sponsor: National Institutes of Health
  Funding: $392,000
  Award period: 4/1/2012–3/31/2013
- **The MIND USA (Modifying the Impact of ICU-Induced Neurological Dysfunction-USA) study**
  Principal investigator: Andrew Masica, MD
  Sponsor: Vanderbilt University/National Institutes of Health
  Funding: $51,204
  Award period: 3/1/2012–2/28/2013
- **Study of attitudes and factors affecting infant care**
  Principal investigator: Olha Prijic, RNC, BSN
  Sponsor: Trustees of Boston University/National Institutes of Health
  Funding: $3,080
  Award period: 8/1/2011–7/31/2012
- **Systems biology of cardiovascular biomarkers in psoriasis**
  Principal investigator: Alan Menter, MD
  Sponsor: National Psoriasis Foundation
  Funding: $100,000
  Award period: 4/1/2012–3/31/2013
- **Improving physician and nurse communication with serious gaming**
  Principal investigator: Yan Xiao, MD, PhD
  Sponsor: University of Texas, Arlington/Agency for Healthcare Research and Quality
  Funding: $64,347
  Award period: 4/1/2012–3/31/2013
- **Controlled trial of venlafaxine XR for depression after spiral cord injury: a multisite study**
  Principal investigator: Ann Marie Warren, PhD
  Sponsor: University of Washington/US Department of Education
  Funding: $152,651
  Award period: 1/1/2012–12/31/2013
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PHILANTHROPY NOTES

- Galderma Laboratories pledges additional $450,000 for dermatology residency program
  Galderma Laboratories LP, a global pharmaceutical company focused exclusively on dermatology, has pledged $450,000 to help support the dermatology residency program at BUMC. The pledge brings Galderma’s support of the program to $900,000 since its inception.

- BUMC launched a dermatology residency program in 2009, with the leadership of Alan Menter, MD, and Dan McCoy, MD, program directors for the residency program and physicians on the medical staff at BUMC. The program provides a comprehensive 3-year experience with opportunities for residents to learn how to provide quality care and participate in research and scientific publications. The program offers six residency training positions, with two residents selected each year. The cost of educating a dermatology resident is approximately $225,000 for the 3-year program.

- Legacy of Doc Hutch lives on in cardiovascular research, education
  Whether he was making house calls or accepting watermelons as payment for medical care, Z. W. Hutcheson Jr., MD, epitomized the characteristics of an exceptionally dedicated “country doctor.” Generous and hardworking, and never without his legendary black medical bag, “Doc Hutch,” as he was known to friends and patients, served the medical needs of Andrews, Texas, for four decades.

  To honor the memory of this “one-of-a-kind doctor, family man, and citizen,” an anonymous donor pledged $500,000 to the BHCS Foundation to establish the Dr. Z. W. “Doc Hutch” Hutcheson Endowed Fund in Cardiovascular Research and Education. Doc Hutch passed away in 2009 at the age of 91, but his legacy will live on at BUMC, where future physicians may benefit from the dedication to service that he exemplified and the growing body of knowledge that the fund bearing his name will help share.

- McKinney Steering Committee raises $1.4 million
  Never before has a fundraising effort preceded the construction of a BHCS community hospital, and what an effort it has been. Since forming in 2009, the BHCS Foundation’s Baylor McKinney Steering Committee has surpassed its initial fundraising goal of $1 million and has raised more than $1.4 million in support of Baylor Medical Center at McKinney. A number of generous, civic-minded donors supported Baylor McKinney with gifts of $25,000 or more through the Founder’s Circle Campaign. Their gifts will be recognized in a unique, artisanship display in the main lobby of the hospital.

  This impressive fundraising effort was fueled by the hard work and dedication of the committee’s nine members: chair, Jan Hall, and members Erin Botsford, Dale Conrad, Mark Denissen, Judy Gay, Russ Lessmann, Ron Lockard, Nan Rierderer, and Bob Sanford. The committee has pledged to continue its fundraising efforts until July 2013.

  Opening in July 2012, the 95-bed, full-service hospital will meet the needs of the growing population in McKinney and the surrounding area, which has grown nearly 35% since 2006. As the community grows, Baylor McKinney is prepared to grow with it. The infrastructure of the main hospital will be built to accommodate more than 400 beds.

A book edited by a member of the Baylor medical staff

**Case Studies in Hematology and Coagulation**, edited by Gene Gulati, Joanne Filicko-O’Hara, and John R. Krause


This book features 173 case studies, 27 self-study challenge cases, and 586 images. The editors have compiled an invaluable collection of cases covering common and rare entities—from anemias and acute leukemias to plasma cell, platelet, and coagulation disorders. Cases are presented in an easy-to-follow format, grouped by related conditions.

UPCOMING CME PROGRAMS

- **Triage and Primary Care of Orthopedic Injuries**, August 25, 2012, from 7:30 AM to 12:15 PM, at the Royal Oaks Country Club, Dallas, Texas

- **2nd Annual North Texas Multidisciplinary Lung Cancer Symposium**, September 29, 2012, at Baylor Charles A. Sammons Cancer Center at Dallas

- **Baylor All Saints Advances in Cardiovascular Therapy Conference**, October 6, 2012, at the Omni Fort Worth Hotel, Fort Worth, Texas


For more information, call 214-820-2317 or visit www.cmebaylor.org.
Tributes to Gordon Hosford, MD

**Robert L. Allday, MD**

My long association with Gordon Hosford began when I joined the internal medicine practice of Thomas, Binion, and Hosford in October 1968. The three of them—Paul Thomas, John Binion, and Gordon—were welcoming and encouraging, but I was perhaps closest to Gordon because he was the next-youngest partner and had just joined the practice 3 years before me. He had graduated from Harvard Medical School and trained at Barnes Hospital in St. Louis and Stanford before returning to Dallas to practice. As my mentor, he was immensely helpful in showing me the ropes at Baylor and introducing me to “real-world” medicine.

I soon learned that the group was a close-knit team, with similar approaches to medicine. The intellectual quality was high, as we took care of many patients with difficult diagnostic and therapeutic problems. We cared for all types of patients—from the wealthy and influential to those of limited means. They were all treated the same; the patient always came first.

Gordon would frequently invite me into his office, which was next door to mine, to discuss difficult diagnostic problems. We would review the patient’s history, lab reports, and x-rays and then examine the patient together. In turn, I would invite him into my office to help me evaluate patients. This was a critical learning tool for both of us, combining didactic teaching, as in formal medical school and residency training, and real-world medicine. I can still see him sitting in his Harvard chair, with x-rays on the viewing box, the chart and lab reports spread out on his desk as the patient awaited further attention in the exam room.

Gordon served a year as president of the Dallas Chapter of the American Heart Association and was the long-time medical director of the Visiting Nurse Association.

While he was devoted to his practice, he also made time for travel with his family, French lessons, sailing, going to baseball games, and playing tennis. After Gordon and I both retired, my wife and I enjoyed going to several baseball games with the Hosfords, as well as having occasional dinners together.

Gordon’s memorial service in Cox Chapel of Highland Park United Methodist Church was filled with family, friends, professional colleagues, and former patients. His very talented relatives contributed many family anecdotes, as well as vocal and instrumental music. During his final illness, at least one of his three daughters—Dr. Sarah Hosford, a gynecologic oncologist in Atlanta, GA; Julia Hosford Barnes, an attorney in Santa Fe, NM; and Lisa Hosford Jensen, an attorney and teacher in Washington, DC—visited him every weekend, a true expression of their love and devotion.

I am grateful for my very long association with Drs. Thomas, Binion, and Hosford, and, later, Dr. John Brooks. The truly ideal practice of medicine by all the partners far exceeded my medical school dreams. I am especially grateful to Gordon for his guidance during the early years of my practice and for our long-term relationship as friends and professional colleagues. I miss him very much.

**John Brooks, MD**

It was a privilege to be associated with Gordon Hosford during an 11-year partnership that started upon completion of my residency at Baylor University Medical Center at Dallas. Gordon had many dedicated and distinguished patients and took great interest in their medical and personal lives. Gordon was a well-read academic individual who grew up as a son of a Southern Methodist University professor. He understandably took great pride in his medical degree from Harvard, but was even more proud of his three daughters, all of whom attended Stanford. During those years, we had many entertaining and thoughtful discussions regarding medicine, politics, and history. I would often find it humorous when criticizing his favorite politicians and he would, in turn, criticize my favorite conservatives. I benefited greatly from his medical and worldly insights.

Gordon gave over 20 years of his time serving on the Visiting Nurse Association board as well as several other charitable organizations. When asked about this service, his response was that he wanted to return to the community that had been so generous to him. This timeless advice and service contributed immensely to the Baylor medical and Dallas community. His unselfish contribution will serve as an example to us all.

**Sarah Lynn Hosford, MD**

One of my earlier memories, from somewhere around the fourth grade, is of helping the family cat deliver her kittens in my closet. This experience gave me such a feeling of accomplishment that I was sure I wanted to be a veterinarian when I grew up. It was my father who ultimately made me change my mind about this.

Even when I was only in elementary and junior high school, Dad would sometimes take me along on his weekend hospital rounds. It was there that I first got a taste of what a physician’s
work life is like. I was impressed with the warm, collegial relationships he had with hospital staff and other physicians, the deep and respectful regard given him by his patients, and the respectful attention he gave to them. Gradually I became aware of the fact that Dad enjoyed a particularly rich and rewarding professional life and that he worked as hard as he did because he truly loved his work. Although I don’t remember exactly when, at some point I decided that this was what I wanted to do with my life as well.

As a teenager I sometimes helped to fill in at Dad’s office: filing x-rays and patient records, answering phones, and doing odd jobs. I remember the office atmosphere as being wonderfully warm and friendly. His staff all seemed to enjoy their jobs and each other as coworkers and, following Dad’s lead, found it quite natural and effortless to exhibit extraordinary dedication and selflessness in the service of patients. This atmosphere is something I have always sought to recreate in my own practice, although the constraints on physician practice nowadays can sometimes make this difficult.

The summer after my freshman year in college—I remember it was the summer that Elvis died—Dad got me a job working in the medical laboratory in his office building, where I learned to draw blood, take x-rays, and use some of the other equipment. The next summer I worked the 3:00 to 11:00 shift as an EKG technician at Baylor, where I once almost passed out at the sight of blood in the ER!

Dad never sought to influence my career choice. When I became a physician in my own right, he never sought to influence how I practiced medicine. But his influence has been enormous nevertheless. I continue to be impressed at the extent to which I pattern myself after him: by giving sufficient time and attention to each patient, by being respectful of them as people and of their concerns, and even in little things like personally going out to the waiting room to call them back. These things may seem like quaint hearkening to the past, but to me they are the heart and soul of good patient care.

It was very gratifying to both of us during the years when we were both in practice to enjoy a collegial relationship in addition to our familial one. Sometimes he would call me to ask about a gynecologic problem. Once when a terminal patient of mine was moving back to Dallas he took charge of finding her hospice care. On a handful of occasions we were able to attend medical courses together.

Dad had a profound influence on my choice of career, and I have sought to emulate the wonderful philosophy that guided his practice of medicine. But his legacy as a parent and family man resonates maybe even more strongly. Sometimes patients would ask about the photograph of his three daughters hanging on his office wall, and Dad would explain that one was a physician and the other two lawyers. Often he would get the comment, “Oh, you must be especially proud of your doctor daughter!” to which he would invariably reply, “I’m proud of all of my daughters.” He was a wonderful physician and a wonderful father, and I miss him very much.

Stuart F. Owen, MD

My medical partners and I shared night and weekend call with Gordon Hosford for the last few years that he worked. He was an old-fashioned physician in the very best way: he took care of his patients, without fuss or wasted effort. He usually typed short notes that contained the essence of the patient’s problem, his findings, and his plan; I remember him sitting at his desk in Suite 1005, typing. He included enough, and not too much, detail. This is how good physicians practice.

Dr. Hosford did his job without complaining. If he covered for you overnight and received a call from the emergency room about a patient to be admitted, he would get out of bed and admit the patient. There was no equivocating, no “call me for orders when the patient gets up to the ward,” no “I’ll see him in the morning.” He would just get up, go to the ER, and take care of the patient.

He was straightforward in all his work-related activities. He did his part, taking his turn quietly and graciously. He was grateful about what you did for him. I will try to remember and emulate these simple traits in my own professional life.
Exploring the obesity epidemic

Carolyn M. Matthews, MD

In our lifetime we are experiencing never before seen rates of obesity, with a 68% rate of overweight in adults. In my field of gynecologic oncology, our surgical cases have become tremendously challenging due to the large size of our patients. When I was in residency training in the mid 1980s, it was rare to have a patient over 200 lb. Now it is uncommon to have a patient under 200 lb.

Our hospitals have had to make accommodations for the rising tide of obesity, increasing the sizes of beds, wheelchairs, operating instruments, and scales. I’ll never forget the time when my brother came to Baylor for magnetic resonance imaging (MRI) as recently as 1998 and was turned away because he was over the weight limit of 375 lb. Now we have machines that can perform an MRI on patients up to 550 lb.

No one chooses to be obese. Science has shown that gluttony and sloth are not the major culprits. While some genes will predispose to obesity and insulin resistance, our genes wouldn’t have changed enough in 20 years to account for the drastic change between 1990, when no state had a 20% obesity rate, and 2010, when all states had obesity rates of ≥20%.

There has to be a reason why we’ve had such a drastic change in the human phenotype—the way we look—in the last 20 years. Our genes just don’t evolve or change that quickly. If our genes haven’t changed, what has?

Our environment. While multiple factors contribute to obesity, the major game-changers that have contributed to this perfect storm are foods that had not previously been consumed during human evolution: proteins from genetically modified (GM) organisms, high fructose corn syrup (HFCS), and ever-increasing quantities of refined sugar and grains, as well as persistent organic pollutants.

GM foods, most commonly soy and corn, were introduced in the 1990s, just as the obesity epidemic was starting. Humans had never consumed GM foods, yet they are now rampant in our grocery stores and are typically found in processed foods and fast foods. In Morgan Spurlock’s month-long experiment of eating only fast foods, he gained 25 lb in 30 days!

Our immune system resides in our gut, and one important task is for our immune system to develop tolerance to the dietary nutrients that then become incorporated into our cells. It makes sense that if our immune systems had not encountered proteins from GM foods before, an inflammatory reaction could be generated. GM foods may be close to a wild-type food but have enough subtle differences that our immune systems react as if the molecules are a possible threat.

While numerous 90-day feeding studies of rats in well-controlled environments suggest safety and “substantial similarity” between regular foods and GM foods, no clearly reassuring long-term multigenerational studies have been conducted. A recent study from France looked at how feeding three different GM strains of corn affected young adult rats, comparing them to isogenic rats fed non-GM foods. The results are particularly intriguing given our worldwide obesity epidemic: the researchers found sex- and dose-dependent changes in numerous metabolic functions. Females fed MON 863 corn had up to 40% increases in serum triglycerides and glucose levels, a physiological state like metabolic syndrome. Hepatorenal effects, thought to be related to the pesticide residues produced as a result of the genetic modification, were prominent in all groups (1). Until there is long-term safety data on GM foods in laboratory animals, it would be prudent not to include these foods in our diet, and certainly Americans should have the option, like Europeans, of knowing whether the food they are eating contains molecules of GM food or not.

We’ve been evolving for millions of years, yet we’ve only had farming for 10,000 years, so we’ve had grains in our diet for the blink of an eye in evolutionary terms. Both grains and sugar are now readily available in massive quantities year round, and we are eating or drinking grains and sugar in unprecedented quantities. Medical anthropologists suggest that in the Paleolithic age, we consumed 20 teaspoons of sugar a year in the form of vegetables and fruits; now the average American consumes about 27 teaspoons a day. Refined sugars now comprise approximately 20% of our dietary caloric intake (2).

Since the industrial revolution, which enabled us to refine both grains and sugar, we have been eating huge quantities of...
high–glycemic index carbohydrates, which are digested and absorbed quickly. It is commonplace and socially acceptable to sit down with a soda; most sodas have close to our Paleolithic annual intake of sugar in one fell swoop—oops, I meant swallow!

Not only is the quantity of sugar a problem, but much of it has been replaced by HFCS, which doesn’t occur in nature. Fructose is found in some vegetables and fruits in small quantities, but we consume huge quantities with the most common form of HFCS, normally 55% fructose and 42% glucose (3).

A technique to industrially produce HFCS was developed in 1966 by a Japanese scientist, Dr. Y. Takasaki. It was introduced to the American market in 1975 when it was still fairly rare to see an obese person. The dramatic rise in obesity has paralleled the rise of HFCS in our diet (4). HFCS is metabolized in the liver in a way that promotes hepatic lipogenesis (4), contributing to fatty liver and metabolic syndrome. We are now consuming 63 lb of HFCS per person in this country annually, often in baked goods but also in sodas and other foods. Why? It is inexpensive! Our tax dollars make corn inexpensive.

Also contributing to these environmental changes are the persistent organic pollutants that surround us—the billions of pounds of chemicals that have been poured into our environment, mostly in the last 100 years, in the form of industrial byproducts, pesticides, herbicides, and now pharmaceutical byproducts (oral contraceptives and hormone replacement therapy) that are contaminating our water supplies. We’ve never before in our evolution been exposed to chemicals in these amounts or these combinations. Many are known carcinogens and have been banned (like DDT, banned now in the United States but still used in many countries) but are persistent in nature. Many act as endocrine disruptors, interfering with our hormonal system, which is intimately involved in the way we burn and use energy.

While it is not clear precisely how the environmental contaminants interfere with our hormones, we do know through the work of Dr. Duk-Hee Lee and collaborators that there is a striking dose-response relation between blood levels of persistent organic pollutants and the prevalence of diabetes mellitus: individuals with the highest level of persistent organic pollutants have a 37-fold increased risk of diabetes compared to those in the lowest quartile (5). In fact, obesity doesn’t even seem to be related to type 2 diabetes in individuals with low serum concentrations of persistent organic pollutants (6).

