The coincidence of infective endocarditis (IE) caused by the organism Streptococcus gallolyticus (subsp gallolyticus, also referred to as Streptococcus bovis biotype I) and colon carcinoma has piqued the interest of infectious disease clinicians since an association between enterococcal endocarditis and sigmoid carcinoma was first documented in 1951 [1]. For more than 5 decades, the association between S. bovis IE and carcinoma of the colon has been the subject of numerous case reports [2–4]. In fact, statistics from the 1980s suggest that upwards of two-thirds of patients with S. bovis endocarditis were subsequently found to have malignant gastrointestinal tumors [5]. This well-documented association of IE of suspected S. bovis origin with colon carcinoma has changed contemporary clinical practice such that a diagnosis of S. gallolyticus subsp gallolyticus (SG) endocarditis or bacteremia often results in immediate referral of the patient for colonoscopy, in many cases prior to discharge from the hospital. Despite more than 2 dozen case reports, there has been no explanation for the coincidence of SG IE and colon carcinoma, and, in fact, this area of research has been relatively neglected until the past decade.

In this issue of the Journal, Boleij and colleagues [6] provide important data pointing to several virulence characteristics of SG that may play key roles in the pathogenesis of this remarkably adaptable organism. These investigators replicated the route of SG infection in vitro by using differentiated human epithelial colorectal adenocarcinoma cells (Caco-2) in a series of assays focusing on both bacterial and host cell responses. These studies focused on SG adhesion, invasion, translocation, biofilm formation, and ability to elicit an immune response in order to identify virulence characteristics that could provide an explanation for the link between SG IE and colon carcinoma. The results of this work suggest that this species of bacteria is uniquely able to translocate in a paracellular fashion across malignant intestinal epithelium without eliciting a significant immune response and then adhere to collagen-rich surfaces and form biofilms. These data are exciting in that they address the key putative first steps in the dissemination of the bacteria from the gut environment to the bloodstream and ultimately to other locations more favorable for colonization, such as collagen-rich surfaces of cardiac valves. Future studies can now build on this work by focusing on specific virulence factors responsible for these specific characteristics observed for SG, but not for other related streptococci and other far more numerous bacterial species inhabiting the gut.

What is unique about SG that it can exhibit these distinct properties? SG is a mannitol fermentation-positive member of the S. bovis group of group D streptococci and is found in the gastrointestinal tract of birds, ruminants, and a small proportion (2.5%–15%) of humans [3, 7]. Consumption of a high-sugar diet by ruminants can cause SG overgrowth, resulting in an overproduction of lactic acid in the gut, a condition called feedlot bloat [8]. SG grows in pairs or chains, is nonmotile, and is non-γ-hemolytic or minimally γ-hemolytic. Historically, this strain has been referred to as S. bovis biotype I, but within the past decade, the S. bovis group of organisms was divided into 4 major Streptococcus species (S. galloyticus, S. infantarius, S. macedonicus, and S. pasteurianus), of which S. galloyticus is the species most often linked to cases of IE [9], although infection by other streptococcal strains has also been linked to colon carcinoma [2]. Recent data
point to the role of distinctive metabolic and cell surface properties of SG that could contribute to both its adaptability to changes in the human gut environment and its ability to cause disease. Rusniok and colleagues [10] completed the first complete genome sequence of an SG isolate from a patient with IE and a colon carcinoma and found the presence of genes encoding proteins and enzymes that may provide a clear selective advantage in the gut as well as contribute to its pathogenicity. Unique to streptococcal strains was the presence of genes encoding enzymes that may be involved in the digestion of plant cell wall polysaccharides and tannins (a toxic byproduct of which is gallate, which this bacterium is uniquely capable of using as a carbon source) and biosynthetic pathways for pantothenate, nicotinamide adenine dinucleotide, and glutamate. These metabolic characteristics likely provide this organism with the ability to utilize diverse carbohydrates in the gut and give it a clear survival advantage over other species. Furthermore, numerous genes encoding possible virulence factors were identified in the study by Rusniok et al [10], including genes likely responsible for production of a polysaccharide capsule, glucan mucopoly saccharides (including hemi-cellulose, a putative component of biofilm produced by this species), 3 types of pili, and collagen-binding proteins. In addition, there is evidence that some of these genes may have been acquired by lateral gene transfer from other gut organisms. The proteins encoded by these genes may allow the organism not only to establish a niche in the harsh gut environment but also to become invasive and establish endovascular infection. Consistent with the findings from genome analyses are data showing that SG isolates from patients with IE express collagen-binding adhesins and pilus proteins [11] and adhere to extracellular matrix proteins found in aortic valves, including collagen types I and IV [12], and to endothelial cells [13].

