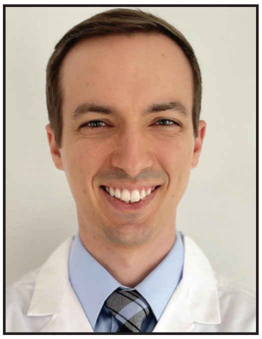
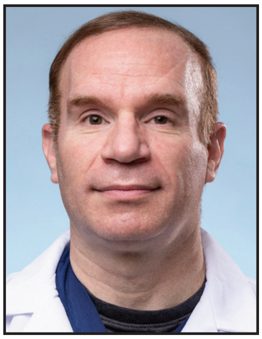
Douglas G. Adler MD, FACG, AGAF, FASGE, Series Editor

Endoscopic Management of Esophageal and Gastric Anastomotic Strictures



Michael B. Andrews



Douglas G. Adler

INTRODUCTION

Esophageal and gastric anastomotic strictures can be challenging to treat. Minimally-invasive therapeutic endoscopic intervention has overtaken surgical re-intervention as first-line therapy. This literature review aims to assess the technique, efficacy, and adverse events of the many currently available options for endoscopic management.

Esophageal Anastomotic Strictures

Etiology

Esophageal anastomotic strictures (EAS) are most commonly a post-operative adverse event following esophagectomy and esophageal atresia repair. The most common indication for esophagectomy is treatment of malignancy, but rarely, it may be indicated for treatment of benign esophageal disease in cases of severe obstruction, perforation, or dysmotility.[1] EAS remains a common problem. The reported rate of EAS following esophagectomy ranges between 5-46% with a large retrospective cohort study performed by Honkoop et al. demonstrating EAS development in 114 out of 269 (42%) patients.[2,3]

Esophageal atresia is a rare congenital anomaly affecting 1 in 3,500 births.[4] There are four types (A-D) of esophageal atresia of which type C is seen in 80-85% of cases and presents anatomically with a closed off upper esophagus and aberrant connection of the lower esophagus to the trachea.[5,6]

(continued on page 32)

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(continued from page 30)

Surgical repair is required, but post-operative EAS has been reported to develop in approximately one-third to one-half of patients.[4,7,8]

Risk Factors

Patient risk factors for EAS include pre-operative cardiovascular disease and diabetes.[2,9] Mendelson et al. reported lower risk for EAS in patients who had previously received neoadjuvant chemotherapy when esophagectomy was performed for malignancy.[10]

Surgical risk factors have been more extensively studied with data supporting post-operative anastomotic leakage as a driver of tissue ischemia, inflammation and eventual stricture development.[2,9] Anastomotic closure techniques, hand-sewn versus stapled, have also been analyzed without clear evidence to suggest one increases risk for EAS more than the other.[11,12]

Clinical Manifestations

Dysphagia is the most common clinical manifestation of EAS, described by patients as the inability to swallow, food becoming stuck in the throat, or regurgitation of food.[13] Dysphagia can be graded using the Atkinson's classification: grade 0 (ability to tolerate normal diet), grade 1 (ability to swallow some solids), grade 2 (ability to swallow semi-solids), grade 3 (ability to swallow liquids), and grade 4 (inability to swallow anything).[14]

Bougie and Endoscopic Balloon Dilation

Technique – Bougie Dilation

Bougie dilators are reusable push-type dilators available in various sizes with a fixed diameter exerting radial and longitudinal forces simultaneously as they pass through the stricture.[15] Hurst and Maloney bougie dilators (Medovations, Milwaukee, Wisc, and Teleflex Medical, Research Triangle Park, NC) do not use a guidewire and are instead pushed blindly with gravity assistance from tungsten within the dilator.[15] Savary-Gillard (Cook Medical, Winston-Salem, NC) and American Dilation System bougie dilators (ConMed, Utica, NY) utilize a guidewire placed endoscopically followed by passage of the bougie dilator over the wire, with or without fluoroscopic guidance.[15] Available diameters range from 16-60 French (Hurst), 36-54 French (Maloney), and 15-60 French (Savary-Gillard and American Dilation System).[15]