So what can we do? Something has to change; this path of ever-increasing obesity with its associated diseases is not sustainable in our society. My recommendation is to vote with your fork and your wallet: if we don’t buy it, food producers will adjust accordingly. Choose your foods with great discrimination. Lobby your representatives to encourage sustainable farming practices and end subsidies for corn and soy. Eliminate GM foods, limit your intake of refined grains and sugars, and avoid HFCS. Eat in the way we have evolved over the millennia—vegetables, fruits, nuts, seeds, berries, and pasture-raised or wild meats.

Usefulness of collaborating with clergy

Joseph B. VanderVeer Jr., MD

When I attended medical school in Rochester, NY, our second-year course on interviewing patients was run by Dr. George Engel, a teacher certified in both medicine and psychiatry. During the course, for 10 consecutive weeks, he conducted interviews before the class. (We were separated from him and the patient by a one-way mirror. We were in a darkened classroom; he and the patient were in a small, adjacent, brightly lighted room, their voices piped in to us.) Each week, for an hour, he interviewed a different patient. He’d instructed his chief resident to choose 10 patients for him, and he knew nothing about them in advance, except that each was a diabetic.

Over that 10-week period, we became amazed at the various things Dr. Engel brought out in each patient’s history, showing us how various facets of a patient’s life were affected by his or her illness. Indeed, the “take-home” message was that, more often than not, illness affects almost every aspect of a patient’s life. Engel convincingly showed us how the body, the mind, and the spirit reacted and interacted in response to illness or injury. The obvious inference was that we would take better care of our patients if we heeded, respected—and looked for—that interplay.

From that experience in medical school, I became convinced that we need to pay attention to the body, mind, and spirit to have the best chance of helping our patients.

After medical school, I went on to become a general surgeon. In the course of my training I came to realize that not all surgeons are created equal. Here are two illustrative examples. When I was a senior resident, I had joint responsibility for the head and neck service of the Veterans Affairs (VA) Hospital in Portland with an excellent otolaryngology resident named Maurice. As was and is typical of VA patients, many exhibited the ravages of life-long smoking and drinking. In particular, on our service we had many patients who had cancer of the larynx, a sad disease that we often treated with laryngectomy. As a result of the surgery, patients lost their voice, an additional trauma besides the big operation. Pre-operative counseling in these men was crucial, and Maurice and I were dismayed that our own busy schedules didn’t allow us to spend much time talking to these patients preoperatively, for we spent long hours in the operating room and had many patients on the service to round on daily.

To help inform and counsel these patients who were facing loss of their larynx, we formed a team approach involving a nurse, a chaplain, a social worker, and the two of us. One member of this team would spend at least an hour talking with each patient before surgery. It seemed to work, for we noted the patients did better, seemed to have fewer complications, and were better motivated to learn esophageal speech than if we’d not spent the extra time.

It happened that every Friday, the chief—the professor in charge of all the surgical services in that VA hospital—made teaching rounds with all of the residents, walking the wards and seeing every patient. Some were seen very briefly, even just from the door of the room, while others might be examined at the bedside by the chief. The whole process was edifying and educational and took about 3 hours. Besides being a great learning experience for us, it was a way that the chief kept tabs on the service.

On this particular Friday, Maurice and I had been using our team approach for about a month, and we decided it was time to tell the chief about it. So I explained what we’d done and the good results we thought we were getting, concluding with the statement that we were glad we’d instituted the team program, for much as we would like to, we were just too busy to spend an hour chatting with each patient. The chief, a general surgeon who was nationally known for his innovations in vascular surgery, looked at me, cocked his head, and said, “I can’t imagine spending an hour talking to a patient!” Yet we regarded him as a superb surgeon, and he was a man who would spend 3 hours with us operating on a sleeping patient who had an abdominal aortic aneurysm!

Contrast that experience with this vignette about a medical student on the service of Harvey Cushing, the great neurosurgeon. The student was an extern assigned to work up one of Cushing’s brain tumor patients, a middle-aged man who was to have a craniotomy in the morning. As the student, carrying his black bag and notebook, rounded the corner to come into the patient’s room, he saw a man in a dark suit sitting in a chair at the bedside, his back to the student, reading the Bible to the patient. Assuming it was a clergyman, the student said, “I’m sorry, Father. I will come back a little later.” The man turned around and the student recognized Harvey Cushing.

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Perhaps the patient had asked Cushing to read to him, or perhaps Cushing had realized that was what this patient needed at this particular time. Not all of us are as sensitive as Cushing, and probably most of us are not as familiar with the Scriptures as he was. But the story gives a different slant on the surgeon at the bedside than did my previous story. Different patients have different needs, and we need to call upon a variety of others to help if we ourselves cannot meet those needs. Of course, we do this all the time with consultants.

I had a broad but restricted practice; I didn’t do orthopedics or cardiac surgery, for example. In order to excel and to be able to adequately keep up, I restricted the scope of my practice. The logical corollary of that decision is that I could not cover the whole field of surgery, let alone the vast expanse of medicine. So, in desiring to take the best care of my patients, I called upon others and sought consultation outside my own area of expertise. An experience early on in my practice taught me an important lesson. It occurred not long after I completed my surgical residency. I’d stayed on the faculty and was directing surgical residency. I’d stayed on the faculty and was directing the emergency department at the University of Oregon Hospital in Portland at the time.

One afternoon, one of the interns presented the case of a boy named Taddio, a high school cross-country runner with a sore knee. His mother was an immigrant from Poland, although Taddio was born here. He did not recall a specific injury, and the intern, whose exam was negative, asked if he should do an x-ray. I said yes, because on rare occasions in a young man you may discover a bone tumor. So it happened. The x-ray showed that Taddio had a cancer, a sarcoma of the femur, and we referred him to the orthopedic surgeon for further care.

Fast forward about 2 years. I’d taken a job across town as the director of the emergency department in a large Catholic hospital. At the time I was an elder in a suburban Presbyterian church, and one day I got a call from a fellow elder who was a teacher and coach at Lake Oswego High School. He said one of his students was in the hospital, and could I please visit him. His name, he said, was Taddio; he was estranged from his mother and was dying from metastatic cancer. I recognized the uncommon name.

It turned out that back when I’d first met him, the orthopedists recommended that Taddio have an amputation, but he refused, despite his mother’s urging. They had tried chemotherapy to no avail, and now the cancer had spread to his lungs. He was dying and was an angry young man. I visited him alone at first, then several more times with the hospital chaplain and with his mother. I could do nothing about the tumor, but together we were able to effect a reconciliation, a healing of the broken relationship with his mother, before he died. As a young, scientifically trained surgeon, I learned a great lesson: there were other forms of healing besides surgery or medication that we were called to be part of, and there were others, specially trained, who could help.

The well-known medical ethicist Albert Jonsen has described what he terms the central ethical paradox of the practice of medicine, which is the tension between self-interest and altruism. In the context of these two stories, it amounts to asking ourselves, ‘Am I going to put my own interests ahead of those of my patient?’ It’s a question that underlies much of our behavior in medicine and surgery.

In medical education circles today, there’s a lot of interest in professionalism, which as an interested observer I see as an attempt to improve the standing and image of doctors by drawing them back to the great virtues of the profession, many of which have been lost or blunted as modern medicine has been transformed by technology and managed care. (Medicine, in fairness, has suffered from many of the same woes that American society has suffered from over the past 50 years.) Professionalism has been touted as one of the six major competencies that graduating residents should possess, and it includes caring and altruism. Perhaps in days gone by, when we did not have such a wide range of wonder drugs and dazzling techniques, much of what doctors dispensed was care and concern—and doubtless there was less material to master in the medical school curriculum and more time to spend with an individual patient. But I’d submit the fundamental approach has not changed: the secret of the care of patients is truly caring for them, that is, being competent and concerned, able to put their needs ahead of our own.

Since none of us can adequately cover the entire medical or surgical waterfront, and patients’ needs vary widely, it behooves us as competent doctors to be sensitive to their needs—body, mind, and spirit—and to be familiar with a broad range of colleagues with whom to consult to give patients the best care. In that regard, my own religious persuasion is much less relevant than the fact that I am sensitive to some of the issues.

I once shared my concern with a hospital chaplain in Arizona that relations between physicians and pastors need attention. He agreed and said that the problem was universal, in his experience. He’d been a full-time chaplain for several years and said he felt that most of the time he was called in far too late to be of great help and often felt “like the pooper-scooper at the end of the parade.” By that he meant many medical professionals saw his role as picking up the pieces, being relevant only after a patient died, whereas he believed he could assist (and was trained) in a much greater variety of situations: before or after surgery or with a waiting family; when a patient has a serious, painful, severely disabling, or incurable illness or faces an alteration in lifestyle; when a patient seems to need moral guidance or value clarification; when a patient has few or no visitors or is depressed.

Another pastor shared with me an experience he had during a clinical pastoral education training session at a medical center in the Midwest. A head nurse pulled him over one day because an obstetrician on the staff had written an order on the chart that henceforth the chaplain was to see none of his patients. She said that this doctor had come to the ward and saw one of the chaplains seated at the bedside of one of his patients; the woman was crying and obviously distraught. He was angry that the chaplain had obviously gotten her emotionally riled up. But what the head nurse knew (and the attending doctor did not appreciate) was the patient was grieving over the loss of her stillborn baby, and the chaplain was helping her through the process. My pastor friend, who knew the doctor pretty well,
said he did something then (this was about 20 years ago) that he probably wouldn’t have the guts to do today: namely, he went up to surgery, put on a set of scrubs and cap and mask, and went in to the operating room where the doctor was doing a hysterectomy. He told the surgeon that he’d gone off half-cocked and hoped he’d reconsider the order he’d written. The doctor was understanding (and humble) enough to benefit from the conversation, and he did indeed rescind the order.

In closing, it might be worth suggesting a way that physicians can inquire about the spiritual concerns of their patients. In history taking, the simple mnemonic SPIRIT (1) can bring to mind six areas of inquiry:
S – Do you have a Spiritual belief system?
P – Do you have any Personal spiritual Practices?
I – Integration: Are you part of a spiritual community?
R – Do you have any Religious restrictions?
I – Does your faith have Implications for medical care?
T – (Near the end of life) What about Terminal events planning?

Approached with tact and sensitivity, most patients do not mind such inquiries, and the information obtained is often valuable in helping care for patients and attend to their needs and desires. I’ve also found it worthwhile, when a patient is a member of a religious community, to ask if they would like to have their pastor or rabbi made aware that they were in the hospital. If so, the nurse could contact the appropriate clergy. Before privacy became a big issue, hospitals used to keep lists of patients’ religious preferences that could be consulted by visiting clergy—but by law, that happens no more. Yet I have found that clergy welcome knowing when their parishioners are hospitalized.

When I was a first-year medical student, I went to India on a program called the Experiment in International Living, in which I lived with five Indian families. As you may know, Indians greet one another with hands together—hands held as depicted in Albrecht Durer’s famous etching of the Hands—as they bow slightly and say “Namaste.” I was impressed at that time, and have continually been impressed since, with what an appropriate symbol that remains of the totality of life. You can regard the two hands as symbolic of faith and reason. Both are needed, in balance, in our lives. Carrying that analogy a bit further, it could apply to balanced care of our patients: we need medicine and religion, physicians and pastors, to adequately care for the whole person.


**Reader comments**

**Dear Dr. Roberts:**

Just a quick note to say how much I’ve enjoyed reading the Proceedings and what a good job you’ve done with the editing. I’ve liked the “Facts and Ideas from Anywhere” column in particular, as it lets me catch up in a number of valuable fields. I’m a regular reader of JAMA and Journal of the American College of Surgeons, and reading your column helps me keep up.

—JOSEPH VANDERVEER, MD, Phoenix, Arizona
A 49-year-old hypertensive woman with cardiac failure, due to a nonischemic cardiomyopathy with a left ventricular ejection fraction of 35%, had normal sinus rhythm and left bundle branch block with a QRS duration of 148 milliseconds on her electrocardiogram. She received a biventricular pacemaker that initially functioned normally in the A-V synchronous mode with a P-R interval of 100 milliseconds. Four days later at a sinus rate of 100 beats/minute, alternate P waves were followed by an electronic biventricular pacemaker-initiated QRS and by a QRS with a left bundle branch block configuration in the absence of a pacemaker spike (Figure); i.e., the pacemaker failed to pace after alternate P waves.

The pacemaker had functioned normally at a rate of 118 P waves per minute, so an atrial rate exceeding the pacemaker’s programmed upper rate limit was not the problem. Instead, the problem was oversensing. The postventricular refractory period of the paced complexes was too short, allowing the pacemaker to sense the T wave of the pacer-induced complex as an R wave (interpreted by the pacemaker as a PVC). This caused the pacemaker to be reset and allowed the next sinus P wave to be conducted with the T wave of the native beat not sensed, an unusual cause of a bigeminal rhythm (1). The problem was solved by lengthening the postventricular refractory period of the paced complexes.

Closed traumatic flexor injuries of the hand involving the pulley mechanism are a relatively common injury seen in rock climbers but are very rare in nonclimbers, including bowlers. The injury was first described in 1990. Since then, several studies have shed more light on the diagnostic and therapeutic considerations. Early diagnosis of pulley injuries is crucial since delayed diagnosis can lead to limited range of motion, particularly at the proximal interphalangeal joint. Flexion contractures at the proximal interphalangeal joint have also been cited in the literature. We discuss a case of pulley injury in a bowler and briefly review the anatomy of the pulley architecture, mechanism of injury, imaging manifestations, and clinical management of this injury.

CASE REPORT

A 34-year-old man visited an orthopedist 3 weeks after sustaining an injury to the right long finger. The patient mentioned that his right long finger got stuck in a bowling ball at the time of throwing the ball. He had initially gone to the local emergency room, where radiographs were taken and did not show any evidence of fracture. Finger strain was suspected, and the patient was discharged. Later, at an orthopedist’s office, his right long finger was noted to be tender. He had pain directly over the A2 pulley. His proximal phalanx at its palmar aspect was somewhat swollen. The range of motion in this finger was intact. No neurologic or vascular deficits were noted. A strain or A2 pulley rupture of the right long finger was clinically suspected. Magnetic resonance imaging (MRI) was ordered for further clarification.

MRI of the right hand revealed prominent edema between the flexor tendons and proximal phalanx of the long finger, with abnormal separation of the flexor tendons from the proximal phalanx (Figures 1 and 2a). The A2 pulley appeared discontiguous, consistent with rupture (Figure 1). The metacarpophalangeal and interphalangeal collateral ligaments were intact. Mild to moderate tenosynovitis of the long finger flexor tendon was noted (Figure 2). No bony injury was identified.

DISCUSSION

The flexor pulley system is composed of focal thickened areas of the flexor tendon sheath (1). It consists of five annular pulleys (A1–A5) and three cruciate pulleys (C1–C3), which reinforce the structure of the flexor tendon sheaths (Figure 3). These pulleys also provide a fulcrum to elicit flexion and extension. Variations in the pulley anatomy have been reported; however, the A2, A3, and A4 pulleys are relatively constant in their anatomic locations (2). A2 and A4 pulleys are most important biomechanically, since the compromise of one or both of them can lead to significant loss of power and “bowstringing” of the flexor tendon in relation to the bone (3).

Bollen and Gunson first described injury to the pulley mechanism in 1990 after examining 67 rock climbers in Britain. Pulley rupture is relatively unique to the rock climbing population, mostly because of the stress involved. One of the two key positions in rock climbing is the crimp position. In this position, the distal interphalangeal joints are extended, the proximal interphalangeal joints are flexed, and the metacarpal joints are extended. The carpal bones are rotated, which puts

Figure 1. Axial short T1 inversion recovery (STIR) image demonstrates prominent edema (dashed arrow) between the flexor tendons and proximal phalanx of the long finger with abnormal separation of the flexor tendon from the proximal phalanx. Rupture of the A2 pulley was also noted (arrow).
increased stress on the ring finger, which along with the long finger is most often involved in injury. Imaging plays a crucial role in diagnosing injury to the pulley mechanism because the clinical exam is often limited by pain and soft tissue swelling of the involved finger (2, 4, 5). Evaluation of the injury by ultrasound, computed tomography (CT), and MRI has been described.

Klauser et al designed a study using 64 extreme rock climbers with finger injuries and evaluated the distance between the flexor digitorum profundus (FDP) tendon and the adjacent phalanx (TP distance) using ultrasound to indicate the presence of bowstringing. The symptomatic fingers with evidence of bowstringing on ultrasound were confirmed with MRI. The pulley thickness was <0.3 mm in nonruptured pulleys in asymptomatic fingers. Incomplete rupture, complete rupture (A2 or A4), or complete combined rupture (A2 and A3) demonstrated a TP distance of at least 0.9 mm. Ultrasound was 98% sensitive and 100% specific for depicting finger pulley injuries. One of the biggest drawbacks of ultrasound is interoperator variability (3, 5). However, its low cost and real-time imaging of anatomic structures make it an attractive option.

Similarly, Le Viet et al used CT scans performed at 1.5 mm slice thickness to image the involved fingers as well as the contralateral asymptomatic fingers. Imaging was performed in both passive and active/dynamic positioning. The dynamic images were found to be superior for diagnostic purposes. Although the sample size in the study was small (7 patients), the study successfully identified pulley injuries in all cases. They noted lack of adherence of the FDP tendon to the adjacent bone (bowstringing) in the symptomatic digits and an absence of bowstringing in the contralateral digits. Additionally, fibrous tissue was noted to be interposed between the phalanx and the FDP tendon. Several advantages of CT scans were noted over MRI, including lower cost with CT, better resolution (although this is debatable since MR technology has advanced since the original paper was published), and dynamic imaging (3, 6).

