# CLINICAL REVIEW: HEALING IN GASTROINTESTINAL ANASTOMOSES, PART I

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Gastrointestinal healing is a topic rarely reviewed in the literature, yet it is of paramount importance to the surgeon. Failure of anastomotic healing may lead to life-threatening complications, additional surgical procedures, increased length of stay, increased cost, long-term disability, and reduced quality of life for the patient. The goal of this article is to review the biological response to wounded tissue, to outline discrete differences between skin and gastrointestinal healing, to discuss local and systemic factors important to gastrointestinal healing, and to compare methods of measuring collagen content and strength of the newly formed anastomosis. Part II of this review will focus on techniques and therapies available to optimize anastomotic healing. © 2006 Wiley-Liss, Inc. Microsurgery 26:131–136, 2006.

Rapid and effective wound-healing is of paramount importance to the surgeon. Failure of wound-healing generally leads to potentially life-threatening complications, additional surgical procedures, increased length of hospital stay, increased cost, and long-term disability. Gastrointestinal healing is a topic rarely reviewed in the surgical literature. However, it is an essential aspect of any procedure involving the gastrointestinal tract. Despite many recent advances in surgical technology, our patients continue to suffer from anastomotic disruptions and strictures. In the United States, there were almost 50,000,000 surgical operations performed in 2003, and over 5 million of these were for diseases of the digestive system.[1] There is an estimated 10–20% anastomotic leak rate following an esophageal or colorectal resection.[2,3] This translates into an astronomical economical burden to society, and an even greater intangible cost to the patient in terms of disability, discomfort, and diminished quality of life.

The aim of this article is to review the biologic response to injured tissue, and to outline discrete differences between skin and gastrointestinal tissue healing. We will discuss local and systemic factors that influence gastrointestinal healing, and compare methods of measuring the collagen content and strength of the newly formed gastrointestinal anastomosis. Part II of this review will concentrate on the effect of local perfusion on gastrointestinal healing, with a focus on techniques and therapies aimed at improving anastomotic healing.

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## BIOLOGIC RESPONSE TO TISSUE INJURY

A wound is a disruption to the normal structure and function of tissue after a noxious insult. Wound-healing is a series of carefully regulated steps designed first to reestablish an immune barrier, and second to repair injured tissue. Initiation of the pathway begins immediately once a wound occurs, and follows a predictable, orderly reparative timetable (Fig. 1). The classic phases of wound healing have been studied extensively in skin, and are described below:[2,4]

1. *Inflammation or "lag" phase*: Platelets first create hemostasis at the site of injury by the formation of an insoluble fibrin-based clot. Increased permeability of vessels adjacent to the injury facilitates the efflux of inflammatory cells into the wound. Neutrophils are initially the dominant cell type, and their role is to rid the wound of invading microbes. Within 2–3 days, monocytes and tissue macrophages predominate. Macrophages synthesize and release a multitude of tissue growth factors, which are absolutely critical to the normal progression of tissue repair.
2. *Proliferation*: The proliferative phase begins with the arrival of fibroblasts at the wound site. Fibroblasts become the major cell type by day 4, and their arrival is regulated by various growth factors, including platelet-derived growth factor (PDGF), transforming growth factor (TGFβ), and basic fibroblast growth factor (bFGF). Fibroblasts replace the provisional matrix (established through the inflammatory phase) with collagen-rich granulation tissue. Normal soft tissue contains 80% type I collagen and 20% type III collagen. In contrast, acute wound granulation tissue contains approximately 30–40% type III collagen. Collagen synthesis requires hydroxylation of lysine and proline residues. Cofactors necessary for hydroxylation include ferrous iron, molecular oxygen, alpha-ketoglutarate, and vitamin C. Angiogenesis occurs

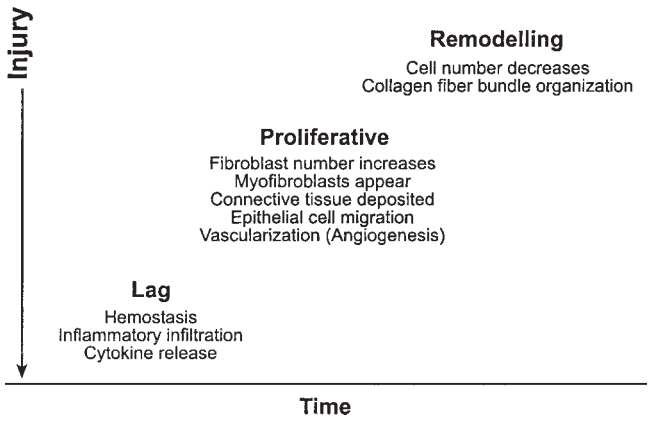


*Figure 1. Three time-limited phases of wound healing: 'lag' or inflammation, proliferative, and remodeling (adapted from Robson et al.,[2] 'Wound Healing: Biologic Features and Approaches to Maximize Healing Trajectories,' Curr Probl Surg 2001;38:71–140, with permission from Elsevier, Inc.).*

at this time to allow good oxygenation, and to supply essential nutrient building blocks to the healing wound.