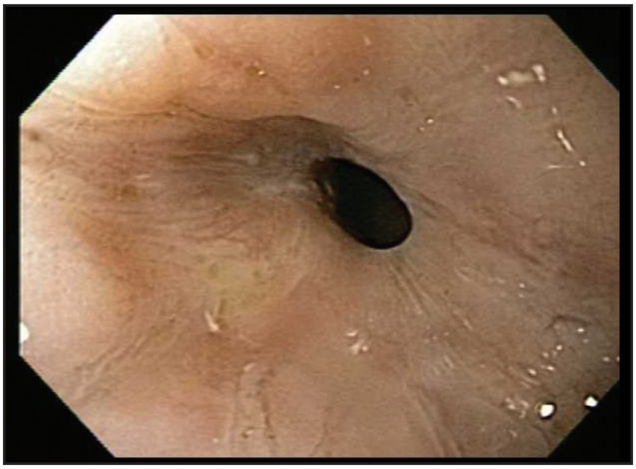

Figure 1a. Severe anastomotic stricture in the esophagus

Technique – Endoscopic Balloon Dilation

Balloon dilators are single-use, inflatable dilators of various diameters (6-20mm) designed to supply a radial force against the stricture.[15] The most common technique utilizes a through-the-scope (TTS) balloon dilator passed over a guidewire to position the balloon within the stricture prior to inflation with injection of saline or contrast.[15] Others are designed to be placed through the scope under endoscopic visualization without a guidewire, but these are rarely used in modern clinical practice.[15]

Efficacy

Results across multiple studies are similar for both bougie and endoscopic balloon dilation (EBD) with initial clinical success rates ranging from 70-90% following a median of two to nine dilation sessions, emphasizing how refractory some of these strictures can be.[2,14,16,17] van Halsema et al., in a retrospective cohort study of 179 patients, reported a stricture recurrence rate of 73.7%.[18] Risk factors for recurrence include diabetes and strictures longer than 10mm.[17] van Halsema et al. also showed significantly increased dilation-free days (92 vs. 41 days) and decreased recurrence rates (68.1% vs. 79.5%) with dilation >16mm diameter compared to 16mm.[18] There were no significant differences in adverse events including perforation between the two groups.[18]

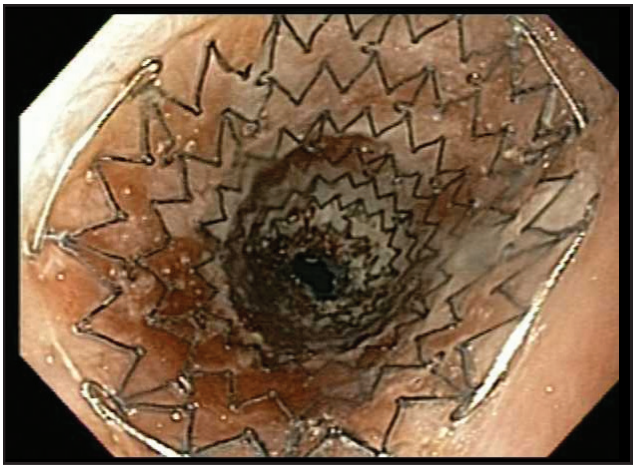

Figure 1b. Same stricture after placement of a fully covered esophageal stent

Adverse Events
van Halsema et al. reported an overall adverse event rate of 5.3% per patient and 1.0% per procedure.[18] The most notable adverse events were perforation rates of 3.6% per patient and 0.6% per procedure with bleeding in <1% of patients.[18]

