

The evolution and the natural selection process in the stenting of malignant bile duct obstruction: size does matter!

The history of nonsurgical decompression of malignant biliary strictures began in relatively recent times with the introduction of the first internal, indwelling plastic stent (PS), as initially reported in 1980 by Soehendra and Reynders-Frederix.¹ However, apropos of this being the 200-year anniversary of the birth of Charles Darwin, the topic does lend itself to an extension of the principles of natural selection regarding the evolution and current status of the technology. The article by Loew et al² in the current issue of *Gastrointestinal Endoscopy* is a multicenter randomized trial comparing different self-expanding metal stents (SEMSs) in the palliation of common bile and common hepatic duct biliary malignant strictures and adds significantly to the understanding of this ever-evolving technology.

As with the introduction of any new genus and subsequent species into an environment, the arrival and subsequent survival not only present new challenges, but also raise questions pertaining to the survival of the fittest. The questions raised will determine which technology will survive and which will evolve further to thrive. In the environment of biliary stenting, the factors leading to natural selection may be divided into 2 broad categories: (1) form and structure and (2) adaptation to surrounding conditions. Form and structural considerations include (1) selection of material, (2) shape, (3) conformation to the local geography or terrain, and (3) length and diameter. The factors necessary to adapt to natural environmental conditions comprise (1) delivery systems and technique, (2) complications resulting from use, (3) occlusion rates and etiologies, (4) longevity, (5) indication and location of use, and, finally, (6) cost. With these evolutionary factors in mind, the emerging trends in the development and optimal application of the technology become evident and dependent on which of the variables will become the dominant force for selection and survival.

The earlier, more primitive technology used plastic stents of varying materials, and after several years of evolution, the final material selected for plastic stents was polyethylene, although Teflon (DuPont, Wilmington, DE) has also been used effectively. This material was found to be the most stable, having the best combination of flexibility, stiffness,

and durability. Once the question of which was the best plastic material was resolved, a series of alternate stent species evolved, all trying to address the most significant survival issues of the time, which included stent migration, stent patency, and associated complications such as cholangitis, stent obstruction, and stent dislocation. Several of the variations included the single pigtail, double pigtail, straight, and physiologically curved straight stents. Additional subspecies were introduced that differed according to the

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presence of drainage holes on the sides, ends, or both; the number of drainage holes; and finally the development of side flaps located in a myriad of patterns and numbers and various stent widths. As natural selection would have it, the issue of stent obstruction was determined to be attributable to 2 main factors. Initially, the flow dynamics were thought to be the main consideration leading to stent occlusion, which is ruled by the physical law that flow is equal to $1/\text{radius}^3$. This caused the variations with side holes and pigtails to become extinct because of the inherent design compromise of flow dynamics and to give way to the “genetic” predisposition of the straight-type, wider stents in the 10F to 12F range with improved flow characteristics.³ Yet, even with these developments, stent occlusion was still a frustrating problem, necessitating the exchange of stents every 3 to 6 months. Thus, the second important factor was subsequently identified as the development of biofilm, or a combination of biliary and bacterial sludge.⁴ Attempts to introduce alternative designs to combat this problem such as the Tannenbaum design or concomitant antibiotic administration, also fell short from an evolutionary perspective and, as such, currently have a marginal existence.^{5,6} As for the stent migration issue, this was largely addressed with the introduction of anchoring side flaps, which have all but ensured the extinction of the pigtail stent species. Despite these adaptations, it became evident that the size or, more specifically, the width was vital. In this domain of

the PS, although the 11.5F to 12F PSs still exist, the 10F size is more widely used. This is owing to an evolutionary limitation, namely, the restriction of the size of endoscope channel and therefore an attendant difficulty in manipulation of the stent. Combined with the fact that the slight increase in width from 10F to 11.5F to 12F was not accompanied by a corresponding increase in stent life, the forces of natural selection favor the more agile and sleeker 10F species.⁷

As in any system of natural selection, the diameter restrictions of the plastic stents, the associated problems of obstruction, and short effective life span lead to the development of the next generation of stents. This next rung in the evolutionary ladder is represented by the development of the self-expanding open mesh metallic stent or SEMS. Initially introduced in 1990, the Wallstent (Boston Scientific, Natick, Mass) is an SEMS, compressible to 8F, which expands to 10 mm, allowing relatively easy delivery through a standard duodenoscope. The nature of the material used in the SEMS made the proper positioning somewhat challenging because of the expected foreshortening of the stent during expansion to a final 10-mm diameter. In theory and in practice, the vastly larger diameter improved stent patency by limiting susceptibility to the deposition of biofilm and sludge, which plagued the progenitor PS.^{8,9} Although deployment-related migration was occasionally an issue, once the stent was correctly placed, migration was rare, owing to the anchoring of the larger-diameter SEMS into the tissue of the bile duct. As with any new arrival on the evolutionary scene, there are always species-specific weaknesses, and for the SEMS, the weakness was related to limited available lengths, obstruction caused by tissue ingrowth through the open mesh of the SEMS, tumor overgrowth of the end of the prosthesis, and the deposition of debris. Despite these problems, numerous well-powered studies comparing PS and SEMS demonstrated significantly longer patency, on the order of 3 to 6 months versus 9+ months, respectively.¹⁰ However, given the significantly higher expense of an SEMS, selection of the stent type needs to be based on the expected longevity of the patient with malignant obstruction of the bile duct.¹¹