3. *Remodeling*: With time, newly formed granulation tissue undergoes remodeling, and the density of macrophages and fibroblasts is reduced. Thin collagen fibers transform into thick collagen bundles, and the percentage of type III collagen reduces to 20%. Wound contraction occurs as fibroblasts pack thick collagen bundles into contractile units.

## HEALING IN THE GASTROINTESTINAL TRACT

### Anatomy

The gastrointestinal (GI) tract consists of four layers (with the exception of extraperitoneal structures such as the esophagus and the lower third of the rectum): mucosa, submucosa, muscularis propria, and serosa (Fig. 2). The mucosal layer consists of epithelium (generally columnar cells), lamina propria (loose connective tissue containing collagen), and muscularis mucosa (a thin layer of smooth muscle cells). Mucosal disruptions are repaired by migration and hyperplasia of epithelial cells. This seals the defect, and creates a barrier to luminal bacteria. Direct apposition of mucosa allows repair in as few as 3 days. In 1887, Halsted discovered that the submucosa provides the GI tract with the majority of its tensile strength.[5] The bulk of collagen is contained within this layer, along with blood vessels, lymphatics, and nerve fibers. Type I collagen predominates (68%), followed by type III collagen (20%) and type V collagen (12%).[5,6] The muscularis propria consists primarily of smooth muscle cells intermixed with a network of collagen. The collagen content in this layer increases significantly in response to chronic obstruction.[6]

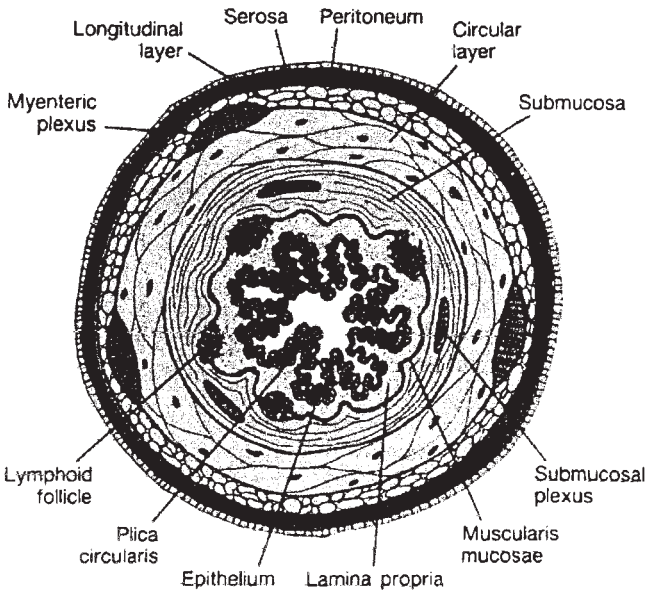


*Figure 2. Cross-section of large intestine illustrates four principal layers of gastrointestinal tract. Submucosal layer provides majority of strength to anastomosis, and is critically important during 'lag' phase of wound-healing. Extraperitoneal structures (such as esophagus and distal rectum) do not have serosal layer (reprinted from Thornton and Barbul,[5] 'Healing in the Gastrointestinal Tract,' Surg Clin North Am 1997;77:549–573, with permission from Elsevier, Inc.).*

The serosa is a thin layer of connective tissue that covers the muscularis propria. When creating an anastomosis, direct apposition of this layer minimizes the risk of leak.[5]

