A Primer on Wound Healing in Colorectal Surgery in the Age of Bioprosthetic Materials

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Abstract

Wound healing is a complex, dynamic process that is vital for closure of cutaneous injuries, restoration of abdominal wall integrity after laparotomy closure, and to prevent anastomotic dehiscence after bowel surgery. Derangements in healing have been described in multiple processes including diabetes mellitus, corticosteroid use, irradiation for malignancy, and inflammatory bowel disease. A thorough understanding of the process of healing is necessary for clinical decision making and knowledge of the current state of the science may lead future researchers in developing methods to enable our ability to modulate healing, ultimately improving outcomes. An exciting example of this ability is the use of bioprosthetic materials used for abdominal wall surgery (hernia repair/reconstruction). These bioprosthetic meshes are able to regenerate and remodel from an allograft or xenograft collagen matrix into site-specific tissue; ultimately being degraded and minimizing the risk of long-term complications seen with synthetic materials. The purpose of this article is to review healing as it relates to cutaneous and intestinal trauma and surgery, factors that impact wound healing, and wound healing as it pertains to bioprosthetic materials.

Keywords

- wound healing
- gastrointestinal
- anastomosis
- bioprosthetic mesh

CME Objectives: On completion of this article, the reader should understand healing related to cutaneous and bowel injury and surgery, and how wound healing applies to bioprosthetic meshes and some of the advantages and disadvantages to their use for abdominal wall surgery.

The human bodies' ability to heal after injury to various tissues is one of its most remarkable characteristics. This process has been studied for centuries but remains understood at a very basic level. Our knowledge of the process of cutaneous healing can be extended to many tissue types in the body, including hollow viscera. This report reviews the concept of wound healing as it relates to cutaneous injury and bowel surgery and factors that affect wound healing and describes healing as it pertains to biologic implants, specifically bioprosthetic meshes.

Overview of Wound Healing

For simplicity, wound healing has been described in four discrete phases (► **Table 1**). However, healing is a dynamic process that flows along a continuum, relies upon multiple cell types that function during multiple phases of healing, and employs complex molecular signaling that makes clear that our organization into phases is quite random and arbitrary and not completely true to the elegant process. Timing of the phases begins immediately after injury with a predominant vascular response consisting of vasoconstriction and arrival of platelets to the injured site.¹ The inflammatory phase begins shortly after vasoconstriction, typically lasting from day 1 to approximately day 10 and is heralded by the arrival of neutrophils followed by macrophages.² Fibroblast arrival indicates the beginning of the proliferative phase of

Table 1 Overview of wound healing

Phase of healing	Timing	Cell types involved	Extracellular factors	Notes
Hemostasis	Immediate	Platelets	ADP, PDGF, EGF, IGF-1, TGF- β	Clot/fibrin plug formation
Inflammation	Days 1–10	Neutrophils	TNF- α , IL-1, collagenase, elastase	Growth factor elaboration
		Macrophages	TGF- β , PDGF, TGF- α , bFGF, HB-EGF, IL-1, TNF- α	
		T-lymphocytes	FAF, TNF- α	
Proliferation	Days 5–21	Fibroblasts	IGF-1, bFGF, TGF- β , PDGF, EGF	Collagen deposition (overlap with inflammatory phase)
		Endothelial cells	VEGF, bFGF, PDGF	
		Smooth muscle cells		
		Epithelial cells	TGF- β , TGF- α , KDAF	
Remodeling	Day 21–1 year	Fibroblasts	Collagenases, MMPs	Collagen cross-linking

Abbreviations: ADP, adenosine diphosphate; bFGF, basic fibroblast growth factor; EGF, epidermal growth factor; FAF, fibroblast activating factor; HB-EGF, heparin-binding epidermal growth factor; IGF-1, insulin-like growth factor; IL-1, interleukin; KDAF, keratinocyte-derived autocrine factor; MMPs, matrix metalloproteinases; PDGF, platelet-derived growth factor; TGF- β , transforming growth factor; TNF- α , tumor necrosis factor; VEGF, vascular endothelial growth factor.

