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EDITORIAL

Systemic hernial disease protects against cancer: an hypothesis

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Abstract Research by herniologists from around the world has shown that abdominal defects, in the adult, are not caused by wear and tear but systemic hernial disease (herniosis), a disorder of connective tissue which affects the extracellular matrix (ECM). Wound healing may be affected, leading to recurrences after hernia repair or primary incisional herniation. Women with genitourinary prolapse show signs of herniosis in the pelvis. Diverticulosis coli, commonly seen in the elderly, like hernia, was once attributed to stress and strain from constipation. It is now suspected that herniosis weakens the colonic ECM, allowing the mucosa to form diverticula by herniating alongside the vasa recta. Remarkably, clinical studies of Saint's triad extending over the past 60 years have repeatedly demonstrated a highly significant relationship between colonic diverticula and abdominal herniae. Krones et al. (Int J Colorectal Dis 21:18–24, 2006) reported that diverticula and cancer are rarely coincident in the colon, despite aging. Their data indicate that the two pathologies arise in different ECMs. Klinge et al. (Int J Colorectal Dis 22:515–520, 2007), quoting Paget (Lancet 1:571–573, 1889), "Tumor cells can like seeds only grow if they fall on congenial soil," suggested that certain genes prevent stromal malignancy by influencing the microenvironment to stop epithelia from becoming cancerous. Thus, damage to the colonic ECM from hernial disease is conducive to diverticulosis, but hostile for cancer. Hernial disease being systemic, a similar ECM should be present throughout the body. Coincident diverticulosis and herniae support this hypothesis. Its validation requires further research involving the lifetime risk of cancer in patients with and without hernia. Since smoking causes both herniation and cancer, data from indulgers will have to be analyzed separately from abstainers.

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Introduction

Hippocrates (460–377 B.C.) [1] blamed abdominal protrusions on wear and tear. Russell [2] challenged this dogma when, influenced by pediatric hernias, he championed the congenital saccular theory for adults, encompassing inguinal, femoral, umbilical, obturator, and sciatic defects. Cure was sac excision, and recurrence indicated surgical error. In 1906 [3], he denied hernia could be acquired pathologically. Hessert [4] described atrophy associated with inguinal herniation, blaming it on congenital anatomic variation. Harrison [5] considered pathologic failure of the transversalis fascia to be the etiology of groin herniae. He was supported by Keith [6], "We are so apt to look on tendons, fascial structures and connective tissues as dead passive structures. They are certainly alive and the fact that hernias are so often multiple in middle aged and old people leads one to suspect that a pathological change in the connective tissues of the belly wall may render certain individuals particularly liable to hernia." Nevertheless, the surgical establishment maintained Russell's theory, McVay [7] insisting, "The treatment of hernia is surgical repair of a defect in normal musculo-aponeurotic structures."

Hernial disease

Read [8] encountered atrophy of the rectus sheath and transversalis fascia in the groin of a 27-year-old man with a direct hernia. His immediate diagnosis was 'connective

tissue disorder' based on experience with cardiovascular surgery performed on patients with formes frustes of Marfan's syndrome, a heritable disease of connective tissue [9–12]. Subsequent biochemical research on cases of inguinal herniation revealed disordered connective tissue metabolism in the extracellular matrix (ECM), resulting in diminished and abnormal collagen [13–16]. Biopsies of skin and pericardium showed similar pathology, signifying systemic disease [17]. These findings were confirmed and extended to other abdominal defects by herniologists from around the world. Similar signs of herniosis [18] have been reported by gynecologists in the pelves of women with genitourinary prolapse [19].

Diverticulosis coli

This condition is common in Western countries, where it affects a third of people over the age of 45 years. Unusual in the young, its incidence doubles in the aged. Like herniae, diverticula were once attributed to mechanical forces (heightened intraluminal pressure, intensified by straining, because of constipation related to slow transit of a fiber-deficient diet). Diverticulosis, which occurs mainly in the left colon, has an early onset in patients with heritable diseases of connective tissue, such as Marfan's and Ehlers–Danlos syndromes [20, 21] or polycystic kidney disease [22], along with their formes frustes. Interestingly, these pathologies also produce hernias.