Adjunctive Triamcinolone Injection
Technique
Intralesional injection of triamcinolone acetonide has been studied in multiple randomized control trials as adjunctive therapy to dilation of EAS.[19,20] Local steroid injection is thought to inhibit fibrotic healing and scar contracture following dilation.[21] While widely employed, steroid dosages and injection techniques vary based on operator preference and institutional experience. A meta-analysis by Dasari et al. reported dosages ranging from 40-50mg with multiple intralesional injections using a 25-gauge needle.[19,22]

Efficacy
Hanaoka et al. performed a randomized control trial of 65 patients and observed a two-fold reduction in the median number of dilation sessions required to achieve clinical success with adjunctive steroid injection compared to dilation alone.[19] The patients in the treatment arm also had a significantly higher six-month recurrence-free rate of 39% compared to 16% in the control arm (p-value < 0.01).[19] Pereira-Lima et al., in a randomized control trial limited by a small sample size of only 19 patients, had previously reported similar findings with a significantly higher six-month recurrence-free rate of 62% in the treatment arm compared to 0% in the control arm (p-value <0.01).[20]

Adverse Events
Neither Hanaoka et al. nor Pereira-Lima et al. reported any adverse events in their 84 combined patients including bleeding, pain, perforation, or Candida esophagitis.[19,20] However, in a more recent meta-analysis published in 2020, Dasari et al. reported a perforation rate of 1.4% and a Candida esophagitis rate of 5.5%.[22]

Self-Expandable Metal Stents
Technique
The first endoscopic stent type used to treat EAS was a self-expandable plastic stent (SEPS).[23] SEPS required assembly, were cumbersome to place, had high migration rates, and, despite some good clinical outcomes, are essentially obsolete and have since been replaced by self-expandable metal stents (SEMS).[23,24]

Modern SEMS have strong radial force and are available as uncovered (UCSEMS), partially covered (PCSEMS), or fully covered (FCSEMS) devices.[25] Commercially available stents in the United States include WallFlex stents (Boston Scientific, Natick, Massachusetts, United States), Endomaxx and Alimaxx stents (Merit Medical, South Jordan, Utah, United States), and Evolution stents (Cook Endoscopy, Winston-Salem, North Carolina, United States).[25,26] These stents are available in various lengths (6-16cm) and diameters (12-23mm) and are designed to prevent migration via proximal and/or distal flared ends with various stent designs including fins and scaling to further reduce migation.[25] Stents can be placed via endoscopy, fluoroscopy, or a combination thereof. (Figure 1)

Efficacy
Four retrospective cohort studies have shown clinical success rates ranging from 21-70%, but no individual study contained more than 50 patients with EAS.[27,28,29,30] Wu et al. treated EAS with PCSEMS showing a 12-month stricture-free recurrence rate of 70% and a mean improvement of one point in dysphagia grade.[27] Re-stenting was required in 12 out of 13 patients treated in

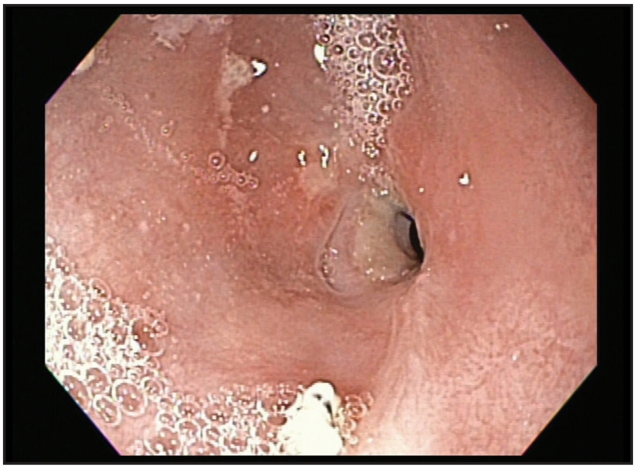

Figure 2a. Severe anastomotic stricture in the esophagus with some surrounding ulceration