healing which overlaps with inflammation and lasts from day 5 to approximately 3 weeks after injury.³ The final phase of healing, remodeling, lasts from the end of the proliferative phase and can continue for up to 1 year after injury and is typified by collagen synthesis and degradation and a replacement of type III collagen by type I within the wound.¹

Hemostasis

The first phase of wound healing when incision or traumatic injury is involved is initiated by vasoconstriction and activation of the clotting cascade at the site of injury and occurs almost immediately after injury.¹ Clot that develops at the site of injury maintains adjacent vascular integrity and provides a scaffold for initiation of healing.⁴ Within the clot itself, conversion of fibrinogen to fibrin and the subsequent fibrin-rich clot is the initial step in construction of the provisional extracellular matrix (ECM).⁵ This scaffold also functions by facilitating inflammatory and mesenchymal cell migration. The presence of thrombin in the clot assists by increasing adjacent vascular permeability, facilitating migration of inflammatory mediators; thrombin may also have a continued role in healing by its involvement in angiogenesis and re-epithelialization.⁵ Fibronectin is a key component of the provisional ECM; deposited in the first 24 hours after injury and promoting adhesion and migration of inflammatory and epithelial cells.⁶ Fibronectin, which is also present in a soluble, nonreactive form circulating in blood, is secreted, bound, and assembled into fibrils in the provisional ECM by local fibroblasts, endothelial cells, and vascular smooth muscle cells. The assembly of fibrils in the ECM is via the polymerization of fibronectin creating a highly adhesive protein which interacts with cells via integrins.⁷ Cross-linking of fibronectin promotes fibroblast adhesion and migration into the provisional ECM and promotes platelet adhesion and aggregation.⁸ Platelets can best be thought of as

early modulators of healing. Platelets, having contacted exposed collagen in the injured microvasculature and dermis of a cutaneous wound aggregate and degranulate. Adenosine diphosphate is released by platelets after their adherence to this exposed collagen, stimulating further aggregation as well as release of inflammatory cytokines and growth factors residing within α granules.¹ The growth factors released from platelet α granules (platelet-derived growth factor [PDGF], transforming growth factor [TGF]- β) effect neutrophils, macrophages, smooth muscle cells, and fibroblasts, illustrating the continuum of wound healing.^{1,9} Growth factors also control cell growth, migration, differentiation, proliferation, and protein production within the wound.

Inflammation

The inflammatory phase of wound healing is associated with local vasodilatation and increased vascular permeability; both mediated by local histamine release, kinin production, prostaglandins (specifically PGE-1 and PGE-2), leukotrienes, and other inflammatory mediators.¹ One mechanism to explain increased vascular permeability includes creation of gap formations between endothelial cells which is mediated by histamine and prostaglandins.¹⁰ Initially, neutrophils, followed by monocytes, are drawn to the site of wounding via various chemoattractants and enter the region of injury including the provisional ECM via adherence to endothelial cells and migration (a process known as diapedesis). Known chemoattractants leading to neutrophil and monocyte migration into the wound include bacterial products, complement (C5a), histamine, PGE-2, leukotrienes, and PDGF. Neutrophils, the first leukocytes to arrive at the wound, assist with bacterial colonization, contamination, and removal of foreign material via phagocytosis.¹¹ Neutrophils also release inflammatory cytokines (tumor necrosis factor [TNF]- α , interleukin [IL]-1) and proteases (collagenase and elastase) responsible for breakdown and removal of damaged tissue.