Finally, MRI has been regarded as the gold standard by several authors (3, 7). Hauger et al simulated pulley injuries on cadavers and compared MRI, ultrasound, and CT techniques by their ability to directly visualize partial and complete rupture of the pulleys and also their ability to detect the indirect sign of pulley system lesions. The indirect sign consisted of measuring the distance between the bone and the FDP tendon in extension, flexion, and forced flexion. They found MRI to be the most accurate in directly visualizing pulley abnormality, especially the A4 pulley, whereas CT was the least accurate in visualizing direct rupture of the pulleys. All three modalities were deemed similar in detecting an indirect sign of pulley injury. Additionally, MRI can help distinguish between tendonitis, peritendon inflammation, and partial ruptures (2). One of the major limitations with MRI is the motion artifact related to forced flexion. Use of dedicated surface receiver coils can reduce this motion and yield better imaging of the pulleys. MRI has also been used in determining adequate treatment of pulley lesions (7–9).
The therapeutic management of pulley injuries has not yet been clearly defined (3). Schoffl et al proposed a grading scheme for closed pulley injuries based on prospective evaluation of 604 climbers, and that has served as a therapeutic guideline. Grade I injuries consist of pulley strains with no increased dehiscence between the bone and FDP tendon. Grade II injuries consist of complete rupture of the A4 tendon or partial rupture of the A2 or A3 tendon. Grade III injuries consist of complete rupture of A2 or A3. Grade IV injuries consist of multiple ruptures (as A2/A3, A2/A3/A4) or single rupture (as A2 or A3) combined with lumbrical muscle or collateral ligament trauma. Schoffl et al treated the Grades I to III injuries conservatively with immobilization of the affected fingers with a splint for 2 weeks and then treatment consisting of early functional therapy with pulley protection. Grade IV injury was managed with surgical repair. The surgical technique proposed by Widstrom et al, which consists of free transplant of the palmaris longus tendon, was favored over other techniques (2, 7).

A chordoid glioma is a rare low-grade tumor that arises from the anterior wall or roof of the third ventricle. It is postulated that this tumor originates from the ependymal cells of lamina terminalis (1). These slowly growing tumors are more common in females and are predominantly seen in the adult population. Most commonly, this tumor presents with clinical signs and symptoms of obstructive hydrocephalus to include nausea and headache (2), although endocrine imbalances, visual disturbances, and dysautonomia have also been reported.

The best imaging diagnostic tool for evaluation of chordoid gliomas is magnetic resonance imaging (MRI) of the brain with gadolinium. Typically, these tumors are well circumscribed, round or oval in shape, with T2 images showing iso- to hyperintense third-ventricle masses with avid homogenous enhancement (2) (Figure 1). Cystic changes are infrequently seen within the periphery of these tumors (3). On computed tomography (CT) scans, a chordoid glioma presents as a hyperattenuating mass arising from the third ventricle that homogeneously enhances following contrast administration (Figure 2).

Differential considerations for an anterior third ventricle mass in an adult include a colloid cyst, germinoma, ependymoma, macroadenoma, and chordoid glioma. A colloid cyst is predominantly a nonenhancing cystic lesion located at the foramen of Monro. Ependymomas usually extend into the third ventricle centered at the foramen of Monro. Macroadenomas are enhancing masses involving the pituitary gland. Germinomas also arise from the pituitary stalk. Therefore, based on the imaging characteristics of this lesion, a chordoid glioma is favored.

Complete surgical resection is considered the treatment of choice for these neoplasms. The deep anatomic location of these tumors places the patient at increased risk of surgical morbidity and mortality. Although the neoplasm is low grade, incompletely resected tumors will continue slowly growing and may require later re-resection with the possibility of poorer clinical outcomes (3).

Our patient initially presented with symptoms of visual disturbance, endocrinopathy, and pituitary dysfunction. Following surgery, the patient's symptoms improved. Radiographic follow-up continues to monitor for tumor recurrence or growth.

Figure 1. MRI images of chordoid glioma. (a) T2 axial, (b) postgadolinium T1 axial, (c) postgadolinium T1 coronal, and (d) T1 sagittal MRI images show a multilobulated homogeneously enhancing mass centered within the region of the anteroinferior third ventricle (arrow). On T2 images, cystic peripheral changes were also present. This lesion was pathologically proven to be a chordoid glioma of the third ventricle.

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surgical resection and stereotactic radiosurgery, the patient experienced improvement in vision, an unchanged endocrinopathy, and no newly acquired pituitary dysfunction.


Figure 2. CT images of chordoid glioma. (a) Precontrast and (b) postcontrast CT images reveal an enhancing mass arising from the inferior recess of the third ventricle (arrow).
A 64-year-old man presented for outpatient evaluation of multiple cutaneous skin lesions that began as erythematous macules approximately 1 year earlier and progressed to areas of brownish hyperpigmentation. Review of systems was significant for fever, night sweats, fatigue, and epistaxis. Physical examination demonstrated bilateral inguinal lymphadenopathy. Bone marrow and lymph node biopsies were subsequently performed and demonstrated evidence of blastic plasmacytoid dendritic cell neoplasm. Baseline 18-fluoro-2-deoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) showed FDG uptake within enlarged left iliac and bilateral inguinal lymph nodes, as well as moderate splenomegaly.

The patient received one cycle of the EPOCH regimen (etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone) and three cycles of hyperCVAD (course A, cyclophosphamide, vincristine, doxorubicin, and dexamethasone; course B, methotrexate and cytarabine). He initially tolerated chemotherapy without evidence of toxicity or opportunistic infection. A posteroanterior chest radiograph obtained following treatment demonstrated an irregular opacity in the left upper lung zone (Figure 1). Subsequent contrast-enhanced chest CT showed an irregular opacity in the anterior segment of the left upper lobe consisting of central ground-glass opacity surrounded by consolidation in a “reversed halo” configuration (Figure 2). Follow-up PET/CT showed intense FDG uptake within the region of consolidation, but only minimal FDG uptake within the central ground-glass opacity (Figure 3).

Bronchoscopy and bronchoalveolar lavage demonstrated one colony of fungal organisms from the genus Paecilomyces, and a regimen of Augmentin and voriconazole was initiated. A left upper lobectomy through video-assisted thoracoscopic surgery was subsequently performed and showed fungal organisms of the order Mucorales. Augmentin was discontinued, and antifungal therapy was modified to amphotericin B and posaconazole.

**DIAGNOSIS:** Pulmonary mucormycosis.

**DISCUSSION**

Mucormycosis is an infection by fungal organisms from the class Zygomycetes, most commonly those within the order Mucorales. Six clinical syndromes of mucormycosis have been described, including rhinocerebral, pulmonary, abdominopelvic, cutaneous, disseminated, and miscellaneous forms. Pulmonary infection is the second most common clinical syndrome, accounting for approximately 30% of cases of mucormycosis (1).

The most common symptoms at the time of presentation include fever, cough, dyspnea, chest pain, and hemoptysis. Risk factors for the development of mucormycosis include immunosuppression, hematologic malignancies, solid organ and stem cell transplantation, graft-versus-host disease, diabetes mellitus, chronic renal failure, treatment with deferoxamine, and severe burn injuries (2). Pathology specimens typically demonstrate...
broad and irregular hyphae and random branching at right angles. Additional findings such as vascular invasion, thrombosis, and necrosis may be present (3).

Treatment of pulmonary mucormycosis may include medical and/or surgical therapies. Medical therapy primarily involves amphotericin B and posaconazole. Although effective in the treatment of aspergillosis, voriconazole is not effective in the treatment of mucormycosis (4). Surgical therapy, such as wedge resection, lobectomy, and pneumonectomy, in combination with medical therapy, has been associated with lower mortality rates. When fatal, the most common causes of death include fungal sepsis, respiratory failure, and hemoptysis (5).

The most common finding on chest radiographs in patients with pulmonary mucormycosis is segmental or lobar consolidation, which may progress to involve multiple lobes over time. Consolidation, which may represent pneumonia, hemorrhage, or infarction, may also involve multiple lobes at the time of initial presentation. Solitary or multiple pulmonary nodules or masses, with or without cavitation, may also be present. Pleural effusions have been described. Chest CT typically confirms these findings and may demonstrate additional findings not discernible on chest radiography. The air-crescent sign, characterized by a crescentic collection of air interposed between the lung parenchyma and centrally necrotic lung, may be present in the setting of invasive mucormycosis but is seen less frequently than in invasive aspergillosis. The CT halo sign, seen as central consolidation surrounded by ground-glass opacity, may be present (6). The reversed halo sign, characterized by central ground-glass opacity surrounded by consolidation, has also been reported in cases of pulmonary mucormycosis. Although initially described in cryptogenic organizing pneumonia, this radiologic sign has also been described in other causes of pulmonary infection such as bacterial pneumonia, tuberculosis, aspergillosis, and paracoccidioidomycosis, as well as other entities such as Wegener granulomatosis, sarcoidosis, lymphomatoid granulomatosis, and pulmonary infarction (7, 8). Additional findings such as ground-glass opacities in the lung parenchyma, endobronchial lesions, and chest wall lesions may also be identified on CT (6).

Anomalous origin of the right coronary artery from the pulmonary trunk demonstrated by electrocardiographically gated computed tomography coronary angiography

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A anomalous origin of the right coronary artery (RCA) arising from the pulmonary trunk (PT) is rare, with an expected incidence of 0.002%. Numerous modalities are available to aid in establishing the diagnosis, including echocardiography, digital subtraction angiography, magnetic resonance angiography, and computed tomography coronary angiography (CTCA). We describe a case of anomalous origin of the RCA in a 14-year-old girl, which was diagnosed with electrocardiographically gated CTCA.

CASE PRESENTATION

A 14-year-old girl presented for outpatient cardiologic evaluation with the chief complaint of dizziness for several months. The dizziness was exacerbated by physically demanding activities such as volleyball and soccer. She denied symptoms such as headache, chest pain, or apparent cardiac arrhythmias.

Physical examination revealed no abnormality. A baseline 12-lead electrocardiogram demonstrated normal sinus rhythm. The origin of the RCA could not be visualized on echocardiography. Electrocardiographically gated CTCA performed on a GE Lightspeed VCT scanner demonstrated an anomalous origin of the RCA from the PT (Figures 1 and 2).

The patient underwent surgical reimplantation of the anomalous RCA into the aorta (Figure 3). Six weeks following reimplantation, a cardiac stress test was normal, and she was released to resume full activities.

DISCUSSION

Variations in coronary artery anatomy are common in the general population. However, the term anomalous is used to describe any variation that is present in <1% of the population. Congenital coronary artery anomalies are present in approximately 0.6% to 1.3% of adults undergoing coronary angiography and rarely involve the RCA (1). Of anomalies involving the RCA, a high anterior take-off from the aorta is most common and is usually asymptomatic. Ectopic origin of the RCA from the noncoronary sinus, left coronary sinus, and PT also occur, though less frequently.

Anomalous origin of a coronary artery from the PT, of which four types have been described, is extremely rare in the general population. An anomalous left coronary artery arising from the PT is the most common of these and typically results in left ventricular ischemia and heart failure early in life. Anomalous RCA arising from the PT is rarer still, with an estimated incidence in the general population of 0.002% (2, 3). Only about 70 cases have been reported (4). Anomalous origin of both coronary arteries from the PT and an accessory coronary artery that arises from the PT have also been described and are usually fatal early in life.

Cases of anomalous origin of the RCA from the PT are usually treated surgically. The most common surgical procedure, performed on over half of all documented cases, is a button-type excision of the anomalous RCA in the PT with reimplantation into the aorta (4). Intrapulmonary tunnel repair, consisting of an intrapulmonary artery baffle with an autologous pericardial patch, has also been described. Additional surgical techniques...
include complete ligation of the anomalous RCA proximally with insertion of a saphenous vein conduit from the aorta to the distal RCA (5–9).

2. Brooks HSJ. Two cases of an abnormal coronary artery of the heart arising from the pulmonary artery: with some remarks upon the effect of this anomaly in producing cirsoid dilatation of the vessels. *J Anat Physiol* 1885;20(Pt 1):26–29.
A 21-year-old man with no significant past medical history presented to the emergency department with sudden-onset left upper and lower quadrant pain, which he described as being sharp and nonradiating. He also complained of nausea and dry heaves. Examination revealed left lower quadrant and left flank pain on palpation with slight protrusion of the left flank. There were no palpable masses. Urinalysis revealed 3+ blood. Computed tomography (CT) of the abdomen revealed a 2 mm obstructing stone in the distal left ureter (not shown), which was likely the source of the patient’s pain, and a heterogenous mass in the retroperitoneum centered within the mesenteric root containing multiple coarse internal calcific deposits (Figure 1). The mass was relatively well delineated of the inferior mesenteric artery from its origin (arrows) without luminal compromise. Again seen is the well-circumscribed nature of the mass and internal calcific deposits.

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circumscribed and encased the inferior mesenteric artery without appreciable extrinsic mass effect (Figures 2 and 3). The mass was subsequently biopsied by CT guidance, and histopathology was consistent with a ganglioneuroma (Figure 4). The neoplasm was resected in its entirety.

Ganglioneuromas are a rare neoplasm of neural crest cell origin. They are typically benign but can undergo malignant transformation in rare instances. The retroperitoneum and posterior mediastinum are the two most common locations for a ganglioneuroma. Patients of all ages are affected, but it is classically seen in adolescents and young adults. Patients are usually asymptomatic but can present with vague abdominal pain. Prognosis is usually excellent after complete surgical excision of the mass.


Figure 4. Photomicrographs of the specimen showing (a) a prominent background of wavy collagen fibers and Schwann cells and (b) mature ganglion cells (arrow), consistent with a ganglioneuroma.
Malignant transformation of endometriosis within the urinary bladder

Shannon Mann, DO, Purvak Patel, MD, Carolyn M. Matthews, MD, Karen Pinto, MD, and Julie O’Connor, MD

Although endometriosis of the pelvic organs is common, endometriosis of the urinary bladder is extremely rare. Malignant transformation of atypical endometriotic foci is an uncommon but well-documented sequela, occurring in approximately 1% of cases. This article reports the fourth case in the English literature of clear cell carcinoma arising from foci of endometriosis within the posterior bladder wall.

Endometriosis, the presence of endometrial tissue outside of the uterus, is usually found in the ovary; the most common extraovarian site is the rectovaginal septum (1). The urinary bladder is involved in <1% of extragonadal endometriosis. Sampson documented the association of endometriosis with malignant tumors in 1925 and outlined three criteria for the diagnosis of malignant transformation: 1) the coexistence of carcinoma and endometriosis at the same site, 2) histological similarities between the carcinoma and endometriosis, and 3) exclusion of a malignant tumor elsewhere (2). In 1953, Scott established the additional requirement of a continuum between benign and malignant epithelium (3). These criteria have been challenging to capture within the same histologic section, but were successfully met in this case.

Seven cases of malignant transformation of endometriosis of the urinary bladder have been published: three involved endometrioid adenocarcinoma, one involved endometrial stromal sarcoma, and three involved clear cell carcinoma (1, 2, 4–7). Here we report the fourth case of clear cell transformation of vesical endometriosis found within the English literature.

CASE REPORT

A 54-year-old Caucasian woman presented with gross hematuria and a recent history of irregular menses. She was otherwise well and not on hormone replacement therapy. On endovaginal sonogram, a large hypervascular mass arising from the posterior wall of the urinary bladder was noted (Figure 1). This finding suggested a mucosal malignancy such as a transitional cell carcinoma. Also found was a 6.1 cm cyst of the right adnexa that was thought to be functional.

A delayed-contrast enhanced computed tomography (CT) examination demonstrated a mass within the bladder lumen extending from the posterior bladder wall and into the bladder lumen (Figure 2). There was associated focal wall thickening along the posterior bladder wall surface abutting the anterior surface of the lower uterus/cervix region. A clear fat plane was not visible, and tumor invasion into the adjacent uterus was suggested. The wall thickening along the bladder wall likely represented the endometriotic foci.

A transurethral resection of the bladder tumor was performed. The histology of the resection showed clear cell carcinoma involving the bladder wall, bladder mucosa, and submucosa with adjacent extensive endometriosis. The carcinoma was CK7 positive, CK20 negative, WT1 negative, P63 negative, and PAX8 positive, indicating probable Mullerian origin, with a metastasis from a primary clear cell carcino ma of the lower uterine tract unable to be ruled out.

The patient was taken back to the operating room for a total abdominal hysterectomy with bilateral salpingo-oophorectomy, cystectomy, lymph node dissection, and anterior vaginal wall

Figure 1. Transverse view through the bladder on an endovaginal sonogram with color Doppler analysis reveals hypervascular flow within the mass (arrow).

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resection. Residual clear cell carcinoma was identified histologically in association with endometriosis that involved the posterior bladder wall into the outer half of the muscularis propria (Figure 3). The tumor had a papillary, glandular, and cystic architecture with individual tumor cells having eosinophilic or clear cytoplasm with prominent hobnailing. The sections with tumor showed a continuum between benign endometriotic foci and malignant epithelium (Figure 4). Atypical epithelium within endometriotic foci was identified adjacent to the tumor and in other areas. These findings supported the idea that the clear cell carcinoma originated from malignant transformation of preexisting endometriosis within the bladder wall.

DISCUSSION

Endometriotic foci can involve the genitourinary tract in up to 20% of cases. The urinary bladder is the most common genitourinary site. Endometriosis predominantly occurs on the serosal surface of the dome of the bladder. These foci can progressively invade through the inner layers of the bladder wall and can present as an intramural mass. This can be indistinguishable from a primary bladder neoplasm on imaging studies (8, 9).

Imaging features of malignant transformation of endometriosis are not well defined in the literature. On ultrasound, the absence of low-level echoes and the presence of nodularity are suggestive of malignancy. Mural nodules within an endometrioma that demonstrate postcontrast enhancement on magnetic resonance (MR) imaging are highly suggestive of malignant transformation. Dynamic subtraction MR imaging is useful in detecting small mural nodular enhancement in a background
of intrinsic T1 hyperintensity (a normal feature of an endometrioma). Enlargement of an endometrioma with loss of T2 "shading" (a relatively normal feature of an endometrioma) is also suggestive of malignant transformation (9–13).

The pathophysiology that leads to malignant transformation of endometriotic foci is not well understood. Endometriosis is generally considered to be a result of implantation or metaplasia, but is not considered neoplastic (14). Two plausible hypotheses have been proposed to explain the relationship between endometriosis and intraperitoneal cancer: 1) genetic defects allowing endometriotic implants to thrive and malignantly transform, and 2) defects in immune function allowing endometriosis to grow, leaving the patient more susceptible to subsequent malignant transformation (15).

It is known that extragonadal endometriosis occurs significantly less often than endometriosis of the ovary. More than 200 published cases of vesical endometriosis have been described, making the urinary bladder the most common urinary tract site of involvement. Vesical involvement includes superficial or deep tissue layers and adjacent perivesical soft tissue (14). Most vesical endometriosis occurs in the reproductive age group, but anecdotal cases have been described in postmenopausal women on hormone replacement therapy and rarely in men receiving estrogen therapy for prostate cancer.