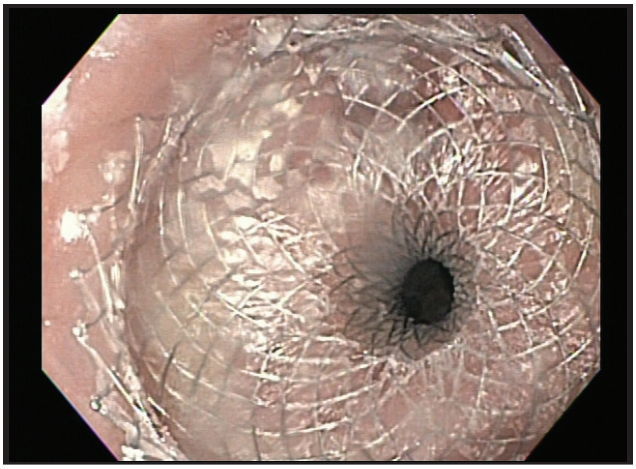

Figure 2b. Same stricture after placement of a lumen apposing esophageal stent

the retrospective study performed by Suzuki et al. using various types of SEMS, reflecting that many of these strictures can be refractory.[28] Bakken et al. and Eloubeidi et al. reported use of FCSEMS with stricture recurrence rates at approximately two months of 30% and 79%, respectively.[29,30]

Adverse Events

Stent migration remains a common adverse event occurring in approximately one-third of patients.[31] Suzuki et al. reported a similar migration rate of 38.5% in EAS patients using various types of SEMS.[28] The two studies that used only FCSEMS reported migration rates of 37.3% and 60%.[29,30] No perforations were reported among the four studies, but there was one incident of food impaction within the stent at day 128.[27,28,29,30]

It should be stressed that sometimes migration is not a true adverse event and may reflect the fact that the stricture has resolved, thus allowing the stent to migrate. This concept was highlighted by Thomas et al. in a large retrospective cohort study of 369 patients with benign or malignant esophageal strictures treated with various FCSEMS.[32] They observed total migration rates of 23-30% with clinically relevant migration rates of only 14-17%.[32]

Migration rates can be reduced using different anchoring techniques.[31] These include endoscopic suturing (which is more technically challenging and expensive) with a reported 17% migration rate.[33] Other techniques include deploying TTS or over-the-scope (OTS) clips with lower reported migration rates of 13% and 6.7-15%, respectively.[31,34] An FDA-approved stent fixation device on the market since 2019, the Stentfix OTS Clip System (Ovesco, AG-Tuebingen Germany), was prospectively studied by Manta et al. who reported a migration rate of only 3.2% and no adverse events when used.[31]

Lumen-Apposing Metal Stents

Technique

Lumen-apposing metal stents (LAMS) were originally approved by the FDA to drain pancreatic fluid collections but have since been widely used for the endoscopic treatment of a variety of other conditions, including EAS, in an off-label manner.[35] LAMS are fully covered, short stents with wide proximal and distal flanges to reduce migration.[35] The only commercially available LAMS in the United States is the AXIOS stent (Boston Scientific, Natick MA, United States) with a 10mm length, 6-15mm diameter, and flanges of 21 or 24mm diameter.[35,36] A guidewire is placed across the stricture under endoscopic and fluoroscopic guidance, and the stent is deployed with or without pre-stent or in-stent dilation.[35,37] (Figure 2) Stent dwell time has been commonly reported between 60-90 days, but is often individualized.[38,39]

Efficacy

LAMS have been used for short (<1cm) EAS with reported clinical success rates ranging from 50-100% among two case series and two retrospective cohort studies that combined reported on 17 patients.[36,37,38,39] The largest of these, an international multicenter retrospective cohort study by Santos-Fernandez, included seven patients with EAS and showed a 30-day symptom resolution rate of >80% which dropped to <50% at 90 days.[36] Larger studies specifically focused on use in EAS patients are needed.