These cells then go on to die and are extruded with the overlying eschar/exudate or are phagocytized themselves by macrophages which arrive later in the inflammatory phase. Interestingly, neutrophils are not essential for wound healing as demonstrated by studies using neutropenic animals.² These reports showed that neutropenic animals exhibited similar hydroxyproline content (a marker of collagen content within healed wounds) as well as wound tensile strength compared with controls.² Next, monocytes arrive mediated by TGF- β and breakdown products of fibronectin.¹² These cells transform into macrophages and migrate throughout the injured tissue assisting in phagocytosis as discussed earlier as well as collagenase and protease production. Macrophages are the main, local source of TGF- β which is responsible for activation of fibroblasts, stimulation of collagen deposition, and inhibition of collagen breakdown; indicating the importance of macrophages in wound healing. Macrophages also secrete PDGF, TGF- α , TNF- α , and IL-1 among other factors, which modulate the local inflammatory response, modulate re-epithelialization, and angiogenesis.^{13,14} T-lymphocytes are also involved and migrate into the ECM, later modulating fibroblast proliferation and collagen synthesis.¹⁵ The persistence of foreign material within the wound or heavy colonization of bacteria can lead to a prolonged inflammatory response with continued neutrophil presence resulting in protease release and presence of reactive oxygen species which can result in damage to the ECM.¹⁶ Continued activation of complement can lead to cytotoxic damage to cell membranes and tissue destruction. Foreign body encapsulation can ensue with resultant granuloma formation which impedes the normal progression of wound healing.¹⁷

Proliferative Phase

Residual platelets from hemostasis and macrophages from the inflammatory phase set the stage via establishment of a cytokine and growth factor milieu that modulates future angiogenesis, fibroplasia, and re-epithelialization during the proliferative phase.¹⁸ This phase is a period of collagen and ECM synthesis, replication, and restoration of the surface epithelium and perfusion of the wound. The cellularity of the

wound increases as a result of cell migration into and proliferation within the ECM. Various cytokines and growth factors predominate due to their production and release by fibroblasts, endothelial cells, and keratinocytes (**►Tables 1 and 2**). Those produced include TGF- β , PDGF, vascular endothelial growth factor (VEGF), and keratinocyte-derived autocrine factor; cumulatively these stimulate and modulate ECM deposition, angiogenesis, and epithelialization of the wound.¹⁸ Undifferentiated mesenchymal cells within the dermis mature into fibroblasts (this cell type plays a key role in the proliferative phase) in response to factors released by platelets, neutrophils, and macrophages.³ The cellularity of the ECM is greatly augmented by the proliferation of both fibroblasts and smooth muscle cells, hence the title of this phase of healing. Proteoglycans (PGs) occur in all tissues and assist with the orchestration of wound healing. They form complexes between other PG and collagen and make up a major component of the ECM; providing substance between cells that populate the site of injury.¹⁹ PGs are composed of a central core protein covalently bound to one or more glycosaminoglycans (GAGs) which categorize the PG function.²⁰ Some common GAGs include keratan sulfate, heparan sulfate, chondroitin sulfates A, B, and C, and hyaluronic acid. GAGs are able to encode functional and structural information by the sequence of amino acids and sugars in their chain with the core protein of PGs adding specific information locating the GAG to specific intracellular or extracellular locations.²⁰ Fibroblasts, mast cells, neurons, and endothelial cells are some of the cell lines responsible for production of the various PGs and GAGs.^{19,21} GAGs have unique adhesive capabilities and thus are able to manipulate cell function. By binding to GAGs, many growth factors and cytokines are activated and thus carry out their specific local function in wound healing. Collagen synthesis is performed by fibroblasts, smooth muscle cells, and endothelial cells; with fibroblasts being the primary source.²² The provisional ECM is replaced by a collagen-rich ECM and results in an acellular scar. The level of collagen within the wound rises for 3 weeks parallel to the decrease in fibroblast numbers. All collagen molecules consist of three polypeptide chains wrapped into a triple helix. Every

Table 2 Comparison of healing between the gastrointestinal tract and skin

Wound characteristics	Gastrointestinal tract	Cutaneous
Flora	Heavy colonization with aerobic and anaerobic organisms	Normal limited flora typically not problematic Infection typically results from external source
Collagen	Types I, III, and V	Types I and III
	Synthesis by fibroblasts and smooth muscle cells	Synthesis by fibroblasts only
Collagenase activity	Marked increase in presence after transection/anastomosis	Minimal role during wound healing
Wound strength	Rapid return to comparable bursting strength of noninjured bowel	Slower process of return to near-normal tensile strength
Effects of corticosteroids	No definitive evidence of detrimental effect on healing	Evidence suggesting a reduction in tensile strength