### Physiology of Anastomotic Healing

As described above, healing in a gastrointestinal anastomosis begins with inflammation, or the "lag" phase. An initial hemostatic response with vasoconstriction is followed by increased vessel permeability. This facilitates the efflux of inflammatory cells (neutrophils) into the wound. Shortly thereafter, macrophages can be seen in the anastomotic site, where they synthesize and release tissue growth factors. Granulation tissue in the anastomosis marks the beginning of the proliferative phase, and wound collagen undergoes both lysis and synthesis. The strength of the anastomosis is mainly derived from collagen fibrils, located within the submucosal layer. During the first few postoperative days, anastomotic strength is low, as collagen is degraded secondary to collagenase activity at the site of the injury. Early anastomotic strength is therefore dependent on the suture- or staple-holding capacity of existing collagen until large amounts of new collagen can be synthesized by both fibroblasts and smooth muscle cells. Postoperatively, the anastomosis will be weak for 1 or 2 days until this occurs (Fig. 3). The final phase of healing involves maturation of the newly formed anastomosis. The density of macrophages and fibroblasts in the anastomosis

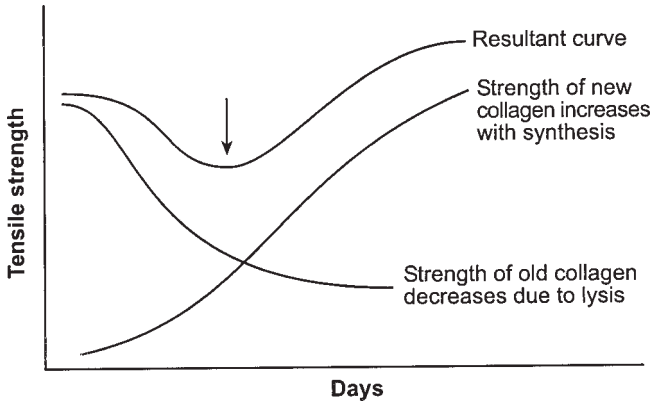


*Figure 3. Wound-healing in gastrointestinal tract is fine balance during 'lag' phase between collagen synthesis and collagenolysis. Line labeled 'resultant curve' shows this balance. Weak time period depicted on graph (arrow) can be prolonged or exacerbated by local or systemic factors that upset equilibrium (adapted from Thornton and Barbul,[5] 'Healing in the Gastrointestinal Tract,' Surg Clin North Am 1997;77:549–573, with permission from Elsevier, Inc.).*

decreases, and newly formed collagen transforms into thick bundles and contractile units.[5,7,8]

## DIFFERENCES BETWEEN SKIN AND GASTROINTESTINAL HEALING

Although the three classic phases of wound-healing were originally studied in skin, they exist in all tissues, including the gastrointestinal tract. However, there are some significant differences between skin and gastrointestinal healing that merit discussion. These differences are listed in Table 1.[5,6,8,9] The GI tract consists of three subtypes of collagen, in contrast to skin, which consists of two subtypes only. While collagen is produced solely by fibroblasts in skin, smooth muscle cells contribute to collagen formation in gastrointestinal tissue. Smooth muscle cells are located in both the muscularis mucosal layer and the muscularis propria of the GI tract. The environment for wound-healing is substantially different in an anastomosis due to the presence of shear stress (secondary to intraluminal bulk transit and peristalsis), and aerobic and anaerobic bacteria. Of utmost importance is the downregulation of vascular perfusion to the GI tract in states of hypovolemic shock. Anastomotic failure can be directly attributed to ischemia in these patients (to be discussed further, below).[5,6,8,9]

Although a more rapid gain in strength occurs in the GI tract than in cutaneous wounds (Fig. 4), neither regain their full preoperative strength. Furthermore, Martens and Hendriks[7] found that collagen synthesis occurs more quickly and to a greater extent in wounded ileum vs. wounded colon in a rat model. Other studies supported this finding, as they found the transient decrease in anastomotic collagen (secondary to collagenase activity) to be less pronounced in the ileum. Small-bowel anastomoses approach the strength of unwounded tissue 4 weeks following injury, while colonic anastomoses approach 75% of normal strength at 4 months.[6,7]

**Table 1.** Differences Between Skin and GI Tract Wound-Healing

| | GI tract | Skin |
|---|---|---|
| Collagen | | |
| Subtypes | 1, 3, 5 | 1, 3 |
| Production | Smooth muscle cells and fibroblasts | Fibroblasts only |
| Regulation[a] | TGF-β | TGF-β, dexamethasone, interleukin-lβ |
| Wound strength | | |
| Rate of healing | Rapid (weeks) | Prolonged (months) |
| Components | Additional strength due to serosa | No serosal equivalent |
| Wound environment | | |
| Shear stress | Increased, secondary to intraluminal bulk transit and peristalsis | Minimal |
| Bacteria | Aerobic and anaerobic, may affect anastomotic healing | Aerobic, rarely cause problems |
| Vascular perfusion | Downregulated in states of hypovolemic shock | Constant |
| Collagenase activity | Increased during first 3 days; causes transient decrease in anastomotic strength | Not significant |