The mean age of patients with ovarian clear cell carcinoma is 57 years old. Approximately one third of ovarian clear cell carcinomas can be associated with endometriosis (16). This raises the question of whether endometriosis should be considered a premalignant condition. Studies have shown that carcinomas associated with endometriosis are usually a lower stage, are in a younger population, and have a better prognosis than similar tumors unrelated to endometriosis. Clear cell carcinoma is the most common tumor complicating ovarian endometriosis, and endometrioid adenocarcinoma is the second most common (14). Approximately 90% of cases of extraovarian endometriosis lead to endometrioid adenocarcinomas, with only a few reported examples of clear cell carcinomas (14).

In making a diagnosis of malignant transformation of an endometriotic foci, it is imperative to establish the criteria described earlier. The continuum between benign and malignant epithelium within the lesion needs to be established, as outlined by Scott. Endometriosis must be distinguished from urachal glandular remnants and primary vesical adenocarcinoma (3). CD10 is positive in endometrial stromal cells and can be used as a helpful marker in suspected extraovarian endometriotic sites (1). Vesical mullerianosis encompasses three lesions: endometriosis, endocervicosis, and endosalpingiosis. Malignant transformation of endocervicosis or endosalpingiosis is considerably less common and must be distinguished from malignant transformation of endometriosis. Attention to architectural and cytologic features is key to making the correct diagnosis (1, 17).

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References

100,000 Hearts: A Surgeon’s Memoir by Denton A. Cooley, MD

Austin, TX: Briscoe Center of American History, 2012.
Hardcover, 323 pp., $29.95.
Reviewed by Charles Stewart Roberts, MD

Each time I opened Denton Cooley’s memoir, intending to breeze through a couple of chapters, I could not close it without advancing 100 pages. Some chapters, such as the “Reconciliation with Mike,” I read twice. No cardiac surgeon could be indifferent to this book. It is a superb memoir of a gifted human being who rose to the peak of his profession. As an intern at Hopkins in 1944, Cooley found cardiovascular surgery a paltry field; he is leaving it a blooming one of his profession. As an intern at Hopkins in 1944, Cooley found cardiovascular surgery a paltry field; he is leaving it a blooming one of his profession.

The first thing that strikes me about the book is its thoroughness. Cooley seems to cover life from early to late, including the highs and the lows, with a full range of telling photographs. In the appendices, we find diagrams, a glossary, various lists (personal contributions to cardiovascular surgery, inventions and products, and selected publications), and a curriculum vitae. The beauty of the book, however, is in the story, told as if he is there in the room.

A cardiac surgeon, Dr. Michael D. Crittenden, with whom I worked at the National Institutes of Health some 25 years ago, used to say, “Cardiac surgery is a brutal business.” For a long, successful career in cardiac surgery, physical stamina is necessary, as well as a kind of emotional resilience, both of which Cooley clearly had. He was a gifted athlete who worked as a surgeon from 6:00 am to 8:30 pm daily for decades—one of the few who were able to continue operating beyond the age of three score and ten. He appears to have lived by the dictum Labor omnia vincit, which means “Labor conquers all.”

Along with endurance, Cooley had that human quality that allowed him to take in stride the brutal lows in cardiac surgery, along with the wonderful highs. Osler called that quality aequanimitas, or equanimity (1). The old television show, Wide World of Sports, used to open with the phrase, “The thrill of victory . . . and the agony of defeat.” I knew one surgeon who would cry in his office after a patient died. Another would hardly speak for a week. Another would take it out on subordinates. Cooley shares with us that a round of golf in the open air helped him move forward.

Thomas Jefferson founded a university; Cooley founded an institute. One expects that the Texas Heart Institute will endure. As a natural leader, Cooley also seems to have lived by the Jeffersonian recommendation to “take things by the smooth handle.” In his autobiography, Dr. Christiaan Barnard, the South African who later performed the first heart transplant, made these observations of Cooley during a visit to the Texas Heart Institute as a young surgeon:

> It was the most beautiful surgery I had ever seen in my life. Every movement had a purpose and achieved its aim. Where most surgeons would take three hours, he could do the same operation in one hour. It went forward like a broad river—never fast, never in obvious haste, yet never going back. . . . Dr. Cooley’s skill was matched by his grace and kindness toward me. He invited me into his theater, showed me everything, and politely answered all questions (2).

Nearly every cardiac surgeon in North America whose surgical career overlapped that of Denton Cooley can find some connection to him. I am no different. Cooley’s book on Techniques in Vascular Surgery, coauthored with Dr. Don C. Wukasch, was my go-to book in vascular surgery (3). Published in 1979, the prose is simple and clear and the illustrations are superb. And yet it is surely one of Cooley’s minor publications.

Another connection was more personal. As an Emory medical student, I spent a month as an extern at Duke in 1985 and happened to board in the same home in Durham in which one of Cooley’s daughters lived while receiving treatment at Duke. The homeowners, who had no children, were very fond of her and lamented her early death, which Cooley described poignantly in his memoir, some 30 years later, as the greatest tragedy of his life.

Cooley spent a year at the Royal Brompton Hospital in London, and his description of that year is delightful. I too spent a year there (1997–98), and my mentor, Mr. Christopher Lincoln, occasionally spoke of Cooley—how he became a “locum consultant” during the medical leave of the thoracic surgeon Oswald Sydney Tubbs, how he had a full operative “list,” and how he wrote in a large handwriting. The impression Cooley made at the Brompton had lasted decades.

In 1999, my chief at the University of North Carolina, Dr. Benson R. Wilcox, handed me a letter that he received from Cooley concerning a book I wrote (4). The letter, handwritten by Cooley, reads:

> Dear Ben,

Not knowing Charles Roberts personally, I am writing you to express my enjoyment of reading his book, Stoking the Fire. Of course my appreciation comes from having spent a similar year in London with Russell Brock and the other surgical dignitaries at the Brompton and the U.K. Dr. Roberts’ observation and descriptions brought back vivid memories which I hold. As an author he has a real talent and may consider a future as a John...
Grisham! Please extend my congratulations and encouragement to him. I wish that I had kept a full diary of my year. I can still quote sayings from Brock, Tubbs, Barrett, and Price Thomas.

I hope the summer is going well—

Sincerely yours,

Denton

The passages in Cooley’s memoir concerning Dr. Michael E. DeBakey (“Mike” as he is called in the book) are interesting to many of us who have observed this rivalry in Houston from afar. Of course, the Cooley memoir represents one perspective. We will have no perspective from DeBakey, though I suspect he would disagree on many points, including various firsts in cardiovascular surgery. Nevertheless, their reconciliation, in the end, was good for the field of medicine. The photograph of the two surgeons together, shaking hands, late in life, is framed in my office, as a kind of inspiration. Both men are founding fathers of cardiovascular surgery in the 20th century.


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100,000 Hearts: A Surgeon’s Memoir by Denton A. Cooley, MD


Reviewed by Allen B. Weisse, MD

During the 1930s and 1940s, a group of outstanding surgeons arose to introduce extracardiac and closed-heart procedures for the relief of congenital and acquired heart disease. In the second half of the 20th century, especially after the introduction of cardiopulmonary bypass, a second generation arose, most of whom have now died: people like John Kirklin, E. Walton Lillehei, Christiaan Barnard, René Favaloro, Michael DeBakey, and Norman Shumway. Denton A. Cooley, now 91 years of age, remains the sole survivor from this group of pioneers. The term “living legend,” so often tritely applied to many individuals, in this case is the most apt description of this outstanding individual. He has now rewarded us with a highly informative and readable account of his professional and personal life.

Denton Cooley was born in Houston in 1920. In a description of his early years, Cooley informs us that he grew up in reasonably comfortable economic circumstances despite the fact that so many other Americans were suffering during the Great Depression. His father was a successful dentist; his maternal grandfather, a physician. Despite such relative affluence, early on Cooley developed a frugality that extended into his later life when he saved whenever he could and even resorted to blood donations to supplement his meager income as a houseofficer.

The relationship of any boy to his father is crucial and, in this respect, his father was far from ideal. Although Cooley “learned many of life’s important lessons” from his father, he describes the relationship as “complicated.” The successful dental practitioner at home was often intemperate and demanding, finally dying prematurely from the complications of alcoholism, as did Denton’s beloved older brother. In contrast to this, Cooley was a remarkable athlete as well as a scholar. This combination of gifts won him recognition on and off the field despite a shyness that seems so out of tune with his later reputation as a successful cardiovascular surgeon.

From the age of 17, upon graduation from high school, the young Denton embarked on a decade and a half–long professional journey that molded him into a surgeon of great promise. The series of events that filled his life during this time, either by choice or by chance, in summary read like the scenario of a surgical Horatio Alger story.

After high school Denton attends the University of Texas (Austin) as a premedical student. Then, on a dare, he visits a nearby emergency room where the intern allows him to suture his first lacerations. He switches to premed. He begins medical studies at the University of Texas Galveston Branch. Academic unrest there motivates him to go elsewhere. Although he had not previously settled on this choice, his family physician, who has friends at Hopkins, directs him to Baltimore. At Hopkins he attracts the attention of Alfred Blalock, who becomes the father figure so sorely missed in the past. Cooley eventually becomes Blalock’s chief surgical resident and assists at the first Blalock-Taussig procedure performed for tetralogy of Fallot. This experience is temporarily interrupted by 2 years of army service as a surgeon in Linz, Austria. After Hopkins he spends a year in London at the Brompton Hospital as senior surgical registrar under Russell Brock. When Brock’s associate is sidelined by tuberculosis, Cooley takes over the practice and doubles the number of cases performed on that service. In 1951, at the age of 31, he returns to the United States to begin a tumultuous 18-year relationship with his new chief, Michael DeBakey, at Baylor Medical School in Houston.

What is surprising is not that the relationship with DeBakey came to an end, but that it lasted as long as it did. Aside from outsized egos and equally large competitive spirits, the two men had little in common. When it came to research, DeBakey was usually inclined to the more traditional approach, beginning in the animal laboratory and then, only gradually, proceeding to clinical trials. For Cooley, his laboratory was often represented by the patients appearing before him on the operating room table. There he had the uncanny ability to assess the nature of the presenting problem, adopt a method of solving it, and do it faster and more successfully than anyone else.
DeBakey's interests and influence extended far beyond the surgical suite. He established and maintained close connections with Washington, serving on a number of policymaking panels. For example, he was instrumental in the establishment of the National Library of Medicine in Bethesda. At Baylor, he became chairman of surgery, then president, and then chancellor in establishing a first-rate medical institution. In contrast, Cooley's focus was mainly on the operating room where, in addition to the work on aortic aneurysms where he collaborated with DeBakey, he extended his expertise to congenital heart disease in response to the tremendous backlog of such cases that had developed in anticipation of open heart repair. He tackled the problem of open heart surgery in Jehovah's Witnesses by popularizing nonblood priming of the pump (introduced by Nazih Zuhdi), which also allowed for streamlining services to other patients awaiting such treatment. His administrative skills were devoted, in large part, to the formation and growth of the Texas Heart Institute. Cooley was also responsible for a number of surgical innovations and devices for use in heart surgery. He is the author or coauthor of over 1400 journal articles and eight textbooks.

Their treatment of subordinates was very different. DeBakey, in his quest for perfection, terrorized his housestaff, while Cooley attempted to lead by inspiring example. Yet trainees emerging from both programs established surgical societies in honor of their respective mentors. Excellent journals emerged from both camps (the Texas Heart Institute Journal under Cooley and the Methodist DeBakey Cardiovascular Journal under DeBakey).

No doubt challenged by the gifted newcomer, DeBakey often slighted his junior associate. Cooley recalls that he was excluded from plans to develop a total artificial heart. When a committee was established by DeBakey to plan for a transplant program, Cooley was again prevented from participation. As a result of such actions, a growing resentment developed in the younger man, long in advance of the debacle surrounding the implantation of a total artificial heart in Haskell Karp. This surgery was performed in April 1969. The patient survived 64 hours with the implanted device and another 32 hours after it was replaced with a donor heart.

In the months preceding this, it was not only Cooley who was chomping at the bit. Domingo Liotta, an Argentinean surgeon, had been hired in 1961 as a research fellow by DeBakey to develop a total artificial heart. When a committee was established by DeBakey to plan for a transplant program, Cooley was again prevented from participation. As a result of such actions, a growing resentment developed in the younger man, long in advance of the debacle surrounding the implantation of a total artificial heart in Haskell Karp. This surgery was performed in April 1969. The patient survived 64 hours with the implanted device and another 32 hours after it was replaced with a donor heart.

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A reading of Cooley's account of the affair is unlikely to change many minds. Some will continue to look upon Cooley as having performed an heroic act in a humanitarian effort to save a dying patient's life. What others cannot ignore is that in order to perform such a procedure, the support of the principal investigator (DeBakey) was required along with approval of the institutional human research committee at Baylor as well as that of the National Institutes of Health (NIH). None of these approvals were obtained.

Of course DeBakey, who was out of town when the surgery was performed, felt betrayed and was furious. He feared at one point that all the research support from the NIH would be withdrawn. Reviews were conducted by the American College of Surgeons, the National Heart Institute, and Baylor University. All three groups found grounds for censure, the most severe rebufke coming from Baylor. Cooley resigned his faculty position at Baylor. The break between Cooley and DeBakey was now complete. Despite repeated overtures from Cooley, DeBakey refused even to acknowledge his presence for 38 years until 2007 when peace was finally declared, with DeBakey accepting honorary membership in the Denton A. Cooley Cardiovascular Surgery Society and appearing to accept the award with a handshake from Cooley. This was shortly before DeBakey’s death in 2008, only 3 months short of his 100th birthday.

Although there are no new startling revelations to be found in Cooley's account, elsewhere, earlier in the book, are possible harbingers of his future behavior. He recalls that, while in the army, he performed a cesarean section without ever having done one before, and during his first operation for a complex skull fracture, a textbook he consulted was his only support in the operating room. At the Brompton he recalls accepting an assignment to perform a bronchoscopy when he had never done one previously. Of course, he succeeds in these escapades, making one wonder, in retrospect, about actions often deemed “daring” when they are successful and “reckless” when they are not. By 1969 restrictions on such autonomy were in place for the protection of patients while, admittedly, at times, the price paid was the stifling of initiative among medical investigators.

Cooley appears to have recovered from the artificial heart episode while hardly missing a beat. He seemed to follow in the footsteps of another prominent southerner, Confederate General Nathan Bedford Forrest, the cavalry commander whose motto was “get there first with the most.” Cooley lists 33 personal firsts in cardiovascular surgery, although surgical scholars might take issue with some of these claims. However, even when not the first, Cooley indisputably followed up with the most. His telegram to Christiaan Barnard after the first human heart transplant characteristically read, “Congratulations on your first transplant, Chris. I will be reporting my first hundred soon.”

The title of the book attests to the success of that goal of 100,000 open heart cases performed by 2001 at the Texas Heart Institute, more than accomplished by any other surgical group in the world. Key to this accomplishment were equipment modifications, scheduling, and innovations such as nonblood pump priming. Not least of all these factors was Cooley’s own energy and enthusiasm. He reports overseeing as many as 30 operations daily, correcting 8 or 10 of the most difficult cases himself. He has personally repaired about 12,000 aortic aneurysms, a remarkable record in itself.

The strength of this book lies in both the candor and completeness of the memoir, with many gaps filled in for those of
us only slightly acquainted with Dr. Cooley’s past history. The lucid prose also makes the book as easy to understand for the general reader as for the professional. For those with medical backgrounds, several appendices are included for further reference. It is hard to find any faults with what Dr. Cooley has written. For those of us with historical bent, at times further background and other viewpoints might have been desired. However, a memoir, by its very nature, is a one-sided affair, and Cooley has done well by it.

The personal touches of the author are particularly engaging. Toward the end of the book he writes of his successful marriage and the joy taken in the five lovely daughters it produced. He reveals that he has made a lot of money, but he has also lost a lot. What he never seems to have lost is his sense of humor.

Once, as a defendant in a medical liability trial, he was asked by the plaintiff’s lawyer if he considered himself the best heart surgeon in the world. When Cooley answered in the affirmative, he was then asked if he was being rather immodest. “Perhaps,” Cooley replied, “but remember, I am under oath.”

And who could argue with that?

The reviewer, Allen B. Weisse, MD, is a retired professor of medicine at the University of Medicine and Dentistry, New Jersey. His most recent book, Notes of a Medical Maverick, was published in 2010.

The Top Five Regrets of the Dying: A Life Transformed by the Dearly Departing by Bronnie Ware


Reviewed by Beverlee Warren, MA, MS

A journey with one Australian caregiver’s experiences in palliative care brings us face to face with our own mortality. If we are willing, there is much to learn from those who have walked their final steps on this earth and been transparent about their regrets. Bronnie Ware’s memoir recounts her years of caregiving to the dying and the wisdom she received and painful personal growth that emerged from those experiences. It also stands as a warning to those in palliative care to guard against burnout.

The top five regrets of the dying are not surprising, but they are woven through the lives of the people Bronnie cared for in such a powerful way as to pull us into the emotion of the lament. The regrets are universal, and if we took the time to think for a moment, we would probably come up with similar statements. The challenge is to remember those axioms and care enough to change our behavior before we are at death’s door. Given the changes brought about in Bronnie’s life from exposure to the dying, learning from our experiences seems to be the theme of the book.

A secondary theme is the warning against burnout in caregiving. After several years in the profession, Bronnie suffered a catastrophic depression. She admits she overinvested emotionally in her dying patients to the neglect of herself and suffered the fallout of abandonment of her own needs. Bronnie’s account of her own emotional despair is likely a hazard inherent to caregivers, whether they support the ill or dying.