Adverse Events

Out of the 17 patients, there were three (17.6%) stent migrations, two (11.8%) angulations, and development of a new proximal stricture made of granulation tissue in one case requiring balloon dilation to remove the stent.[36,37,38,39] No study reported bleeding or perforation.[36,37,38,39]

Biodegradable Stents

Technique

Biodegradable stents (BDS) made of synthetic polymers such as polydioxanone are designed to apply a radial force for approximately six weeks then degrade via hydrolysis over an additional six to 24 weeks.[40] This eliminates the need for a removal procedure, but the currently available BDS require assembly and supply a weaker radial force than traditional SEMS.[40] The SX-ELLA BDS (ELLA-CS, Hradec Kralove, Czech Republic) is the only commercially available BDS for esophageal use and is available in many lengths (60-135mm) and diameters (18-25mm).[41] This device is not approved for use in the United States. Once assembled, BDS are loaded onto a delivery system, advanced over a guidewire, and deployed with endoscopic and/or fluoroscopic visualization using radiopaque markers on both ends.[41]

Efficacy

There are limited studies on BDS for treatment of EAS. Sanchez Munoz et al.'s case report described an ideal sequence of events with successful placement, initial stent degradation at four weeks, complete stent resorption at five months, and a patent anastomosis without symptoms at 20-month follow-up.[42] Three prospective cohort studies with a combined 21 EAS patients reported clinical success rates of 25-60% with median dysphagia-free time of three to six months.[43,44,45] However, several patients experienced stricture recurrence requiring up to three BDS replacements to maintain long-term patency.[43,44,45]

Adverse Events

Using BDS, Hirdes et al. reported bleeding, stent migration, and food impaction in 11% and pain in 7% of patients.[43] van Boeckel et al. reported bleeding, pain, food impaction, and tissue overgrowth in 11% and stent migration in 22% of patients.[44] van Hooft et al. reported food impaction in 10% and obstruction due to stent epithelialization in 20% of patients.[45] Perforation was not reported in any of the studies.[43,44,45]

Endoscopic Incisional Therapy

Technique

Endoscopic incisional therapy (EIT) was first used to treat Schatzki rings and has been applied to refractory benign esophageal strictures as well.[46] Radial incision and cutting (RIC) is one method using an insulation-tip (IT) knife (KD611L, IT2, Olympus, Japan) or a standard needle knife to make radial incisions around the circumference of the stricture, sometimes with removal of the fibrotic tissue in-between incisions.[47,48,49,50] Radial incisions of operator-dependent length and depth are made perpendicular to the stricture.[49,50]

Efficacy

Clinical success of EIT ranges from 50-100% across multiple studies.[46,47,48,49,50] Two retrospective cohort studies with a combined 104 patients showed 50-63% of patients remained asymptomatic at six months.[46,47] In a case series of 20 patients, Hordijk et al. observed the 12 patients with strictures <1cm long remained asymptomatic at 12 months whereas 8 patients with strictures >1cm long experienced dysphagia recurrence.[49]

Jimoh et al. performed a meta-analysis showing EIT significantly reduced the odds (OR 0.32, p-value 0.03) of stricture recurrence in naïve EAS compared to EBD.[51] Muto et al.'s retrospective cohort study showed similar results with significantly higher 6-month (65.3% vs. 19.8%, p-value <0.005) and 12-month (61.5% and 19.8%, p-value <0.005) recurrence-free rates in patients treated with EIT compared to EBD.[47]

Adverse Events

Chest pain (up to 26%) was a commonly reported adverse event among published studies.[46,48] Bleeding was reported in 10% of patients.[46] There were no reports of perforation.[46,48,49,50]

Gastric Anastomotic Strictures

Etiology

Gastric anastomotic strictures most commonly develop following Roux-en-Y gastric bypass (RYGB) surgery but may also result following gastric resections for benign or malignant disease.[52,53] Gastric anastomotic strictures account for half of RYGB post-operative adverse events affecting 3-28% of patients.[52,53]