[a]*Serum interleukin-lβ and dexamethasone inhibit collagen synthesis in skin fibroblasts but not in colon fibroblasts. Transforming growth factor-β (TGF-β) stimulates collagen synthesis in dermal fibroblasts, but inhibits process in colon fibroblasts.*

## FAILURE OF GASTROINTESTINAL HEALING

As described above, wound-healing is a complex process that involves the interaction of predictable, orderly, and time-dependent components. The outcome of healing can therefore be measured over time using a wound-healing trajectory (Fig. 5).[2] The classic acute wound-healing trajectory is a sigmoid-shaped curve with time on the abscissa, and tensile or breaking strength on the ordinate. The curve begins with a flat "lag phase" that represents the beginning of the wound-healing cascade. The risk of wound failure is greatest at this time, especially in gastrointestinal healing, when collagenase activity is greatest. After 48 h, the strength in esophageal anastomoses decreases by almost 40%, while colonic anastomoses lose 70% of their initial strength.[5] Proliferation is depicted on the graph with a steep slope, followed by a flattening out of the trajectory once remodeling begins. This indicates that the anastomosis is becoming stronger up to a point.

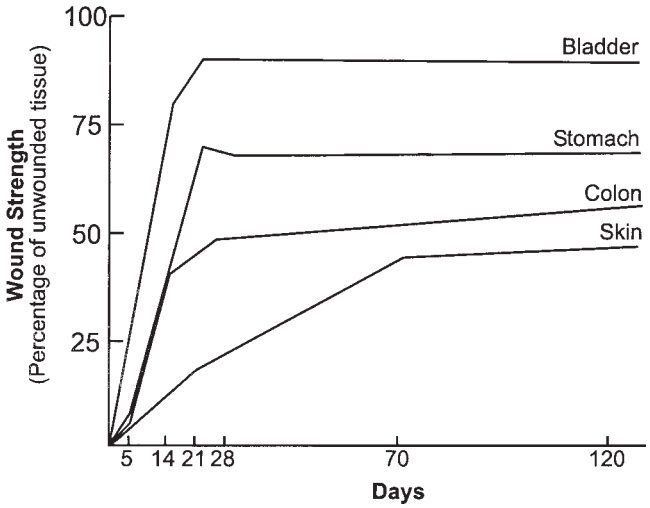


*Figure 4. Comparison of rate of wound-healing in different tissues (assessed by breaking strength). Healing in gastrointestinal tract occurs faster than in skin (adapted from Thornton and Barbul,[5] 'Healing in the Gastrointestinal Tract,' Surg Clin North Am 1997;77:549–573, with permission from Elsevier, Inc.).*

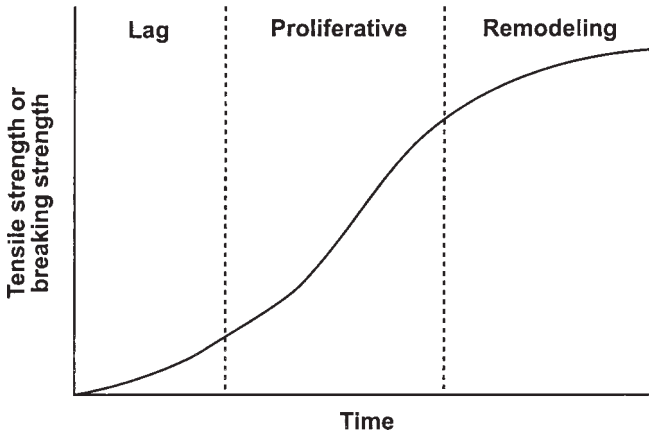


*Figure 5. Acute wound-healing trajectory curve is sigmoid-shaped curve. Tensile or breaking strength is depicted on ordinate, and time on abscissa. 'Lag,' proliferative, and remodeling phases are labeled on curve (adapted from Robson et al.,[2] 'Wound Healing: Biologic Features and Approaches to Maximize Healing Trajectories,' Curr Probl Surg 2001;38:71–140, with permission from Elsevier, Inc.).*

Wound-healing failure occurs when there is an abnormality in either the degree or duration of one of the components of tissue repair. In essence, it is "an interruption in the timely recovery of the injured tissue's mechanical integrity."[10] Factors that deter gastrointestinal healing shift the wound-healing trajectory to the right, and factors that accelerate healing shift the curve to the left. Local and systemic factors that may cause failure of gastrointestinal healing are listed in Table 2.[3,11–18]