Despite the subject matter, this book is uplifting and encouraging with accounts of deep friendships with her patients and times of laughter and delight. In addition, the book is sprinkled with pithy wisdom: “Success doesn’t depend on someone saying yes, we will publish your book or no, we won’t. It is about having the courage to be you regardless” (p. 63); “We are given lessons to heal, though, not necessarily to enjoy” (p. 64); “Expressing our feelings is a necessity for a happy life” (p. 125); “If ever one wants to live in denial about the state of our society, avoid nursing homes. If ever you feel strong enough to look at life honestly, spend some time in one” (p. 135); “Loneliness isn’t a lack of people. It is a lack of understanding and acceptance” (p. 139); and likely her theme statement and the one that buoyed her up while empathizing with the suffering of her patients, “One of the most beautiful things I was learning through palliative care was to never underestimate anyone’s capacity for learning” (p. 154).

This book is an experience in living, not dying. We should probably read a book like this every 10 years to keep our focus on important relationships and objectives—the ones that will keep us from experiencing regrets when the final bell tolls. Of course, anyone serving in palliative care will likely feel camaraderie with Bronnie’s experiences and hopefully heed her warning about burnout.

My interest in this book was not only curiosity in what others were dying found to be regrettable so that I might not find myself in the same straits but also to find out what lessons Bronnie learned as a caregiver. I have been on both sides of the caregiving/care receiving coin. In 1988 my husband was diagnosed with Guillain-Barré syndrome. He was severely impaired for weeks and took months to recover strength and coordination. Our children were ages 11, 9, and 2, and I had lost a baby due to premature birth 7 months earlier. I understand how one can give to the point of self-neglect. I also understand how easy it is to empathize with the patient to a degree of emotional exhaustion. I suspect these two tendencies are pitfalls all extended caregivers risk. I understand now how to support those who are supporting the patient. Experience is an enduring teacher.

In 2008 I was diagnosed with breast cancer. I spent the next year in treatment—chemotherapy, surgery, radiation. I saw the sacrifices my family made through the eyes of the wounded one. I didn’t discover until months later that my daughter was living with the fear that I would be taken from her. She hardly left my side. Although I had an optimistic prognosis, this did not quell an unfounded fear in her mind that my demise was imminent. Thus, I learned how important it is to take the emotional temperature of caregivers and find out how they are doing. They are the shadow soldiers in the battle, where all the attention and support goes to the patient.
Whether experiencing life as the patient or the caregiver, I agree with Bronnie’s declaration, “What may appear as tragic situations to others were also great opportunities for growth and learning for the person involved” (p. 145). Like most people, I haven’t been left out of the proving ground of trials. Like Bronnie, I have chosen to grow and learn and have fought and found victory over sadness and bitterness. As Bronnie concludes and I agree, “So the best way to make the most out of life is to appreciate the gift of it, and choose not to be a victim” (p. 81).

If you have stayed with this review thus far, you are likely hoping for disclosure of the top five regrets of the dying. Hopefully, you have begun to ponder your own list and will find these affirming. 1) “I wish I’d had the courage to live a life true to myself, not the life others expected of me.” 2) “I wish I hadn’t worked so hard.” 3) “I wish I’d had the courage to express my feelings.” 4) “I wish I had stayed in touch with my friends.” 5) “I wish I had let myself be happier” (p. v).

This short work is in the self-help category. It certainly packs a lot of thought-provoking direction into an easy to read and entertaining format. If you read it, be prepared to have your thinking tinkered with.

Bronnie also has a website, www.bronnieware.com, which is a nice companion to her book. The website features a blog, gift shop, and information about her other professional activities.

The reviewer, Beverlee Warren, MA, MS, is senior medical librarian of the Baylor Heart and Vascular Institute at Baylor University Medical Center at Dallas.

Catharsis: On the Art of Medicine by Andrzej Szczeklik, MD

Hardcover, 172 pp., $20.00.
Reviewed by Joseph K. Perloff, MD

**Katharsis (Greek)** is defined as purgation or purification (Oxford English Dictionary) and refers to the Greek chorus that employed music, dance, poetry, and song to purify the soul. The nocturnal acts of healing in the temples of Asclepius employed purification to heal the sick.

Andrzej Szczeklik is a distinguished Polish cardiologist, clinician, research scientist, and chairman of the Department of Medicine at Jagiellonian University, Krakow, founded in 1364. In an enlightening foreword, Czeslaw Milosz, the Lithuanian-born Nobel Laureate in Literature (1980), praised Szczeklik as a learned physician with profound knowledge of the humanities and with a sensitivity to the moral limits that constrain the biomedical sciences. The boundaries of scientific knowledge are fluid, but boundaries do exist beyond which there are worlds inaccessible to science—the worlds of individual values, art, and faith. Plato, through poetic metaphors, captured truths inaccessible to empiricist research.

Szczeklik’s aim is to break down traditional boundaries. Medicine, he argues, is a skill derived from magic in which art and science are inseparably woven into a seamless humanistic, scientific, and cultural fabric that includes the biomedical and physical sciences, ancient mythic history especially Greek, music, morals, and ethics. **Catharsis** provides a unique picture of the eclectic but interrelated origins of the medical profession and the pivotal role it plays between life and death.

Major professions harbor fundamental features that reveal an inner core. In medicine, that feature is an encounter between two people—the patient and the doctor. The patient tells a story while the doctor listens. For the patient who does the telling, the story (case history) is of utmost importance. The doctor doing the listening is well aware that one day the roles may be reversed.

The doctor’s conversation with the patient is an interview designed to gather information—information about illness—a process that has been referred to as **anamnesis**, a Platonic reference to the vital means of gaining knowledge. Before doctors consider what might be wrong, they listen to a story from the past, a story about which they must be genuinely curious so the patient feels that someone, maybe for the first time, is truly interested. The doctor must talk the same language as the patient, **must enter the patient’s world** with its intimate hidden content. To diagnose illness, doctors rely on clinical manifestations, not causes. As the saying goes, “If you hear the sound of hooves, think of horses, not zebras.” Making a correct diagnosis is a skill that eludes rational expression.

But then, as Szczeklik points out, *medicine and art* originate from the same root—*magic*. Incantations were used to break spells and ward off illness. Hippocrates considered medicine an art, and Paracelsus argued that the universe was a living thing with man as a microcosmos built on the same principles as the macrocosmos.

When Alexander the Great was seriously ill, doctors did not dare treat him for fear of losing their lives if he were to die. And when Alexander consulted the Delphic oracle, she made no reply. On the island of Cos, Hippocrates didn’t consult the oracle, but instead analyzed his patients. Paracelsus believed that fate was determined by the stars that were overhead at the time of birth. Our fate, however, is not in our stars but in our genes—our magic genes—that serve as a Pythian oracle for prerrcorded information.

Coronis was unfaithful to Apollo, her husband, while pregnant with his child. Apollo persuaded his sister Artemis to kill his faithless lover with an arrow from her trusty bow, but as Coronis lay dying, she whispered to Apollo that by killing her, he was killing his unborn son. As the flames of the funeral pyre engulfed Coronis, Apollo tore the child from her womb. Szczeklik reminds us that thus came into the world Asclepius, the health-giver, the patron god of medicine.

Asclepius’ skill as a healer embodied him to restore the dead to life, but by resurrecting the dead, he overstepped the limits of human existence, a transgression for which Zeus struck him dead with a thunderbolt. How might Asclepius have
reacted to the practice of resuscitating the dead by restoring life to victims of sudden cardiac death?

The 20th century added about 25 years to the human life span. Here the doctor and patient share the same primeval dream—the search for a "youth gene," an elixir of life. Life without end? Intolerable! Eternal life must be combined with eternal youth lest we confront the fate of the Cumaean Sybil, shriveled and shrunken but still alive. What makes life bearable is the thought that one can leave it. "What is your desire, O Sybil?" "I want to die," she answered.

Alchemy was regarded as a sacred science whose irresistible attraction captivated Sir Isaac Newton. Substances shed their sacred attributes. Chemistry came into its own. Ancient therapies such as ritual reenactments of the creation allowed patients to be born anew, to start life over again. The snake caught man in its spell, and man took snakes into his world of charms. Pharaohs wore a snake on their foreheads. Snakes were coiled in every corner of the Temples of Asclepius in which the sick fell into prophetic dreams amid the silence and gloom of the sanctuary. Each night, the priest-doctor, dressed as Asclepius and attended by a snake and a retinue of servants, went from patient to patient in a procession remarkably like our time-honored ward rounds. By casting off its skin, the snake symbolized regeneration and has been associated with Asclepius ever since, winding around his stick as the symbol of the medical profession.

The act of healing was a ritual performed by symbolic laying on of the hands. After the nocturnal visit, the patient awakened free of illness, having undergone katharsis. By ritual purification, the sick were regenerated and freed of illness.

Children were also brought into the temples. The infant Cassandra and her brother Helenus were left in a sanctuary overnight. The next morning they were found entangled in coils of serpents who were licking their eyes and ears, thus endowing the siblings with second sight and second hearing, and the power to look into the future.

Szczeklik reminds us that the combination of serpent and stick had an expression in the Bible. The Lord said unto Moses, "What is that in your hand?" Moses said, "A staff." And the Lord said, "Throw it on the ground." He threw it on the ground, and it became a serpent. Moses ran from it. But the Lord said unto Moses, "Put out your hand and catch it by the tail." So Moses put out his hand and caught it by the tail, and it became a staff in his hand.

Since time immemorial, the stick has been associated with magic. Magical powers were ascribed to the caduceus, which changed everything it touched to gold. Prospero belonged to the higher order of magicians. Whosoever held Prospero's magic stick was the ruler. So why shouldn't a stick be found in the hand of Asclepius, the patron god of a profession rooted in magic? The stick of Asclepius is entwined by one snake. The stick of Hermes (Mercury), herald of the gods, is entwined by two snakes topped by a pair of wings.

It was not until the Book of Genesis that snake and man were separated. Thousands of years elapsed before snakes made a comeback. It was known that benzene consisted of six carbon atoms linked with six hydrogen atoms, but the structure of the benzene molecule puzzled organic chemists for over a century after its discovery in 1825. August Kekule, a German organic chemist, proposed that benzene wasn't a chain but a ring with one hydrogen atom attached to each carbon atom. The idea came to him in 1865 as he dozed by a fire and dreamed of the benzene molecule as a snake-like ring formed as each snake grabbed its tail in its mouth, thus closing the benzene chain to form a ring. The snake famously found its way into genetics as the serpentine spiral—the double helix—that contains the secret of life's regeneration hidden in the nucleus of every one of the billions of cells in our bodies with instructions on how to create its successor.

Early efforts were made to discover what lies hidden inside man, to plumb the depth of illness, to admit a ray of light into the darkness locked within the human body. In third-century BCE Alexandria, corpses were routinely dissected. Criminals were handed over to learned doctors for vivisection. Galen of Pergamon (129–216 AD) dissected all sorts of animals every day for most of his life, getting to know the innermost secrets of the body, but he never touched a human corpse because it was against the law to do so.

The great anatomist, Andreas Vesalius of Padua, revealed the world inside us in his monumental work De Humani Corporis Fabrica, seven volumes beautifully illustrated by renaissance masters. Vesalius performed the dissections himself, fighting off savage dogs while stealing corpses from graveyards. He kept in his bedroom bodies taken from graves or given to him after public execution. He encouraged students to familiarize themselves with patients and seize their bodies soon after death. Hans Holbein used as his model a corpse borrowed from the city guard in order to render the remarkable life-size rendition of Christ lying on his back tortured to death. Holbein returned the corpse at daybreak after spending all night painting. Dostoevsky was mesmerized by the Holbein painting.

In his chapter “Rhythm and the Heart,” Szczeklik reminds us that the world is overflowing with rhythms. Among primitive peoples, rhythm was associated with the beginning of life. We come into contact with rhythms from the moment we are born. Neutron stars send into the universe radio waves of great intensity and perfect regularity. The centers from which waves originate are called pulsars. The first pulse that stirred man to life may have been a response to pulsars of the universe. Circadian rhythm, the biologic clock located in the hypothalamus, is characterized by rhythmicity and is common to all species from fruit fly to man. However, of the many rhythms inside us, the heartbeat is the one we most care about because it has been considered the hallmark of life. One of the most distinctive features about the heart is autonomy—the independence of its rhythm. The unfailing necessity of the heartbeat is one of the few dogmas that enjoy equal popularity among both cardiovascular physiologists and the lay public. Interestingly, recent data from developmental biology have called into question this most established of physiological and cultural dogmas. The embryonic heart begins to beat 18 to 21 days after conception. At this stage, the heart is non-functional, i.e., it pumps no blood, but if the beat stops, the embryo dies.
In *Catharsis*, Andrzej Szczeklik foregrounds medicine as a skill derived from magic. Art and science are woven into a seamless fabric that dissolves traditional boundaries. The book provides contemporary physicians with access to humanistic sources that are the wellspring of their profession, and provides physicians with biomedical sources to which they have unwittingly but materially contributed.

The reviewer, Joseph K. Perloff, MD, is a cardiologist in the Ahmanson/UCLA Congenital Heart Disease Center, Los Angeles, California.

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*The Social Animal: The Hidden Sources of Love, Character, and Achievement* by David Brooks


Reviewed by Fran Roberts Willard

Over the last few decades, groundbreaking research by geneticists, neuroscientists, psychologists, sociologists, behavioral economists, and others has yielded new insights into the inner workings of the human mind. *New York Times* columnist and bestselling author David Brooks has synthesized this great wealth of data in his book, *The Social Animal*, in which he offers us a new and uplifting view of human nature.

Brooks asserts it is not our rational conscious mind that determines how successful and fulfilled we are in life, but rather it is our unconscious mind, that murky realm of passions, perceptions, social cues, genetic predispositions, drives, and character traits. While our conscious mind might yearn for wealth, status, and applause, that surface definition of success, it is actually our unconscious mind that holds the most sway in determining our character and our ability to build healthy, loving relationships and to achieve our dreams. In a way, we are the outcome of what is happening within us below our own level of awareness.

The good news is our unconscious mind is quite smart. Brooks pictures the conscious mind “as a general atop a platform, who sees the world from a distance and analyzes things linearly and linguistically,” whereas the unconscious mind “is like a million little scouts.” The job of these scouts is to be immersed in the landscape and to send back a constant flow of signals and generate instant responses. It’s from these scouts that we place value on things, that we feel a wave of affection when we see an old friend or outrage when we perceive a situation as unfair. They can save us from danger when we experience fear and lead us towards greater fulfillment. These signals help us interpret our world and guide us. Not surprisingly, people lacking in emotion tend not to lead well-organized lives and often fall into self-destructive or dangerous behavior.

If our emotions are the very foundation of reason, the conscious mind still has the ability to influence them; the two are intertwined. For example, our conscious mind might decide what to order on a menu, but our unconscious mind determines what food we like. Sometimes we have to consciously teach ourselves to like a certain food. It is by being aware of and educating our emotions that we are able to gain wisdom.

Contrary to popular thought, we are not primarily self-contained individuals, but rather we emerge out of our relationships. None of us are self-made. We are deeply interpenetrated with one another. We are social animals from birth. Brook writes:

The truth is, starting even from birth, we inherit a great river of knowledge, a great flow of patterns coming from many ages and sources. The information that comes from deep in the evolutionary past, we call genetics. The information revealed thousands of years ago, we call religion. The information passed along from hundreds of years ago, we call culture. The information passed along from decades ago, we call family, and the information offered years, months, days or hours ago, we call education and advice.

Brooks provides countless sources to back up his points, and this book could have been a dry, scientific read if not for a creative device he adopted from Rousseau to share information and occasionally add a touch of humor. He has created two characters, Harold and Erica, and has told their life stories—their formative years, their falling in love and marrying, their separate careers, their challenges, up until Harold’s death. This allows Brooks to explore the themes of attachment, parenting, education, love, relationships, culture, achievement, politics, morality, aging, death, and more. This is an ambitious book, to say the least.

Harold and Erica are not vivid, fleshed-out characters, but are meant to serve as concrete examples of what the research shows. Both characters come to possess strong noncognitive skills, which are often hard to measure but help determine character. Such skills inform some of the most important decisions we make in life, such as whom to marry and whom to befriend, what our likes or dislikes will be, and how we attain the drive to excel or the ability to delay gratification. As a parent of three young children, I was most interested in learning how we can build up those noncognitive muscles in our young.

Brooks emphasizes the importance of the mother-child bond. Even as a fetus, Harold was already listening to and memorizing the tone of his mother’s voice. At birth the bonding between them needs to begin in earnest, a rather rhythmic “conversation” using touch, tears, looks, smell, and laughter. Babies are born to interpenetrate with their mothers, to learn from them and to begin to build models in their heads of how to understand reality and to relate to others. With strong attachment with his mother or primary caregiver, the child will soon feel safe enough to begin to explore the world around him. Brook writes:

The delightful thing about Harold at this stage was that he was both a psychology major and physics major. His two main vocations were figuring out how to learn from his mother and figuring out how stuff falls. He’d look at her frequently to
make sure she was protecting him, and then go off in search of things to topple.

Securely attached children have parents that are attuned to them and mirror their moods. They have a huge head start in life, as studies show they later tend to handle stress well and have an easier time making new friends. They know how to build good relationships with teachers, which leads to greater academic success. And, this ability to form deep relationships paves the way for greater happiness in life.

Avoidantly attached children have parents who are emotionally withdrawn or unavailable, and they are unable to establish an emotional rapport. These children send signals out but nothing came back. They later have trouble developing close friends and suffer more stress and are unsure in social situations. Studies have borne out that early attachment patterns are a reliable indicator of competence at subsequent stages and of the quality of other relationships later in life, particularly romantic relationships. For example, men with unhappy childhoods find it difficult to choose a partner for them. He likes her waist-to-hip ratio and clear skin, and draws new conclusions. He will be a lifelong learner, imagining your partner as somehow enchanted. Brooks states

Both Harold’s conscious and unconscious minds kick into gear in assessing whether or not Erica would make a good life partner for him. He likes her waist-to-hip ratio and clear skin, both signs of health and fertility. Erica subconsciously is looking for signs of trustworthiness as her own primeval process demands. It will motivate her to choose a man not only for insemination but for continued support. It will entice her to marry a man slightly older, taller, and stronger than herself.

Falling in love is both rational and irrational and involves imagining your partner as somehow enchanted. Brooks states that such love is not so much an emotion as a motivational state: “A person in love is in a state of need,” a need for the other person. The unconscious mind wants limerence, a state of harmony in which we forget ourselves, lose the “skull barrier,” and merge with something or someone. This desire for limerence drives us to seek perfection in our crafts, to fuse with nature and with God. And, we seek it with another. Harold and Erica choose to marry.