Risk Factors

Patient risk factors for gastric anastomotic strictures include pre-operative gastroesophageal reflux disease.[54] Risk for concomitant marginal ulcers increased in patients using tobacco, alcohol, or non-steroidal anti-inflammatory drugs (NSAIDS).[55]

Many studies have examined the impact of anastomotic closure techniques on the risk for developing gastric anastomotic strictures with conflicting results.[52,56,57] Jiang et al. performed a meta-analysis of 13,626 patients showing no significant difference in gastric anastomotic stricture rates between hand-sewn, circularly stapled, or linearly stapled anastomoses following laparoscopic RYGB.[56] However, a more recent meta-analysis by Jin et al. reported patients were at higher risk for gastric anastomotic strictures if circular stapling was used compared to linear stapling.[57]

Clinical Manifestations

Patients often present with obstructive symptoms including nausea, vomiting, early satiety, reflux, and/or dysphagia.[52,58] Carrodeguas et al. performed a retrospective cohort study of 1,291 patients noting mean symptom onset at 52 days (range 20-154 days) following surgery.[58]

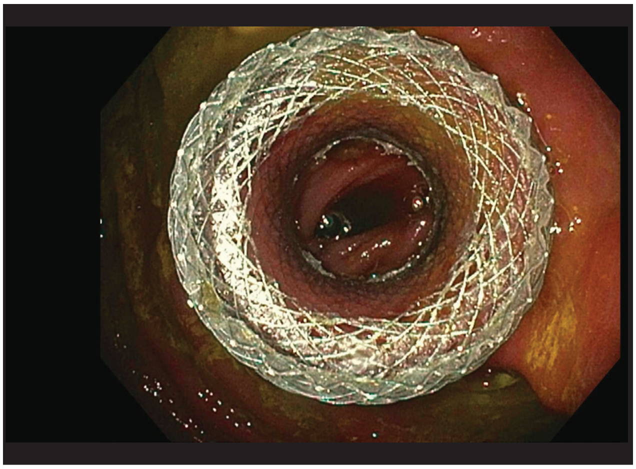

Figure 3. Lumen apposing metal stent placed across a high grade gastrojejunal anastomotic stricture

Endoscopic Balloon Dilation

Technique

TTS EBD is the most utilized method for dilating gastric anastomotic strictures.[59] Clinicians target a RYGB stoma diameter of 10-12mm.[52] The same EBD techniques described previously apply to gastric anastomotic stricture dilation with the balloon dilator positioned with or without a guidewire prior to inflation against the stricture.[15]

Efficacy

Meta-analyses by Baumann et al. (N=896) and Campos et al. (N=760) showed clinical success rates of 97% and 98%, respectively.[53,59] Baumann et al. noted only 38% of patients required multiple dilation sessions, and Campos et al. reported patients required a mean of 1.62 dilation sessions to achieve clinical success.[53,59]

Adverse Events

Perforation occurred in 1.8-2.3% of patients.[53,59] Baumann et al. reported only one incidence of bleeding out of 896 patients.[59]

Self-Expandable Metal Stents

Technique

The main barrier to using SEMS to treat gastric anastomotic strictures is the ability to reach the stricture with the stent delivery system.[60] Many of the previously described esophageal SEMS, especially the Endomaxx stents (Merit Medical, South Jordan, Utah, United States), can be used off-label if the stricture is within reach of the stent's sheath.[25] Cai et al. described successful use of longer FCSEMS Megastents (Taewoong Medical Industries, Kangseo-Gu Songjung-Dong, South Korea) available as 18 and 23cm to reach distal strictures.[52] This stent is designed with flares to reduce migration rates.[52] The Wallstent Enteral and Wallflex Duodenal stents (Boston Scientific, Natick, Massachusetts, United States) are other options available in lengths 60-120cm and diameters 20-22mm.[25]