Once the evolutionary superiority of the SEMS was established, there was a move to diversify the technology. New species of the SEMS were developed with variations in (1) diameters including 6- to 10-mm varieties, (2) metal composition with the use of nitinol, (3) conformation and size of the wire opening, (4) delivery system improvements with elimination of foreshortening, and, more recently, (5) plastic coating of the wire mesh.

With the birth of the different varieties of new SEMSs have come the usual vetting process to determine which was the fittest to survive, considering the need to address the issues of occlusion, potential complications, migration, and ease of use. Although a number of studies began to emerge to answer these evolutionary questions, there was always one shortcoming, and that was size. Not the size of the SEMS, but rather the size of the sample or population being analyzed.¹²

Returning to the study by Loew et al,² known as MO-ZART I, in the current issue of *Gastrointestinal Endoscopy*, the issue of size, both of the sample and the SEMS, is addressed in such a manner as to shed light significantly on some of the selective issues regarding SEMSs. Different SEMSs were compared, specifically examining differences in width, materials, surface conformation, occlusion, biological factors of patency, longevity, ease of insertion, and complications. All patients in the study had unresectable common bile duct and/or common hepatic duct malignant strictures.

More specifically, the standard 10-mm Wallstent (Boston Scientific) and the 6- and 10-mm Zilver stents (Cook Medical, Winston-Salem, NC) were compared on an intent-to-treat basis. Interestingly, the 6-mm diameter arm was included based on the theory that by using a stent size that more closely approximated the normal bile duct wall size, there could be potentially less tissue ingrowth. Statistical considerations determined that to appropriately power the study, the sample size needed to contain 87 patients in each arm. In the two 10-mm SEMS arms, this was achieved; however, the 6-mm arm fell short of the goal because of early termination of that arm because of a significant and unacceptable rate of stent occlusion noted at the planned midpoint interim analysis. The characteristics of the patients in all 3 treatment arms were similar.

Despite a theoretical advantage of the 6-mm Zilver stent, there was a statistically significant and higher-than-expected occlusion rate of 39% and median patency length of 143 days compared with occlusion rates of 21% to 23% and median patency of 185 to 186 days in both 10-mm arms. These differences prompted discontinuation of the 6-mm arm at the interim analysis. There were no differences in ease of placement, cause of occlusion, or mechanism of placement. There were no complications of bleeding, cholangitis, perforation, or pancreatitis reported and no significant differences in patient survival in all 3 groups. When occlusion was noted, most of the time it was caused by tissue ingrowth, occurring 52% of the time, with other causes of occlusion attributable to tumor overgrowth (11%) and debris accumulation (22%). Of particular interest are the findings concerning the cause of the tissue ingrowth. Most of the time, based on biopsy results, the cause was benign epithelial hyperplasia. This occurred 56% of the time, with malignancy documented in only 44% of cases. These data may be limited by the fact that biopsy specimens were obtained in only 40% of the ingrowth cases.

The results of the trial help to clarify several of the factors posed regarding the natural selection of SEMSs. With specific reference to malignant bile duct obstruction, the variability of SEMS metal material type, opening size of the interstices in the metal mesh, ease of use and technique, and complications, there are no differences, and both species have equal chances for survival. Clearly demonstrated, however, is that the one overriding factor in the evolution of the best SEMS is the diameter of the stent.

There are, as always, some additional questions despite the strength of the reported study. The one factor not evaluated was whether the use of a covered SEMS would permit a greater chance for survival in this specific environment. In the literature, there are differing reports of the value of covered SEMSs versus PSs, but in the study by Soderlund and Linder,¹³ the patency and survival rates of covered SEMSs were lower than the rates reported for uncovered SEMSs. This study also did not have the same statistical power as the current study. Other more recent studies of uncovered SEMSs have reported variable occlusion rates upward of 40%. The one significant limiting factor in the survival of any stent, either an SEMS or a PS, still remains occlusion. In the case of SEMSs, the mechanism shifted away from bio-film and sludge to predominantly tissue ingrowth. As demonstrated in the current study and one other study,¹⁴ the predominant pathological etiology appears to be mostly epithelial hyperplasia. Although this may be addressed by a covered SEMS, there are other problems associated with covered SEMSs, such as occlusion caused by debris and migration, which may significantly affect the perceived benefit compared with uncovered SEMSs.