Erica had a vastly dissimilar upbringing from Harold, and she had beaten the odds. Born to out-of-wedlock parents, she’d grown up in poverty and chaos. Her mother was Chinese and suffered from depression. Her father was Mexican. But Erica is tough and determined and had made one vital decision: she changed her environment. Brooks stresses the importance of the conscious mind to make such a change when one is stuck in a troubling situation. Change the environment and then let the new cues work for you. By getting herself enrolled in a charter school with new rules, codes, and expectations, Erica was able to extract herself from her environment and propel herself upward, eventually becoming a high official in a Democratic presidential administration after an illustrious business career.

By adulthood, she had developed self-control and self-discipline through her habits that would enable her to be a high achiever. It was not a question of willpower but of understanding the power of continuing to take small and repetitive action until that action is part of the unconsciousness. Fake it till you make it, so to speak.

Erica had also learned to perceive the world in productive and far-seeing ways. She had developed “street smarts.” She did not just passively take in the world around her, but more crucially, was able to see patterns in her environment. She was attuned to others so she could learn from them what they had to offer. She was open-minded, willing to question her own beliefs and to study the evidence. She also had a clear vision for her future. Her identity was deeply ingrained in her psyche.

The research studies cited in The Social Animal are vast if not particularly full of depth, and there are plenty of interesting facts in the book, such as that a baby’s brain creates 1.8 million new neural connections per second. Or, that a disproportionate high percentage of successful people have a parent die or abandon them in early life, giving them, Brooks concludes, a sense of vulnerability, the awareness that everything could rapidly be taken away, and leaving them with a hunger to establish themselves early.

The story told here is chronological, but it is always now, this same decade in the early 21st century, even though the lives of Harold and Erica span decades. This is not a book to be read as a novel, for the characters never come to life. They’re simply stick figures. It’s the little morsels of scientific fact that are interesting. I wouldn’t advise reading the book through chronologically, as it just didn’t hold my interest from start to finish. That said, you could open the book to any page and read for a while, close it again, and walk away satisfied, until the next time.

The reviewer, Fran Roberts Willard, is a freelance writer in Leesburg, Virginia.
From the Editor

Facts and ideas from anywhere

MAJOR PERSONALITY TYPES

In the late 1970s, while I was a visiting professor of cardiology at Duke University, I learned of the book titled *The Achievers: Six Styles of Personality and Leadership* by Gerald D. Bell (1), a professor in the School of Business at the University of North Carolina, Chapel Hill. The book had a major impact on me. I found its insights to be useful in my dealings with other people and as a consequence bought many copies for family, colleagues, and friends. While attending the American Osler Society meeting in Chapel Hill in April 2012, nearly 40 years after first learning about Bell’s book, I was fortunate to meet the author, who was having a leadership conference also at the Carolina Inn. Professor Bell signed one of his books for me, and I enjoyed immensely speaking with him for a few minutes.

In his book, Bell described six personality styles: the Commander, the Attacker, the Avoider, the Pleaser, the Performer, and the Achiever, and he also described how to deal with each. He emphasized that we all have parts of these personalities within us but usually one of them dominates. The Figure summarizes in part the characteristic features of each of these personalities.

**The Commander:** This person demands an orderly environment. He or she is domineering, uses categorical thinking, sees only one aspect of communication, is close-minded, is self-disciplined, has a routine sexual style, performs well in orderly situations, sets high goals but takes below-average risks, and has moderate psychological health.

**The Attacker:** One of the six or seven publishers I have dealt with during my 30 years as editor of *The American Journal of Cardiology* was an attacker. I learned (from Bell) how to deal with an attacker. Bell’s advice was to attack back. I did so and we became friends. The attacker, according to Bell, is shaped by a domineering, inconsistent, and harsh environment. The attacker is defiant, hostile, rejects responsibilities, acts uncommitted, gives variable commitment, disrupts, imputes evil to others, makes everything an emergency, forms an attack squadron, seldom admits being wrong, is cold personally, has an aggressive sexual style, performs well in independent jobs, and has poor psychological health.

**The Avoider:** One of my bosses at the National Institutes of Health was an avoider. He told me one time to never make a decision until I was pressed against the wall and had to. Bell taught how to deal with that personality: Simply do not take issues to him on which he has to make decisions. I did that, and my boss and I became good friends. According to Bell, the avoider was raised in a fearful and overprotected environment, has low self-confidence, takes few risks, procrastinates, is dependent, is a nonexplorer, is unable to totally give of himself or herself in a relationship or freezes at the thought of intimacy, does not like feedback, performs well in easy jobs, and has poor psychological health.

**The Pleaser:** I also dealt with a pleaser for many decades and learned from Bell’s book how to deal with one: let them please you. The pleaser’s training environment is overcaring.
He or she needs to be accepted, is “other-directed,” is highly persuadable, tends to be passive in lovemaking, has a reservoir of people-pleasing talents (relieves tension with good humor, is sensitive and kind, is the “good guy”), performs well in social tasks, and has average psychological health.

The Performer: This is the dominant personality style in the US, making up just over 40% of the administrators and managers in the country. The performer’s training environment stresses being successful and proper. The performer is an explorer, is skillful at manipulation, uses pseudoparticipation, is a deal-king, engages in joint-image management, takes credit for successes, parcels out compliments, uses anticipatory socialization (develops skills in learning the norms of the status group above him and then acts as they do to be accepted more quickly by them), uses proper timing, is an inside dopester, is counter-clever and is a good one-upman, is hard to pin down—a fence-sitter, masters sensation transference (the process of transferring first impressions about an object into feelings about its contents), controls information, is purposefully courteous, dresses properly (perfectly groomed, fashionably dressed), selects proper friends, acquires proper knowledge (reads the latest books, sees the current “in” movie, knows the most popular music, uses proper habits, disguises his efforts), does not appear to be striving to look good—not too eager, and uses protective devices (shifts from one group to another, never gets close to others because it is exhausting to be on guard at all times), is not quite accurate, but this is the ideal personality type. The Performer:

The Achiever: I think the word used to describe this person is not quite accurate, but this is the ideal personality type. The achiever’s environment warmly encourages independence. He or she has high self-confidence (is self-directed and nondefensive, has an acute awareness of inner feelings), is spontaneous and natural, is self-reliant (self-contained), is goal-oriented, is problem-centered instead of self-centered, is creative (an explorer), has deep genuine human relationships (feels without fear, is content, has compassion, is ethical, has fun), performs meaningful and challenging jobs well (is realistic), develops intelligence, and is 100% psychologically healthy. Bell opines that the only really successful marriages are between two achievers.

COMMONALITY IN GREAT LEADERS

Jack Welch, one of the great chief executive officers of the last century, and his wife, Suzy, ask “What do great leaders have in common?” (2). Their answer: authenticity. That makes people like you, trust you, and follow you. (He actually describes Bell’s achiever.) They speak of “guarded behavior” as something that may minimize the ire of your enemies, but it doesn’t energize anyone either. They stress that leaders let go of the fear of offending people and embrace the authentic side. They offer a short list of “stuff authentic people say.”

1) Why do I get goosebumps during scary movies? Goosebumps are produced by piloerection, a reflex that contracts the muscles around the base of each hair follicle, causing the hair to stand up and small bumps to emerge. Back when humans were hairier, piloerection had two benefits: it helped in keeping people warm by trapping heated air close to the skin, and in scary situations, it made them look bigger and more threatening. Watching a horror flick in an air-conditioned theater provides the perfect setup for piloerection. One is not only frightened but also probably cold.

2) Why does it seem as if mosquitoes bite me preferentially? The bloodsuckers are drawn to a tasty dinner by a variety of signals, including heat, carbon dioxide, movement, and the smell of skin secretions, like lactic acid. One study found that mosquitoes prefer people who have recently drank a beer. No one knows what precise combination mosquitoes find the most irresistible.

3) Why do men get more hair in some places and less in others as they get older? The “George Costanza effect” is a common sign of aging. It’s caused by dihydrotestosterone, a sex hormone to which some men are genetically predisposed to become sensitive. When that sensitivity develops, the hormone often causes the hair follicles on the head to shrink and follicles elsewhere, like on the back or in the ears or nasal passages, to become stimulated.

4) What are hiccups, and how can one stop them? A hiccup is an involuntary contraction of the diaphragm and the muscles between our ribs. A bout of hiccupping is usually the result of overeating or drinking carbonated beverages. (Other causes include sudden excitement, stress, or too much alcohol.) Traditional remedies for bouts include holding our breath, sipping cold water, gurgling, swallowing a teaspoon...
of dry sugar, gently pressing on our eyeballs, or leaning forward to compress our chest. Those with hiccups lasting >48 hours should see a physician. (I remember as a medical student seeing a hospitalized patient who had had hiccups constantly for 3 weeks. She was about the most exhausted human being I had ever seen.)

5) Why does my nose run when it's cold outside? Our nose helps perform a kind of climate control by heating and humidifying the air that we inhale so that it better matches the moist, warm conditions inside our lungs. Glands in our noses produce secretions that add moisture, and blood vessels in our nose dilate to warm the incoming air, acting like miniature radiators. When we breathe super-frigid air, those phenomena are amplified. Cold air tends to be drier, causing the glands in our nose to produce more secretions, and when we exhale warm, moist air out into the cold wind, some of the moisture condenses into droplets of water, which collect at the tip of the nose.

6) Why do I puff and puff climbing stairs when I can easily run a mile on a treadmill? As anyone who has used a rolling suitcase knows, it's a lot easier to pull a heavy object along a flat surface than it is to pick one up. When running on a treadmill, we barely lift any of our body weight up and down. Walking up a typical 45-degree staircase, on the other hand, requires moving 70% of our body weight against gravity.

ANTIBIOTICS IN FARMS

In March 2012, a federal court judge in Washington, DC, ordered the Food and Drug Administration (FDA) to take action on its own 35-year-old rule that would stop farmers from mixing antibiotics into animal feed, a practice that has led to a surge in drug-resistant bacteria (4). In 1977, the FDA concluded that the overuse of antibiotics in livestock, poultry, and other animals weakened the treatment's effectiveness in humans. The agency at that time issued an order that would have banned nonmedical use of penicillin and tetracycline in farm animals unless drug makers could show that the drugs were safe. But the rule was not enforced after vigorous opposition from Congress and lobbyists for the agriculture and drug industries. Judge Theodore Katz said the FDA must now begin steps to withdraw approval of antibiotics for routine use in animals, siding with four consumer-safety groups that brought a lawsuit against the agency. The court ruling, unfortunately, will not immediately halt the use of antibiotics in farms. The FDA must first give drug companies a chance to respond and schedule a public hearing.

Nearly 80% of all antibiotics sold in the USA are given to farm animals used in food production! Farmers mostly use the drugs in healthy animals to spur growth and to keep them from getting sick in crowded, unsanitary feedlots. Nevertheless, after constant use, some animals develop organisms that are immune to antibiotics. These germs, often called “superbugs,” can then pass to farmworkers and their families or blow into neighboring communities in dust clouds or runoff into lakes and rivers during heavy rains or sometimes contaminate steaks and chops we eat. So, 35 years later, some effort is under way.

HOSPITALS CLOSING

According to the book The New Health Age: The Future of Health Care in America by David Houle and Jonathan Fleece, of the approximately 5764 registered hospitals in the USA in 2011 (housing 942,000 hospital beds along with 36,915,331 admissions), about one third will be closed or reorganized into entirely different types of health care service providers by 2020 (5). Hospitals make substantial imprints in the US; many are one of their community’s largest employers and economic drivers. Of the total annual American health care dollars spent, hospitals account for more than $750 billion.

Several factors drive this “inevitable and historical shift.” First, the US must bring down its health care costs. The average American worker costs his or her employer $12,000 annually for health care benefits, and this figure is increasing more than 10% every year. US businesses cannot compete in a globally competitive marketplace at this level of spending. Additionally, federal and state budgets are getting crushed by the cost of health care entitlement programs, such as Medicare and Medicaid. Hospitals, as a consequence, are vulnerable since they make up the highest percentage of health care costs in the USA. These authors suggest that health care reform will make connectivity, electronic medical records, and transparency commonplace in health care. This may mean that any American in the near future considering a hospital stay will go online to compare hospitals’ relative infection rates, degrees of surgical success, and many other metrics. They suggest that the hospital market will become more open and competitive.

FIVE THINGS PHYSICIANS AND PATIENTS QUESTION IN CARDIOLOGY

The American College of Cardiology provided a list of five things for physicians not to do (6). 1) Don't perform stress cardiac imaging or advanced noninvasive imaging to evaluate patients without cardiac symptoms unless they have very high-risk markers. 2) Don't perform annual stress cardiac imaging or advanced noninvasive imaging for routine follow-up of asymptomatic patients. 3) Don't perform stress cardiac imaging or advanced noninvasive imaging for operative assessment in patients scheduled to undergo low-risk noncardiac operations. 4) Don't perform echocardiography as routine follow-up for mild, asymptomatic valvular disease in adults with no change in signs or symptoms. 5) Don't perform stenting of nonculprit lesions during percutaneous coronary intervention for uncomplicated hemodynamically stable ST-segment elevation myocardial infarction.

DEMENTIA IN PRISONS

Dementia in prisons is a fast-growing phenomenon, one that many prisons are unprepared to handle (7). It is a consequence of long sentences that have created a large population of aging prisoners. According to Pam Belluck of The New York Times, about 10% of the 1.6 million inmates in US prisons are serving life sentences, and an additional 11% are serving >20 years. And, many older people are being sent to prison. In 2010, a total of 9560 people aged ≥55 were sentenced, more than twice...
as many as in 1995. Also in 2010, the number of inmates ≥55 years almost quadrupled to nearly 125,000. Thus, the dementia population in prisons is obviously growing.

Many prisons would like to transfer inmates with dementia to nursing homes, but these individuals are often violent criminals, making states reluctant to parole them and nursing homes reluctant to take them. New York has established a separate unit for cognitively impaired inmates and uses professional caregivers at a cost of about $93,000 per bed annually compared with $41,000 in the general prison population. Other states, notably Louisiana and California, train prisoners to handle many of the impaired inmates’ daily needs. These caregiving prisoners also protect inmates with dementia from prisoners who may try assaulting, abusing, or robbing them. Problems, problems.

MEDICAL TATTOOS
Some medical tattoos are taking the place of bracelets that list a person’s allergies, chronic diseases, or even end-of-life wishes (8). Recently, a photograph was published of a physician who had “No CPR” tattooed over his sternum. Another had “type I diabetic” tattooed on her left forearm. But, medical tattoos do not appear to carry much legal weight. The National Tattoo Association, a nonprofit group that raises awareness about tattooing, does not track the number or styles of tattoos. A spokesman for the association, however, said he does about one medical tattoo a year at his shop in Orlando. Nine out of 10 medical tattoos relate to an allergy—usually, to penicillin or peanuts.

TEEN BIRTHRATES
US birthrates for teens aged 15 to 19 years in all racial and ethnic groups are the lowest since 1946 (9). In 2010, there were 34 births per 1000 teens, down from 62 births per 1000 teens in 1991. The all-time high was 96 during the Baby Boom year of 1957. The birthrate for Asian teens was 11; for whites, 23; for blacks, 51; and for Hispanics, 56. The report showed no change in 1991. The all-time high was 96 during the Baby Boom year of 1957. The birthrate for Asian teens was 11; for whites, 23; for blacks, 51; and for Hispanics, 56. The report showed no change in 1991. The all-time high was 96 during the Baby Boom year of 1957. The birthrate for Asian teens was 11; for whites, 23; for blacks, 51; and for Hispanics, 56. The report showed no change in the percentage of sexually active teen girls but significant increases in the use of contraception. The report also noted a decline in the percentage of teenage girls “who said they wanted to get pregnant.” Good news.

VOLUNTEER DOCTORS AT ATHLETIC EVENTS
At running races and triathlons, volunteer doctors are getting fewer, and the reason appears to be an inability to get 1-day malpractice insurance to serve participants at these events (10). In 2011, 13 Americans died during running races and another eight died while competing in triathlons. About 13 million Americans enter running races each year, and 2.3 million compete in triathlons. The rising number of participants highlights the need for quality medical care at these events, and that usually comes from volunteer physicians. In the April 16, 2012, Boston Marathon, 27,000 started the race. About 70 physicians and 1300 first-aid volunteers, including nurses, medical students, and physical therapists, were on hand. About 1500 runners required some level of medical attention during or immediately following the race. Despite the worry about malpractice insurance, no American physician has been named in an event-related lawsuit, apparently because plaintiffs typically go after race organizers, who have deeper pockets. The Good Samaritan laws cover physicians only if they are bystanding fans and not official event volunteers.

Because of the shortage of physicians at these events, the World Road Race Medical Society and the medical director for the Chicago Marathon teamed with USA Track and Field and Sports Insurance Company to create policies specifically for volunteer medical teams. Beginning in 2009, all five major US marathons—Chicago, New York, Twin Cities, Boston, and Houston—bought the plan at a cost of $50 to $60 per physician. The US Triathlon began offering the program in 2011. But even at the $60 per-physician cost, not all event-marketing companies have jumped on board to cover their physicians. Some large adventure races hire paramedic services to be on standby. Still, smaller events use uninsured volunteers. There seems to be very few things where lawyers are not involved.

SOME AMAZING ATHLETES OVER 40 YEARS OF AGE
A recent article (11) highlighted numerous athletes over the age of 40. Here are some of the better-known examples:

- **George Foreman**: He earned the heavyweight crown at age 25 and successfully defended it twice before losing to Muhammad Ali in 1974. At age 45 (1994), he regained the title.
- **Nolan Ryan**: At age 44 he threw his seventh no-hitter.
- **Jack Nicklaus**: The “Golden Bear” at age 46 won his sixth Masters golf tournament and 20th major.
- **Dara Torres**: At age 41, she became the oldest swimmer ever to qualify for the Olympics and won three silver medals.
- **Martina Navratilova**: At age 49 and 11 months, she won her 49th Grand Slam title by winning the US Open mixed doubles tournament.
- **Kareem Abdul-Jabbar**: The 19-time NBA All Star led the Los Angeles Lakers to back-to-back titles after turning 40.