**Table 2.** Detrimental Local and Systemic Factors in Gastrointestinal Healing

| Local | Systemic |
|---|---|
| Tissue hypoperfusion | Malnutrition |
| Anastomotic tension | Blood transfusion |
| Poor apposition of wound edges | Hypovolemia/shock |
| Local infection | Medication (e.g., cisplatin) |
| Radiation injury | Immunodeficient state |
| Distal obstruction | Poorly controlled diabetes |
| | Jaundice |

## Tissue Perfusion

Ischemic tissue does not heal well. Wound-tissue oxygenation is contigent on three factors: vascular anatomy, vasomotor control, and arterial tissue oxygen pressure ($pO_2$). Therefore, the surgeon needs to ensure that the patient has good local perfusion to the healing anastamosis, adequate cardiac output, and optimal oxygen saturation levels. Local tissue perfusion is dependent on preservation of vascular arcades, and avoidance of anastomotic tension. Tension is least tolerated in the colon. It is important to avoid hypovolemia in the perioperative period, as perfusion to the GI tract will be downregulated to support critical organs. Finally, adequate oxygen delivery is necessary for the synthesis of collagen. Mature collagen formation fails when $pO_2$ drops below 40 mm Hg. Below 10 mm Hg, growth factors, angiogenesis, and epithelialization are all impaired, and anastomotic failure will occur. Of interest, anemia has not been shown to impair wound-healing, as long as perfusion is sufficient. Hematocrit levels up to 15% below normal are tolerated as long as patients have good cardiac output and no peripheral vasoconstriction.[2,12,19,20]

## Other Factors Detrimental to GI Tract Healing

Wound-healing requires energy and adequate nutritional intake by the patient. Malnourished patients are predisposed to wound failure, as they lack some of the necessary vitamins and minerals for repair. These include vitamins A, C, and $B_6$, all of which are required for collagen synthesis and cross-linking, as well as zinc and copper.[2,10] Zinc and iron act as cofactors to many reactions involved in DNA synthesis, protein synthesis, and cellular proliferation.[2] Deficiencies in zinc and/or iron result in suboptimal fibroblast proliferation, and impaired collagen synthesis.[2] Low iron levels indirectly impair anastomotic healing, secondary to reduced oxygen transport during anemia. Blood transfusions were shown in an animal model to impair the healing of small-bowel and colonic anastamoses.[5,12] This is thought to be due to an alteration in the inflammatory phase of wound-healing, specifically, an impairment of migration or function of macrophages present in the wound. As described above, macrophages are essential to wound-healing, and significantly impair the process if neither present nor functioning.

Local infection impairs wound-healing by prolonging the inflammatory phase, and inducing the increased expression of tissue proteases. Elevated tissue proteases digest growth

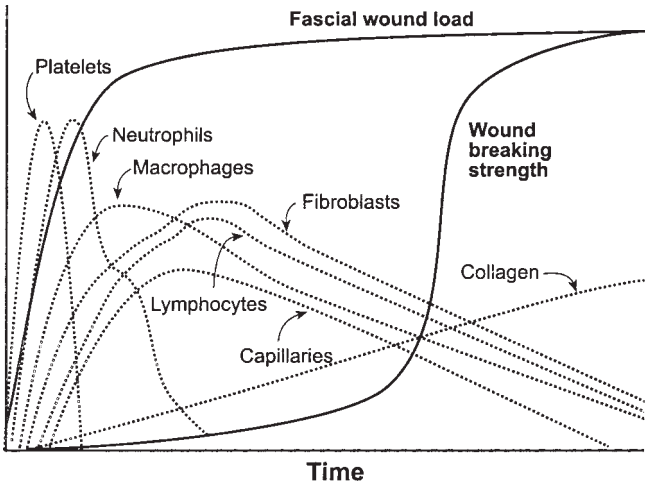


*Figure 6. Acute wound-healing failure occurs when load placed across wound exceeds resistive capacity of suture line and provisional matrix. During 'lag' phase of wound healing, wound is dependent on suture-holding capacity of submucosal layer. As proliferation occurs, breaking strengths are achieved that are capable of offsetting increased loads placed across anastomosis (adapted from Dubay and Franz,[10] 'Acute Wound Healing: The Biology of Acute Wound Failure,' Surg Clin North Am 2003;83:463–481, with permission from Elsevier, Inc.).*