Efficacy

Limited data exist regarding treatment of gastric anastomotic strictures with SEMS.[60,61,62] Randhawa et al. performed a prospective cohort study with six gastric anastomotic stricture patients showing an 83.3% clinical success rate.[61] Bakken et al.'s retrospective cohort study with 12 gastric anastomotic stricture patients described a clinical success rate of 75% at the time of stent removal but a 77% recurrence rate.[62]

Adverse Events

Stent migration is a commonly experienced adverse event seen in up to 50% of patients.[61,62] Previously described SEMS anchoring techniques may be used to reduce stent migration.[61] Randhawa et al. observed a decrease in migration rate from 28.6% to 0% when more than one endoscopic suture was applied to the FCSEMS.[61] Only one perforation was reported out of 19 patients.[60,61,62]

Lumen-Apposing Metal Stents

Technique

LAMS can be used in an off-label manner to treat gastric anastomotic strictures using the same technique described above for EAS.[63] (Figure 3) While operator dependent, Skidmore et al. described a case series of 14 patients where pre-stent dilation was avoided with the goal of reducing stent migration.[64]

Efficacy

Clinical success using LAMS ranges from 60-100% across many studies including a retrospective cohort study of 109 patients performed by Mahmoud et al. who reported 98.4% of patients were asymptomatic at 30 days.[63,64,65,66,67,68] However, stricture recurrence requiring re-intervention occurred in approximately half of patients.[68]

Adverse Events

Stent migration occurred in 10-27.3% of patients.[64,67,68] Chest pain was experienced by as many as 10-14% of patients.[64,68] Mahmoud et al. reported bleeding in 3.9% of patients.[68] Only one perforation was reported out of 154 total patients across all studies.[64,65,66,67,68]

CONCLUSION

Treatment of esophageal and gastric anastomotic strictures remains a significant challenge despite advancement in therapeutic endoscopic options. For esophageal anastomotic strictures, bougie and endoscopic balloon dilation remain first-line therapy despite high recurrence rates which are improved with adjunctive steroid injection. Other modalities include stent placement with SEMS, LAMS, or BDS, each with varying degrees of efficacy and adverse events, as well as endoscopic incisional therapy. Endoscopic management options for gastric anastomotic strictures are similar including endoscopic balloon dilation, if technically feasible based on stricture location, and stent placement with SEMS or LAMS. ■

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(continued from page 38)

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Answers to this month's crossword puzzle:

1 S	W	2 A	L	3 L	O	4 W	■	5 C	R	6 O	H	7 N	S	■
T	■	U	■	A	■	A	■	Y	■	R	■	E	■	8 E
9 R	O	T	A	V	I	R	U	S	■	10 G	L	A	11 N	D
E	■	O	■	A	■	■	■	T	■	A	■	12 R	B	I
13 T	R	I	G	G	E	14 R	S	■	15 A	N	U	S	■	B
T	■	M	■	E	■	E	■	16 A	■	I	■	■	17 A	L
18 A	C	M	E	■	■	19 S	T	R	I	C	T	20 U	R	E
■	■	U	■	21 S	■	E	■	R	■	■	■	P	■	■
22 K	I	N	E	T	I	C	■	23 H	U	24 E	■	25 P	E	26 P
E	■	E	■	A	■	T	■	Y	■	M	■	E	■	L
27 T	M	■	■	28 S	H	I	F	T	■	29 B	U	R	S	A
O	■	30 C	■	I	■	O	■	H	■	O	■	G	■	C
31 S	H	U	T	S	32 I	N	■	33 M	A	L	A	I	34 S	E
I	■	R	■	■	C	■	35 P	I	■	U	■	■	36 A	B
37 S	W	E	A	T	E	D	■	38 A	B	S	■	39 A	G	O