ELDERLY DRIVERS
They are safer than the younger ones. A recent 3-year study by the Insurance Institute for Highway Safety involving 1437 drivers aged ≥75 years found a decline of 45% in fatal accidents per 100 million miles traveled—a greater reduction than that in any other age group (12). Drivers ≥85 years still have a higher rate of deadly crashes than any other age group except teenagers. That is partly because seniors tend to avoid highway driving, where crash rates per mile are lower. Also, the older drivers are more likely than the younger ones to die in crash accidents because they tend to be more frail. Safe driving courses for older drivers are available through AARP and AAA. Many states require them, and most mandate insurance-premium discounts for seniors who take them. A free car assessment program, called “CarFit,” cosponsored by AAA, AARP, and the American Occupational Therapy Association, is available in most states to help seniors adjust or modify their vehicles to be safer. Seniors, don’t let anyone take those car keys away.
WEATHER AND CLIMATE DISASTERS IN 2011

Tornadoes, droughts and fires, storms and flooding, and hurricanes contributed to a record 14 weather and climate disasters in the USA in 2011 that caused $1 billion or more in damage (14). Previously, the largest number of disasters was nine in 2008 and eight in 1998. The total cost for US natural disasters in 2011 was $55 billion, nowhere near the $160 billion price tag in 2005 ($144 billion of which was contributed by Hurricane Katrina). Although the cost was relatively low, 669 people died in these 2011 weather disasters. Half of these billion-dollar events were tornados, causing 551 fatalities. The Joplin, Missouri, tornado alone killed 161 people, the deadliest single tornado strike in the US since modern recordkeeping began. From spring to fall, heat and a lack of precipitation caused droughts and wildfires in the South. By the end of July, 84% of the southern plains had moderate to exceptional drought. In Texas, over 3 million acres were burned. Persistent rainfall, nearly 300% of normal precipitation amounts in the Ohio Valley, paired with melting snow caused historic flooding along the Mississippi, Missouri, and Souris Rivers. Seven states saw a record year. It was rain, not wind speed, that caused damage in 2011 from Hurricane Irene and Tropical Storm Lee. The Northeast saw extensive flood damage. Let’s hope 2012 is better.

DRIEST YEAR IN TEXAS HISTORY

The driest year in Texas history (2011) caused a record $7.62 billion in agriculture losses, billions more than previously estimated (15). Texas is the nation’s number three producer of agricultural products, behind California and Iowa, so when crops and cattle fail in the Lone Star State, prices rise nationally. The drought has cost Texas more than $14 billion in agricultural losses since 1998. Many ranchers sold off or slaughtered cattle after ranch lands dried up and the price of hay skyrocketed. The state now has its smallest herd since the 1950s after losing about 660,000 cows during the drought. Cattle account for about half of Texas’ agricultural production, which makes up 9% of its economy. Cotton losses are estimated at $2.2 billion and corn losses at $736 million. The remaining losses were largely in hay, wheat, and sorghum production. Let it rain.

THE JAPANESE DISASTER—A YEAR LATER

The massive earthquake and tsunami that struck Japan on March 11, 2011, killed >19,000 people and unleashed the world’s worst nuclear crisis in >25 years (since Chernobyl) (16). The quake, a 9.0 on the Richter scale, was the strongest recorded in Japan’s history. It set off a tsunami that inundated >50 square miles of land along 500 miles of the eastern coastline and damaged 29 railroads, 45 dikes, 78 bridges, nearly 4000 roads, and over 1,100,000 properties, 36,000 of which were inundated. Still today, some 325,000 people left homeless remain in temporary housing. While much of the debris has been gathered into massive piles, very little rebuilding has begun.

The Japanese government says that the damaged Fukushima Daiichi nuclear plant, where three reactor cores melted down after the tsunami knocked out their vital cooling systems, is stable and that radiation coming from the plant has subsided significantly. The plant remains, however, in a fragile state. Only two of Japan’s 54 reactors are now running, while those shut down for regular inspection undergo special tests to check their ability to withstand similar disasters. They all could go offline by May 1, 2012, if none are restarted before then. The Japanese government has pledged to reduce reliance on nuclear power, which supplied almost 30% of the nation’s energy needs before the disaster. The magnitude of that disaster is difficult to comprehend.

WASTED FOOD

CleanMetrics Corp, a software firm that analyzes the environmental impact of products and businesses, has found that vegetables are the most commonly wasted food in US homes, making up 25% of avoidable waste (17). Most grocery shoppers create food waste by overbuying. People tend to overestimate what they need at the store when they are well stocked at home and to underestimate what they need when they don’t have enough. The average US family of four spends $500 to $2000 on food each year that ends up in the garbage. Of trash in a home, fruit and juices make up 16%; milk and yogurt, 13%; vegetables, 25%; and grains, 14%. Just over half of avoidable food and drink waste comes about because products were not used in time. About 40% of this waste is made up of leftovers, characterized as “cooked, prepared, or served too much.” In the US, fears about foodborne illness and confusion about product “sell-by” dates are to blame for some food waste. In the UK, food waste is a public concern and a rallying point for politicians and corporations, similar to the issue of childhood obesity in the US. In recent years, UK grocery stores have tested ways to discourage overbuying, including “buy one, get one later” promotions at various chains. Today, spending on restaurant...
and take-out meals makes up about half of food expenditures in the USA. That probably decreases the scraps.

NOW IT'S THE PACIFIC OCEAN

Ben Lecomte in 1998 became the first person to swim across the Atlantic Ocean (18). A native of France, but now a US citizen, Lecomte undertook the 73-day, 3700-mile journey to raise money for cancer research in memory of his father, who died of colon cancer in 1991. He moved from France to Texas when he was 23 years old. Now, Lecomte, age 44, an alumnus of the University of Texas at Arlington, is training for his next adventure—a swim across the Pacific Ocean. His planned route is 5400 miles long. He hopes to start in May 2012 and finish in <6 months. His plan is the following: He will average about 40 miles a day, swimming 8 hours in two 4-hour segments. He will have a GPS device, which will help him when he takes breaks in the boat that will trail him; he will be able to start again exactly where he stopped. Aside from meals, he will have energy bars and fresh water. As with his first transoceanic swim, he will dedicate the adventure again to his father, who taught him how to swim. He will take on the Pacific, with the sharks and jellyfish and 30-foot swells.

DANIELLE STEEL

She has sold more than 800 million copies of her 100-plus books worldwide, 600 million in the US alone! Her novels have been on The New York Times bestseller list for 400 consecutive weeks, and 22 have been adapted for television (19). She often is writing, editing, or researching five books at a time, and she says that she is never lonely. Although overall national divorce rates have declined since spiking in the 1980s, “gray divorce” has risen to its highest level on record (20). In 1990, only 1 in 10 people who got divorced were aged ≥50 years; by 2009, the number was 1 in 4. More than 600,000 people aged ≥50 years got divorced in 2009. A 2004 national survey found that women are the ones initiating most of these breakups: among divorces by people aged 40 to 69, women reported seeking the split 66% of the time. Cheating does not appear to be the driving force in “gray divorce.” In the same 2004 survey, infidelity was cited by 27% as one of the three top reasons for seeking a divorce, a figure not out of line with estimated infidelity as a factor in divorce in the general population. The reason for these late divorces is unclear, but it springs at least in part from boomers’ status as the first generation to enter into marriage with goals largely focused on self-fulfillment. Some marriages that in previous generations would have ended in death now end in divorce. In the past many people did not live long enough to reach the 40-year itch.

According to Susan Brown and I-fen Lin of Bowling Green State University, among people aged ≥50 years, the divorce rate has doubled over the past 2 decades. Professor Brown describes three phases of American views of marriage in the past century. First was the institutional phase, in the decades before World War II, when marriage was seen largely as an economic union. In the 1950s and 1960s, the companionate phase appeared, in which a successful marriage was defined by the degree to which each spouse could fulfill his or her role. Husbands were measured by their prowess as providers and wives by their skills in homemaking and motherhood. In the 1970s, the boomers initiated the individualized phase, with an emphasis on the satisfaction of personal needs—a more egocentric focus.

For many boomers, a late divorce is not their first marital split. Of the people ≥50 now getting divorced, 53% have done so at least once before. Having been married previously doubles the risk of divorce for those aged 50 to 64, and, for those aged ≥65, the risk factor quadruples. For boomers who have had trouble maintaining commitments in the past, hitting the empty-net phase seems to trigger thoughts of mortality and of vanishing possibilities for self-fulfillment. Professor Brown predicts that the number of over-50 divorces by 2030, based on current trends, could top 800,000 per year.

NET WORTH OF US PRESIDENTS


BILLIONAIRES IN THE USA

California has 94 billionaires; New York, 70; Texas, 48; Florida, 29; Illinois, 18; Michigan, 12; Connecticut, 11; Wisconsin, 10; Maryland, 9; and Washington, 8. There are no physicians on the list, although Carl Icahn was a medical school dropout. The richest family in the USA is the Waltons, of Wal-Mart fame, divided among Christy, Jim, Alice, and Robson Walton. The wealthiest single individual in the USA is Bill Gates, with $61 billion from Microsoft, and next, Warren Buffett, with $44 billion from Berkshire Hathaway. The richest in the world is Carlos Slim Helu and family in Mexico, worth $69 billion.

ATTRACTIVE CITIES

The “hot-spots” survey, sponsored by CitiGroup, attempts to measure how attractive a city is to talent, capital, tourists, and businesses. The top 25 attractive cities are listed in the Table. Dallas tied for 25th with Vienna. New York was number
VACATIONING AT THE BEST HOTELS IN THE USA

Denmark tied for 23rd. 1, and London was number 2. Houston, Copenhagen, and

NEW LONDON, TEXAS, 75 YEARS AGO

According to a piece by Betsa Marsh (24), here are the top US hotels: The Greenbrier, White Sulfur Springs, West Virginia; The Grand Hotel, Mackinac Island, Michigan; West Baden Springs, French Lick, Indiana; Casa Monica, Saint Augustine, Florida; US Grant Hotel, San Diego, California; and Mohawk Mountain House, New Paltz, New York.

NEW LONDON, TEXAS, 75 YEARS AGO

In the 1930s, the Great Depression was in full swing, but the New London School District in New London, Texas, was one of the richest in the USA. A 1930 oil find in Rusk County had boosted the local economy, and educational spending grew with it. The New London School, a large structure of steel, was constructed in 1932 at a cost of $1 million (about $17 million in 2012 dollars). Its football stadium was the first in Texas to have electric lights. The school was built on sloping ground, and

a large dead-air space was contained beneath the structure. The school board had overridden the original architect’s plans for a boiler and steam distribution system, instead opting to install 72 gas heaters throughout the building.

Late in 1936, the superintendent, with quiet approval from four board members, disconnected the school from commercial natural gas and tapped into a free unregulated and widely available byproduct of gasoline refining: waste natural gas. The switch would save the school district, perhaps the richest school district in the USA in 1937, $250 per month. Refineries pumped the waste gas back to oil rigs, where rig operators were required to dispose of it. Most released it into the air through tall pipes and burned it, lighting the night sky with orange flames. One of these waste gas lines passed 200 feet from New London School.

The connection to the waste gas line was performed in early January 1937 by a school janitor, two bus drivers, and a welder that the school had hired.

On March 18, 1937, students prepared for the next day’s interscholastic meet. At the gymnasium, the PTA met. At 3:17 pm, an instructor of manual training turned on a sanding machine in an area which, unknown to him, was filled with a mixture of gas and air. The switch ignited the mixture and carried the flame into a nearly closed space beneath the building, 253 feet long and 56 feet wide. Immediately, the building seemed to lift in the air and then smashed to the ground. Walls collapsed. The roof fell in and buried the victims in a mass of brick, steel, and concrete debris. The explosion was heard 4 miles away, and it hurled a 2-ton concrete slab 200 feet away.

Fifteen minutes later, the news of the explosion had been relayed over telephone and Western Union lines. Physicians and medical supplies came from Baylor Hospital in Dallas and from surrounding towns. Workers began digging through the rubble looking for victims. Flood lights were set up. The rescue operation continued through the night. Within 17 hours, all victims and debris had been taken away. Of the 500 students and 40 teachers in the building, 298 died. Only 130 students escaped serious injury. It was the worst school disaster in American history. The news spread around the world. Even Adolph Hitler sent condolences.

Today, fewer than 1000 live in New London. It contains a few buildings and houses; a convenience store that sells gas, microwave pizzas, sandwiches, lotto tickets, and a few groceries; a small bank branch office; a donut shop; and two churches. On a small island in the middle of State Highway 42, there is a pink granite cenotaph complete with classical figures carved into the apex. It is an imposing monument, particularly for a tiny town, flanked on one side by the school and on the other by a combination of café, soda fountain, and museum.

Two books on this disaster appeared in 2012 (25, 26). Saving money sometimes costs a lot of money and even lives.

RMS TITANIC: 100 YEARS LATER

On April 12, 1912, the RMS Titanic embarked on its maiden voyage, sailing from South Hampton, England, to New York City (27). It was the largest and most luxurious passenger liner ever built, and it was also considered “unsinkable.” On April
14, however, the ship struck an iceberg, and 2.5 hours later it sank. Of the approximately 3000 people on board, about 1500 perished. Because of the tragedy, the Titanic became perhaps the best known ship in the world, capturing the public’s imagination and inspiring books and movies. After the 1985 discovery of its wreckage, interest in the famed liner further increased.

The vessel was 883 feet long (three football fields), 92.5 feet wide, and 104 feet from keel to bridge. She had eight steel decks and a circular double bottom 5.25 feet through (the inner and outer “skins”). The ship was divided into 16 compartments by 15 transverse “water-tight” bulkheads, well above the water line. Communication from the engine rooms and boiler rooms was through water-tight doors that could be closed instantly from the captain’s bridge. The crew numbered nearly 900, with 320 engineers and 65 navigators. The machinery and equipment of the Titanic were the finest attainable and represented the last word in marine construction. Her structure was of steel, of a weight, size, and thickness greater than that of any other ship. The cruising speed was 21 knots (24 miles per hour) with a maximum of 24 knots (28 miles per hour).

The Titanic was equipped with three engines—two reciprocating four-cylinder, triple-expansion steam engines and one centrally placed Parson’s turbine—each driving a propeller. The two reciprocating engines had a combined output of 30,000 horsepower and the turbine, 16,000 horsepower. The two reciprocating engines were each 63 feet long and weighed 720 tons. They were powered by steam produced in 29 boilers and 159 furnaces. The boilers were nearly 16 feet in diameter and 20 feet long, and each weighed 91.5 tons and held 48.5 tons of water. They were heated by coal, 7703 tons of which could be carried on board. The furnaces required over 6 tons of coal a day to be shoveled into them by hand, requiring the services of 176 firemen working around the clock. One hundred tons of ash a day had to be disposed of by ejecting it into the sea. The work was relentless, dirty, and dangerous, and the firemen had a high suicide rate. Titanic’s rudder was nearly 79 feet tall and 15 feet long, and it weighed >100 tons. It required steering engines to move it. The ship had its own waterworks capable of heating and pumping water to all parts of the vessel via a complex network of pipes and valves. The main water supply was taken aboard while Titanic was in port, but in an emergency she could also distill fresh water from the sea.

Titanic was equipped with two 1.5 kW spark-gap wireless telegraphs located in the radio room on the Bridge Deck. One set was used for transmitting messages, and the other, located in a soundproof booth, for receiving them. The system, one of the most powerful in the world, had a range of 1000 miles.

The passenger facilities met the highest standards of luxury. The ship could accommodate 739 first-class passengers, 674 second-class, and 1026 third-class, plus 900 crew members. In all, she could carry 3339 people. Passengers could use an onboard telephone system, a lending library, and a large barbershop. The first-class section had a swimming pool, a gymnasium, a squash court, a Turkish bath, an electric bath, and a veranda café.

Although the Titanic was primarily a passenger ship, she also carried a substantial amount of cargo. Under contract with both Royal Mail and the US Postal Department, she had 26,800 cubic feet of space in her hull allocated for storage of letters, parcels, and specie (bullion, coins, and other valuables). The ship’s passengers brought with them a huge amount of luggage; another 19,500 cubic feet was taken up by first- and second-class baggage. In addition, there was considerable cargo: furniture, food, and motor cars. Titanic was equipped with eight electric cranes, four electric wenchs, and three steam wenchs to lift cargo and baggage in and out of the hull. It was estimated that the ship used 415 tons of coal in South Hampton, simply generating steam to operate the cargo wenchs, heat, and light.

Titanic carried 20 lifeboats: 14 standard wooden lifeboats with a capacity of 65 people each and four collapsible lifeboats with a capacity of 47 people each. All lifeboats were stored securely on the Boat Deck connected to davits by ropes. Additionally, two emergency cutters with a capacity of 40 people each were available. Each boat carried food, water, blankets, and a spare lifebelt. Titanic had the ability to carry up to 64 wooden lifeboats, which would have been enough for 4000 people. The White Star Line, however, decided that only 16 wooden lifeboats and four collapsible lifeboats would be carried, which could accommodate 1178 people, only one third of Titanic’s total capacity. The Board of Trade’s regulations at the time required British vessels >10,000 tons to carry only 16 lifeboats with a capacity of 990 occupants, so Titanic actually provided more lifeboat accommodation than was legally required.

For the maiden voyage, 885 crew members were recruited. She did not have permanent crew and, like most vessels at the time, employed mostly casual workers who came aboard the ship only a few hours before she sailed from South Hampton. Titanic’s passengers numbered 1317: first class, 324; second class, 284; and third class, 709. The ship was considerably under capacity on her maiden voyage, as she could accommodate 2439 passengers. Some of the most prominent people of the day booked a passage aboard the Titanic. The exact number of people aboard is not known, as not all of those who had booked tickets made it to the ship; about 50 cancelled for various reasons, and not all of those who boarded stayed aboard for the entire journey.