Over the past two decades, biochemical analyses of the colonic ECM in patients with diverticulosis have revealed disordered collagen metabolism [23]. Increased cross-linking was associated with a decrease in mature Type I fibrils, while the weaker Type III collagen increased. Lowering of the collagen Type I/Type III ratio facilitates mucosal herniation through clefts in the bowel wall alongside the vasa recta. These findings mimic those reported in the abdominal and pelvic walls of those with either hernia or prolapse. Similar changes in the skin have been ascribed to systemic hernial disease (herniosis).

Saint, a remarkable diagnostician and surgeon, noticed in the 1940s that the elderly frequently aggregated diverticulosis coli, hiatus hernia, and cholelithiasis. In 1948, Muller, his student, reported on three such patients with 'Saint's triad' [24]. Foster and Knutson [25] concluded that this relationship appears seven to nine times more often than would be predicted by chance alone. Recent research [26], using a large retrospective database, found a highly significant coincident relationship between diverticulosis and either hiatal or any abdominal hernia ($P < 0.0001$). The authors concluded that herniosis was the likely cause of Saint's triad, thereby, supporting Keith's [6] prescient suggestion that diverticula of the colon are herniae of the bowel.

Diverticulosis and colon cancer

These diseases, which are common in Western countries, share several epidemiologic features. Both are unusual in the young, but their incidence steadily increases in the elderly. A diet low in fiber but rich in fat with delayed transit has been blamed for their pathogenesis, which has a genetic predisposition, as demonstrated by positive family histories. The close relationship between diverticula and cancer, arising mainly in the left colon, was not considered to be a problem until the early 1980s, when an endoscopic study [27] reported an increased risk of malignancy in patients with diverticulosis coli. Subsequent investigations gave conflicting results [28], diverticula being associated with increased risk, decreased, or having no association. This inconsistency has been attributed to faulty research design. Most studies were retrospective diagnoses having been obtained by either barium enema or endoscopy, which is often partial. Patient numbers were frequently small and analyses conducted without controlling for ethnicity, age, smoking, previous surgery, or follow-up. Some analyses included adenomata, polyps, crypts, and inflammation, along with invasive cancer.

In 2006, Krones et al. [29] reported a retrospective analysis of almost 2,000 patients operated on, after complete colonoscopy, for either diverticulosis coli or cancer of the colon. The colons of those with malignancy had a statistically significant reduction in the incidence of diverticula. Their explanation for the disparity was that oncogenesis requires a different ECM to that which produces diverticula. This hypothesis was tested in the following year [30] using segments of colon resected from patients because of either diverticulitis or cancer. An exhaustive analysis of ECM parameters in tumor-free colonic tissue in cancer patients was compared with those present in non-infected bowel from those having diverticulosis. Distinct differences were found, the most striking being found in those with malignancy, a significant decrease in the expression of TGF-beta. Since this cytokine is a tumor suppressant, invasive neoplasia is facilitated different to the ECM in the group with diverticula. The authors cited Paget [31], who likened tumor cells with the seed of plants, "that can only grow if they fall on congenial soil." They and others have pointed out that this concept is still valid [32].

Hypothesis

The foregoing data regarding the etiology of diverticulosis coli indicate that hernial disease causes defects in the bowel wall which allow mucosa to herniate. Since this malady is systemic, the ECM in other parts of these

patients' bodies should be similar to that in their colons, i.e., hostile to cancer. Further, others who present with an abdominal hernia, because of their highly significant and coincident relationship with diverticulosis coli [26], will also have a body resistant to malignancy, as they share systemic hernial disease. This antagonism to neoplasia will not apply to smokers who not only develop hernial disease, but also have a heightened risk of cancer [33].

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