**Table 3.** Methods to Measure Collagen Content or Strength of Gastrointestinal Anastomosis

| Method | Definition |
|---|---|
| Bursting strength/pressure | Maximum intracolonic pressure at burst when inflating anastomosed segment to disruption<br>Can only be used for first few days after operation<br>Reflects weakest site of anastomosis<br>Bursting site is usually outside suture line >7 days |
| Breaking strength | Maximum distractive forces required to break anastomosis<br>Early breaking strength reflects suture-holding capacity of two ends of of bowel<br>Reflects entire suture line<br>Correlates with collagen synthesis >4 days |
| Hydroxyproline content | Collagen content in anastomosis after acid-hydrolysis |
| Collagen deposition rate | Rate of in vivo collagen synthesis in anastomosis per hour<br>Venous injection of $^{14}$C-proline 4 h later, determine production of $^{14}$C-hydroxyproline in anastomosis<br>Collagen deposition rate of intact colon = 14.6% per day (0.6% per hour) |

factors, and thus delay epithelialization and collagen deposition.[2] Localized preoperative or perioperative bowel irradiation was not shown to compromise anastomotic healing in an animal model. It is hypothesized that if radiation is given *prior* to the influx of macrophages into the wound, a normal healing cascade will occur.[5,18]

It is important to note that several factors are conspicuous in their absence from the above list. These include age, steroid administration, and bowel preparation. A well-designed study by Stoop et al.[21] demonstrated that advanced age alone does not affect the collagen content or strength of either ileal or colonic anastomoses in a rat model. These results correlate well with retrospective studies that did not find age to be an independent risk factor for anastomotic complications. The issue of corticosteroid administration is less clear. Mastboom et al.[17] found no reduction in collagen content or anastomotic strength (measured by hydroxyproline content and bursting pressure) in ileal and colonic anastomoses in rats receiving methylprednisolone. However, Furst et al.[14] found a decrease in bursting pressure in colonic anastomoses after postoperative day 4 in an animal model. It is unclear whether malnutrition in these animals was a confounding factor. A recent meta-analysis by Slim et al.[22] concluded that omission of bowel preparation prior to elective colorectal surgery has no influence on the occurrence of postoperative anastomotic leakage. Furthermore, subgroup analysis suggested that mechanical bowel preparation with polyethylene glycol actually increases the risk of anastomotic leakage.[22] Two recent randomized studies, not included in the above meta-analysis, also support these findings.[23,24] The surgical dogma that bowel preparation is necessary before colorectal surgery should certainly be reconsidered.

## MEASUREMENT OF GASTROINTESTINAL HEALING

Failure of gastrointestinal healing occurs when the radial forces on an anastomosis exceed the resistive forces generated by the sutures and early scar (Fig. 6). A few methods exist to measure collagen content and anastomotic strength in the gastrointestinal tract. These are outlined in Table 3.[10,25] Methods to quantify anastomotic strength include bursting strength or pressure and breaking strength. Tensile strength normalizes breaking stength to the surface area of the wound edge. It therefore measures the physical property of the specific wound. It is rarely used in current studies, and is therefore not included in Table 3. Methods to measure collagen content include hydroxyproline content and collagen deposition rate.

Gastrointestinal anastomoses lose much of their strength during the first 2–3 days. Bursting pressure is therefore lowest during the first 3 days, after which anastomotic strength is rapidly gained. Bursting pressure is 50% of normal in small-

bowel anastomoses, and 35–75% of normal in large-bowel anastomoses at 2–3 days postoperatively. Bursting pressure approaches 100% at 7 days, after which the intestine will generally burst outside of the suture line. Breaking strength is regained at a slower pace. It was found to be 50% that of a normal colon at 10 days postinjury.[26,27]

## CONCLUSIONS

Wound-healing in the gastrointestinal tract occurs by inflammation, proliferation, and remodeling. Important differences, however, exist between cutaneous and gastrointestinal healing. The most striking differences include the production and regulation of collagen synthesis, the importance of the submucosal layer to anastomotic integrity, and the effect of collagenase activity early in the acute wound-healing trajectory. A few local and systemic factors may cause failure of both gastrointestinal and skin wound-healing. Of note, age, steroid administration, and bowel preparation have not definitively been shown to alter the collagen content or strength of a gastrointestinal anastomosis. It behooves the surgeon to be aware of all factors important in gastrointestinal healing. This will allow the surgeon to optimize his/her operation, and ultimately decrease the dreaded complication rate of an anastomotic leak.

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