On her third day out, Saturday, April 13, Titanic crossed a cold weather front with strong winds and waves up to 8 feet. These died down as the day progressed but by the evening of Sunday, April 14, it became clear, calm, and very cold. Titanic received warnings from other ships of drifting ice in the area of the Grand Banks of Newfoundland; nonetheless, the ship continued to steam at full speed, standard practice at the time. It was generally believed that ice posed little danger to large vessels. At 11:40 PM, one of the lookouts spotted an iceberg immediately ahead of Titanic and alerted the bridge. The first officer ordered the ship to be steered around the obstacle and the engines to be put in reverse, but it was too late. The starboard side of Titanic struck the iceberg, creating a series of holes below the waterline. Five of the ship’s watertight compartments were brecched. The ship was doomed as she could not survive >4 of its 16 compartments being flooded.

Titanic began sinking bow first with water spilling from compartment to compartment as her angle in the water...
became steeper. Those aboard Titanic were ill-prepared for such an emergency. The crew had not been trained adequately in carrying out an evacuation. The officers did not know how many they could safely put aboard the lifeboats and launched many of them barely half full. Most third-class passengers were trapped below decks as the ship filled with water. A “women and children first” protocol was generally followed for loading the boats, and most of the male passengers and crew were left aboard. Two hours and 40 minutes after Titanic struck the iceberg, her forward deck dipped under water and the sea poured in through open hatches and grates. As her unsupported stern rose out of the water, exposing the propellers, the ship split apart. The stern remained afloat for a few minutes longer. At 2:20 AM it sank, breaking loose from the bow section. Then, the ship split apart. The stern remained afloat for a few minutes longer. At 2:20 AM it sank, breaking loose from the bow section.

Earlier, distress signals had been sent by wireless devices, rockets, and lamps, but no ships responded or were near enough to reach her before she sank, except the Californian, which saw her flares but failed to assist. At about 4:00 AM, RMS Carpathian arrived on the scene in response to Titanic’s earlier distress calls. Only 710 people were found alive and conveyed by earlier distress calls. At about 4:00 AM, RMS Carpathian arrived on the scene in response to Titanic’s earlier distress calls.

How could such a magnificent ship built like a battleship be sunk by an iceberg which was not seen until the ship was virtually on top of it? One hundred years ago across the Atlantic, it was entirely the responsibility of the lookouts to spot an iceberg, and they could do so 9 miles ahead, providing at least 30 minutes for the ship to maneuver its course. The Titanic lookouts spotted the iceberg only 37 seconds before the starboard side of the ship hit it, opening up a 100-yard gash. At the time of the collision, it was a most unusual night—quite still, with innumerable stars in the sky. The lookouts, in other words, were unable to see the difference between an iceberg and a star in front of them since the warm sky was clear but covered with stars. One passenger commented later that she had never seen so many stars in the sky. The lookouts, in other words, were unable to see the difference between an iceberg and a star in front of them since the stars came down essentially to water level. Likewise, the captain of the Californian was unable to see the huge Titanic because of confusion with the innumerable stars in the sky. The warm air suddenly mixing with the cold air also apparently played a prominent role.

The sinking of the Titanic led to many changes in maritime rules: to have adequate lifeboats for every passenger and crew member on every ship, to perform lifeboat drills on every passenger ship, to man wireless equipment on every passenger ship around the clock, and to set up an ice patrol to monitor the presence of icebergs in the North Atlantic.

William Clifford Roberts, MD
11 May 2012

2. Welch J, Welch S. What do great leaders have in common? They're authentic. Fortune, April 9, 2012.
Cardiac transplantation in adults with aortic valve disease with focus on the bicuspid aortic valve

Roberts WC, Roberts CC, Ko JM, Hall SA, Capehart JE

Am J Cardiol 2012 Jan 17 [Epub ahead of print]. Reprinted with permission from Elsevier.

The frequency of congenitally bicuspid aortic valves in patients having cardiac transplantation (CT) is unknown. We reviewed 243 explanted hearts in patients having CT at Baylor University Medical Center, Dallas from June 1997 through November 2011 to determine the frequency of a bicuspid aortic valve in this population. Of the 243 explanted hearts, 7 (2.9%) were found to have a congenitally bicuspid aortic valve: 3 had severe aortic valve stenosis and before CT had had the aortic valve replaced; the other 4 had normally functioning bicuspid valves and underwent CT for cardiomyopathy (ischemic in 1, idiopathic in 2, and hypertrophic in 1). Review of previously published reports of CT and aortic valve disease disclosed that 4 patients had had aortic valve replacement (AVR) from 2 to 8 years before CT, 3 had AVR or aortic valve repair of the donor heart at the time of CT, and 4 had AVR or transcatheter aortic valve implantation from 1 to 14 years after CT. Some of these aortic valve replacements, before, at the time of, or after CT were in patients with congenitally bicuspid aortic valves. In conclusion, congenitally bicuspid aortic valves were found in 7 of 243 explanted hearts in patients having CT at a single medical center in a 14-year period: 4 had functioned normally and 3 were severely stenotic. Previous reports of patients having AVR or repair before, during, and after CT were reviewed.

Effect of coronary bypass and valve structure on outcome in isolated valve replacement for aortic stenosis

Roberts WC, Roberts CC, Vowels TJ, Ko JM, Filardo G, Hamman BL, Matter GJ, Henry AC 3rd, Hebeler Jr RF

Am J Cardiol 2012 Mar 1 [Epub ahead of print]. Reprinted with permission from Elsevier.

Reports differ regarding the effect of concomitant coronary artery bypass grafting (CABG) in patients who undergo aortic valve replacement (AVR) for aortic stenosis (AS), and no reports have described the effect of aortic valve structure in patients who undergo AVR for AS. A total of 871 patients aged 24 to 94 years (mean 70) whose AVR for AS was their first cardiac operation, with or without first concomitant CABG, were included. Patients who underwent mitral valve procedures were excluded. In comparison with the 443 patients (51%) who did not undergo CABG, the 428 (49%) who underwent concomitant CABG were significantly older, were more often male, had lower transvalvular peak systolic pressure gradients and larger valve areas, had lower frequencies of congenitally malformed aortic valves, had lighter valves by weight, had higher frequencies of systemic hypertension, and had longer stays in the hospital after AVR. Early and late (to 10 years) mortality were similar by propensity-adjusted analysis in patients who did and did not undergo concomitant CABG.

CANCER BIOLOGY AND THERAPY

Boswellic acid induces epigenetic alterations by modulating DNA methylation in colorectal cancer cells

Shen Y, Takahashi M, Byun HM, Link A, Sharma N, Balaguer F, Leung HC, Boland R, Goel A

Cancer Biol Ther 2012 May 1;13(7) [Epub ahead of print]. Reprinted with permission from Landes Bioscience.

Accumulating evidence suggests that chemopreventive effects of some dietary polyphenols may in part be mediated by their ability to influence epigenetic mechanisms in cancer cells. Boswellic acids, derived from the plant *Boswellia serrata*, have long been used for the treatment of various inflammatory diseases due to their potent anti-inflammatory activities. Recent preclinical studies have also suggested that this compound has anti-cancer potential against various malignancies. However, the precise molecular mechanisms underlying their anti-cancer effects remain elusive. Herein, we report that boswellic acids modulate DNA methylation status of several tumor suppressor genes in colorectal cancer (CRC) cells. We treated RKO, SW48 and SW480 CRC cell lines with the active principle present in boswellic acids, acetyl-keto-beta-boswellic acid (AKBA). Using genome-wide DNA methylation and gene expression microarray analyses, we discovered that AKBA induced a modest genome-wide demethylation that permitted simultaneous re-activation of the corresponding tumor suppressor genes. The quantitative methylation-specific PCR and RT-PCR validated the gene demethylation and re-expression in several putative tumor suppressor genes including *SAMD14* and *SMPD3*. Furthermore, AKBA inhibited DNMT activity in CRC cells. Taken together, these results lend further support to the growing notion that anti-cancer effect of boswellic acids may in part be due to its ability to demethylate and reactivate methylation-silenced tumor suppressor genes. These results suggest that not only boswellic acid might be a promising epigenetic modulator in the chemoprevention and treatment of CRC, but also provide a rationale for future investigations on the usefulness of such botanicals for epigenetic therapy in other human malignancies.

CELL CYCLE

Ectopic transgenic expression of NKX2.2 induces differentiation of adult pancreatic progenitors and mediates islet regeneration

Chen S, Shimoda M, Chen J, Matsumoto S, Grayburn PA

Cell Cycle 2012 Apr 15;11(8) [Epub ahead of print]. Reprinted with permission from Landes Bioscience.
To pursue islet regeneration in situ in adult pancreas with a diabetic animal model, we used ultrasound targeted microbubble destruction (UTMD) to deliver islet transcription factor genes to the pancreas of STZ-treated rats, specifically using a piggyback transposon gene delivery system for long-term transgene expression of Nkx2.2 in STZ rat pancreas. Our results show that Nkx2.2 gene induced robust proliferation and differentiation of adult pancreatic progenitors. Our high resolution confocal images precisely displayed how one single pancreatic progenitor cell differentiated into islet-like clusters and, further, into mature islets with normal morphology in situ in postnatal pancreas. Nkx2.2 targeted to the pancreas by UTMD induces pancreatic progenitor cell proliferation and differentiation with subsequent islet regeneration and cure of STZ-induced diabetes for three months.

Cochrane Database of Systematic Reviews

Surgery for small asymptomatic abdominal aortic aneurysms
Filaro G, Powell JT, Martinez MA, Ballard DJ

Background: An abdominal aortic aneurysm (AAA) is an abnormal ballooning of the major abdominal artery. Some AAAs present as emergencies and require surgery; others remain asymptomatic. Treatment of asymptomatic AAAs depends on many factors but an important one is size of the aneurysm, as risk of rupture increases with aneurysm size. Large asymptomatic AAAs (>5.5 cm in diameter) are usually operated on; very small AAAs (<4.0 cm diameter) are monitored with ultrasonography. The optimal timing of surgery would benefit from further evidence.

Objectives: This review compared long-term survival in patients with AAAs of diameter 4.0 to 5.5 cm who received immediate repair versus routine ultrasound surveillance.

Search methods: For this update the Cochrane Peripheral Vascular Diseases Group searched their Specialised Register (February 2012) and CENTRAL (2012, Issue 1). Reference lists of relevant articles were checked for additional studies and the searches were supplemented by handsearches of recent conference proceedings and information from experts in the field.

Selection criteria: Randomised controlled trials in which men and women with asymptomatic AAAs of diameter 4.0 to 5.5 cm were randomly allocated to immediate repair or imaging-based surveillance at least every six months. Outcomes had to include mortality or survival.

Data collection and analysis: Two authors (GF, MAMM) abstracted the data, which were cross-checked by the other authors (DJB, JTP). Due to the small number of trials, formal tests of heterogeneity and sensitivity analyses were not conducted.

Main results: Four trials with a combined total of 3314 patients, the UK Small Aneurysm Trial (UKSAT), the Aneurysm Detection and Management (ADAM) trial, the Comparison of Surveillance Versus Aortic Endografting for Small Aneurysm Repair (CAESAR), and the Positive Impact of Endovascular Options for treating Aneurysms Early (PIVOTAL) fulfilled the inclusion criteria. The four trials showed an early survival benefit in the surveillance group (due to 30-day operative mortality with surgery) but no significant differences in long-term survival (adjusted hazard ratio [HR] 0.88, 95% confidence interval [CI] 0.75 to 1.02, mean follow up 10 years [UKSAT]; HR 1.21, 95% CI 0.95 to 1.54, mean follow up 4.9 years [ADAM]; HR 0.76, 95% CI 0.30 to 1.93, median follow up 32.4 months [CAESAR]; HR 1.01, 95% CI 0.49 to 2.07, mean follow up 20 months [PIVOTAL]). The meta analyses of mortality at one year (CAESAR and PIVOTAL only) and six years (UKSAT and ADAM only) revealed a non-significant association (Peto odds ratio at one year 1.15, 95% CI 0.59 to 2.25; Peto odds ratio at six years 1.11, 95% CI 0.91 to 1.34).

Authors' conclusions: The results from the four trials to date demonstrate no advantage to early repair (via open or endovascular surgery) for small AAA (4.0 to 5.5 cm) and suggest that 'best care' for these patients favours surveillance. Furthermore, the more recent trials focused on the efficacy of endovascular aneurysm repair and still failed to show benefit. Thus, both open and endovascular repair of small AAAs are not supported by currently available evidence.

Diabetes, metabolic syndrome and obesity

Insulin detemir for the treatment of obese patients with type 2 diabetes
Hollander PA

The risk for developing type 2 diabetes (T2DM) is greater among obese individuals. Following onset of the disease, patients with T2DM become more likely to be afflicted with diabetic micro- and macrovascular complications. Decreasing body weight has been shown to lower glycosylated hemoglobin and improve other metabolic parameters in patients with T2DM. Medications used to lower blood glucose may increase body weight in patients with T2DM and this has been repeatedly shown to be the case for conventional, human insulin formulations. Insulin detemir is a neutral, soluble, long-acting insulin analog in which threonine-30 of the insulin B-chain is deleted, and the C-terminal lysine is acetylated with myristic acid, a C14 fatty acid chain. Insulin detemir binds to albumin, a property that enhances its pharmacokinetic/pharmacodynamic profile. Results from clinical trials have demonstrated that treatment with insulin detemir is associated with less weight gain than either insulin glargine or neutral protamine Hagedorn insulin. There are many potential reasons for the lower weight gain observed among patients treated with insulin detemir, including lower risk for hypoglycemia and therefore decreased defensive eating due to concern about this adverse event, along with other effects that may be related to the albumin binding of this insulin that may account for lower within-patient variability and consistent action. These might include faster transport across the blood-brain barrier, induction of satiety signaling in the brain, and preferential inhibition of hepatic glucose production versus peripheral glucose uptake. Experiments in diabetic rats have also indicated that insulin detemir increases adiponectin levels, which is associated with both weight loss and decreased eating.
Reducing diabetes disparities through the implementation of a community health worker-led diabetes self-management education program

Walton JW, Snead CA, Collinsworth AW, Schmidt KL

*N Fam Community Health* 2012;35(2):161–171. Reprinted with permission from Lippincott Williams & Wilkins

Disparities in prevalence of type 2 diabetes and complications in underserved populations have been linked to poor quality of care including lack of access to diabetes management programs. Interventions utilizing community health workers (CHWs) to assist with diabetes management have demonstrated improvements in patient outcomes. Use of CHWs may be an effective model for providing care coordination and reducing disparities, but there is limited knowledge on how to implement this model on a large scale. This article describes how an integrated health care system implemented a CHW-led diabetes self-management education program targeting Hispanic patients and reports lessons learned from the first 18 months of operation.

**JOURNAL OF BIOMEDICAL INFORMATICS**

System engineering approach to documentation: An evaluation of the documentation process in a gastroenterology laboratory

Zhang B, Youngblood L, Murphy GD, Ramsay M, Xiao Y


Documentation processes are an indispensible part of patient care. Timely access to complete and accurate documentation is crucial to patient safety. However, there is no sufficient tool to help health care professionals effectively manage documentation processes. In this study, we developed an evaluation methodology, including a documentation matrix, a documentation process flow diagram, and a document value tool, to analyze the necessity and redundancy of the documentation processes. We applied this methodology in a gastrointestinal lab and improved the transparency of the documentation processes among providers.

**JOURNAL OF CARDIOVASCULAR NURSING**

Disparities in cardiac care for patients with complex cardiovascular care needs

Leeper B, Centeno M


The United States continues to have a prevailing public health problem related to disparities in healthcare. Factors contributing to disparities include ethnicity, gender, socioeconomic status, educational level, geographic location, and hospital characteristics. In cardiovascular care, gaps in care have been associated with lack of conformity to evidence-based therapies known to improve clinical outcomes, including survival, quality of life, and freedom from rehospitalization. Specifically, there are disparities in use of a number of cardiovascular life-saving procedures including cardiac catheterization, percutaneous coronary intervention, coronary artery bypass surgery, and implantation of defibrillators and cardiac resynchronization devices. The purpose of this article was to illustrate the range of disparities that exist in relation to management of patients with acute coronary syndromes, interventional cardiology procedures, cardiac surgery, heart failure, and device implantation. Because the impact on patient outcomes is high, potential interventions to address disparities will be provided.

**MEDICINE**

Cardiac findings at necropsy in patients with chronic kidney disease maintained on chronic hemodialysis

Roberts WC, Taylor MA, Shirani J


Studies of multiple hearts at necropsy are lacking in patients who have been on chronic hemodialysis for chronic kidney disease (CKD). We studied at necropsy 120 patients who had been treated with hemodialysis for more than 1 year (mean, 5.25 ± 4.33 yr). Their ages ranged from 24 to 81 years (mean, 53 yr); 91 (76%) were men. Calcific deposits were present in the heart at necropsy in 74 (62%) patients: in the epicardial coronary arteries in all 74 (62%); in the mitral annular region in 52 (42%) patients; and in the aortic valve cusps in 42 (35%) patients. The frequency and quantity of the cardiac calcific deposits were significantly greater in the older compared with the younger patients, and in those with longer durations of hemodialysis compared with those with shorter durations. Despite the calcific deposits, which were sometimes huge, only 47 (39%) patients had 1 or more coronary arteries narrowed more than 75% in cross-sectional area by atherosclerotic plaques, apparently no patient had clinical evidence of mitral stenosis, and 9 patients had clinical evidence of aortic valve stenosis. Thus, we found that CKD patients with chronic hemodialysis is a major producer of cardiac calcific deposits, some of which can be massive. Only a minority of the calcific deposits, however, appeared to lead to cardiac dysfunction or myocardial ischemia during life.

**NATURE REVIEWS CANCER**

Cancer immunotherapy via dendritic cells

Palucka K, Banchereau J


Cancer immunotherapy attempts to harness the power and specificity of the immune system to treat tumours. The molecular identification of human cancer-specific antigens has allowed the development of antigen-specific immunotherapy. In one approach, autologous antigen-specific T cells are expanded ex vivo and then re-infused into patients. Another approach is through vaccination; that is, the provision of an antigen together with an adjuvant to elicit therapeutic T cells in vivo. Owing to their properties, dendritic cells (DCs) are often called ‘nature’s adjuvants’ and thus have become the natural agents for antigen delivery. After four decades of research, it is now clear that DCs are at the centre of the immune system owing to their ability to control both immune tolerance and immunity. Thus, DCs are an essential target in efforts to generate therapeutic immunity against cancer.
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