In spite of the numerous case reports and interest in the relationship between SG, IE, and colon carcinoma, questions remain regarding the origin of the colon carcinoma and whether the presence of the bacteria facilitates carcinogenesis. Does SG play a causal role in the occurrence or progression of colon carcinoma, or does it simply take advantage of a preexisting colon polyp or carcinoma and use this to enter the bloodstream? A decade ago, Ellmerich and colleagues [14] addressed this question by injecting mice intraperitoneally with the carcinogen azoxymethane, followed by oral challenge with intact S. bovis or extracts containing S. bovis cell wall proteins. The intact bacteria, as well as the cell wall proteins, were found to up-regulate the production of interleukin 8 by up to 4-fold in colonic mucosa and also promote the progression of preneoplastic lesions to adenomas in the colon. These data suggest that the bacteria themselves, perhaps in situations of chronic infection, are capable of expediting the transformation of benign colonic lesions in a carcinogen-rich environment. While the results of the study by Ellmerich et al [14] were intriguing, there still remains a dearth of new data addressing the question of whether SG can be a major contributor to colon carcinogenesis in human populations.

Although the S. bovis carriage rate in the general population is relatively low, patients with colon cancer have been found to have a much higher carriage rate. These statistics have prompted investigators to examine the clinical importance of “silent” S. bovis infections in patients with colon carcinoma in an effort to develop early diagnostic tools for colon cancer. Tjalsma and colleagues [15] reported on the development of an immunocapture mass spectrometry approach to detect S. bovis diagnostic antigen profiles from serum samples from patients with colon cancers and polyps. In this study, serum antibodies were used to capture specific antigens from S. bovis. One diagnostic antigen peak was the surface-exposed histone-like protein (HlpA) on S. bovis, which is hypothesized to be involved in S. bovis attachment to colon cells. Antigen profiles were able to distinguish correctly 11 of 12 patients with colon cancer compared with the control subjects. Tjalsma and colleagues [15] propose that an antigen capture strategy could be used for the early detection of colon cancer, and it is likely that future studies may continue to focus on profiling patients with SG infection to develop these types of early diagnostics.

It is important for more studies to focus on the coincidence of SG IE and colon cancer, both to better understand the pathogenesis and to direct development of new diagnostics. According to the Centers for Disease Control and Prevention, colorectal cancer is the third most common malignancy in the United States and the third leading cause of cancer death among women, presenting clinicians and scientists with both diagnostic and therapeutic challenges and opportunities. The data presented by Boleij and colleagues [6] in this issue of the Journal represent a significant step forward in our understanding of the coincidence of SG IE and colon carcinoma. Their data, as well as data generated over the past decade, point to the incredible adaptability of this organism and its ability to become pathogenic under specific circumstances. Importantly, these studies by Boleij et al [6] point to several virulence characteristics that can now be the focus of targeted mutagenesis studies to determine the role of specific virulence factors in the pathogenesis of SG in IE occurring in the setting of colon carcinoma.

References

3. Klein RS, Recco RA, Catalano MT, Edberg SC, Casey JI, Steigbigel NH. Association of