Another important factor in stent selection in this patient subset is cost, an issue that definitely cannot be ignored. If the anticipated survival of a patient is less than 3 to 6 months, the PS should still be the species that is best adapted to that niche. In the case of longer expected survival and unresectable disease, at least for now, an uncovered SEMS would be better suited to the terrain with both a cost and efficacy advantage. Will a covered SEMS eventually become the dominant species to occupy that space? Only time will tell because well-designed and sufficiently powered comparative studies have yet to be published to answer the question. Of course this does not even begin to answer the question of the environment in which benign biliary strictures dwell. There, the initial reports suggest that the easily removable covered SEMS may have at last found a place where it can become dominant and displace all other competitors.^{15,16} Perhaps one last and novel stent adaptation to consider as evolutionary is the development of stents impregnated with chemotherapeutic agents to help inhibit tumor ingrowth.¹⁷ This may give rise to a whole new generation of SEMS with prolonged stent life aimed at preventing tumor ingrowth.

As we continue, like Darwin, to categorize and observe the effects of natural selection on the interventional environment in which we practice, at least with regard to biliary stenting and statistical analysis, in nature, as is the case more often than not, the dominance and survival of the fittest are most often linked directly to size!

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Abbreviations: PS, plastic stent; SEMS, self-expanding metal stent.

REFERENCES

1. Soehendra N, Reynders-Frederix V. Palliative bile duct drainage—a new endoscopic method of introducing a transpapillary drain. *Endoscopy* 1980;12:8-11.
2. Loew BJ, Howell DA, Sanders MK, et al. Comparative performance of uncoated, self-expanding metal biliary stents of different designs in 2 diameters: final results of an international multicenter, randomized, controlled trial. *Gastrointest Endosc* 2009;70:445-53.
3. Speer AG, Cotton PB, MacRae KD. Endoscopic management of malignant biliary tract obstruction: stents of 10 French gauge are preferable to stents of 8 French gauge. *Gastrointest Endosc* 1988;34:412-7.
4. Leung JWC, Ling TKW, Kung JLS, et al. The role of bacteria in the blockage of biliary stents. *Gastrointest Endosc* 1988;34:19-22.
5. Catalano M, Geenen J, Lehman G, et al. "Tannenbaum" Teflon stents versus traditional polyethylene stents for treatment of malignant biliary stricture. *Gastrointest Endosc* 2002;55:354-8.
6. Luman W, Ghosh S, Palmer KR. A combination of ciprofloxacin and rowachol does not prevent biliary stent occlusion. *Gastrointest Endosc* 1999;49:316-21.
7. Kadakia SC, Starnes E. Comparison of 10 French gauge stent with 11.5 French gauge stent in patients with biliary tract diseases. *Gastrointest Endosc* 1992;38:454-9.
8. Davids PH, Groen AK, Rauws EA, et al. Randomised trial of selfexpanding metal stents versus polyethylene stents for distal malignant biliary obstruction. *Lancet* 1992;340:1488-92.
9. Knyrim K, Wagner HJ, Pausch J, et al. A prospective, randomized, controlled trial of metal stents for malignant obstruction of the common bile duct. *Endoscopy* 1993;25:207-12.
10. Kaassis M, Boyer J, Dumas R, et al. Plastic or metal stents for malignant stricture of the common bile duct? Results of a randomized prospective study. *Gastrointest Endosc* 2003;57:178-82.
11. Yeoh KG, Zimmerman MJ, Cunningham JT, et al. Comparative costs of metal versus plastic biliary stent strategies for malignant obstructive jaundice by decision analysis. *Gastrointest Endosc* 1999;49:466-71.
12. Howell DA, Desilets DJ, Dy RM, et al. Uncoated spiral Z-stents for malignant biliary obstruction: initial experience with endoscopic placement [abstract]. *Gastrointest Endosc* 2000;51:AB195.
13. Soderlund C, Linder S. Covered metal versus plastic stents for malignant common bile duct stenosis: a prospective, randomized, controlled trial. *Gastrointest Endosc* 2006;63:986-95.
14. Shah RJ, Howell DA, Desilets DJ, et al. Multicenter randomized trial of the spiral Z-stent compared with the Wallstent for malignant biliary obstruction. *Gastrointest Endosc* 2003;57:830-6.
15. Kahaleh M, Behm B, Clarke BW, et al. Temporary placement of covered self-expandable metal stents in benign biliary strictures: a new paradigm? *Gastrointest Endosc* 2008;67:446-54.
16. Behm BW, Brock A, Clarke BW, et al. Cost analysis of temporarily placed covered self expandable metallic stents versus plastic stents in biliary strictures related to chronic pancreatitis [abstract]. *Gastrointest Endosc* 2007;65:AB211.
17. Suk KT, Kim JW, Kim HS, et al. Human application of a metallic stent covered with a paclitaxel-incorporated membrane for malignant biliary obstruction: multicenter pilot study. *Gastrointest Endosc* 2007;66:798-803.