third amino acid within the chain is glycine with the formula GLY-X-Y representing a repeating pattern of amino acids with proline frequently occupying the X position and 4-hydroxyproline the Y. Stabilization of the triple helix is a result of hydrogen bonds and water bridges.²³ The collagen superfamily consists of 19 different proteins and can be subdivided into families.²⁴ One family of collagens forms fibrils and is made up of types I, II, III, V, and XI.²³ Within skin, type I collagen makes up 80 to 90% and type III the remaining 10 to 20%; giving a normal ratio of 4:1 for type I:III. This ratio is lower, typically 2:1 in immature and hypertrophic scars. Types II and XI make up cartilage and type IV is found in basement membranes.²⁴ The family of fibril-forming collagens is synthesized as procollagen with extensions at the N and C terminals of their chains. Intracellular steps include cleavage of signaling peptides, hydroxylation of specific proline and lysine residues, and association of C propeptides; initiating the conformation into a triple helix structure. These procollagen molecules are packaged in granules via transport from the endoplasmic reticulum to the Golgi complex, and ultimately extruded from the cell. Once outside of the cell, N and C terminal propeptides are cleaved, nucleation and propagation allow for fibril formation, and covalent cross-linking occurs.^{23,25} By this time, the formal ECM, made up of collagen, fibronectin, and elastin, has replaced the provisional ECM. Next, epithelial cells are replaced after injury originating from the wound edges and epithelial appendages (hair follicles, sweat, and sebaceous glands) within the dermis of the wound itself.²⁶ The process occurs via epithelial cell detachment from the basal cell layer, migration, proliferation, and differentiation. The basal cell layer gives rise to cells along the edge of the wound after they enlarge and elongate, ultimately detaching from the underlying basement membrane; all steps occurring within the first 24 hours of injury.²⁷ Activation of these keratinocytes is mediated by IL-1, IL-8, and TNF- α . In addition, multiple growth factors are involved (keratinocyte growth factor [KGF], epidermal growth factor [EGF], basic fibroblast growth factor, PDGF, and TGF- α).^{18,28} Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases capable of degrading all components of the ECM. MMP-1, 2, 9, and 13 are the principle MMPs involved in ECM metabolism. MMP-1 and 13 are principal enzymes responsible for cleaving fibrillar forms of collagen I/III. MMP-2 and 9 (also known as gelatinases A and B) further degrade these previously cleaved fibrils and separate basal keratinocytes from the basement membrane, and these cells then align with the underlying collagen fibers.^{29,30} The fibronectin within the early provisional matrix mediates keratinocyte adhesion and migration. The separated cells in monolayer divide to proliferate and cover the wound as an advancing epithelial layer; cells on the leading edge phagocytizing debris to facilitate more rapid wound coverage. Once this single layer of cells is complete, further proliferation occurs to provide a multilayer coverage. Keratinocytes then differentiate to give rise to the multiple functional layers of the skin (cuboidal basal cell, squamous and granular cell layers, and stratum corneum).³¹ The process of re-epithelialization results in cutaneous wound closure at a rate of 1 to 2 mm per day. Finally,

underlying fibronectin from the provisional matrix is replaced by keratinocyte-produced fibronectin. Perfusion of the wound and its immature elements is another critical step during proliferation, a process known as angiogenesis. Endothelial cells from tissue deep to the injury infiltrate the provisional ECM via tubular structures forming a network within the matrix. Endothelial cells within injured tissue are activated by tissue destruction and hypoxia. Inflammatory and epithelial cells and cells within adjacent disrupted tissue release various angiogenic factors. Factors released such as VEGF, EGF, and FGF function via stimulating chemotaxis and division of endothelial cells.^{32,33} The ECM, by way of GAGs, directs angiogenesis as well. Endothelial cells with advancing capillary sprouts express specific integrin types which recognize fibrin, fibronectin, and GAGs specific to injured tissue; a process thought to accelerate angiogenesis.³⁴ MMPs, by way of selective degradation of ECM, act to degrade the basement membrane and intervening connective tissue providing capillary sprouts access to a pathway for endothelial growth. Typical of other cell types involved in wound healing, leading edge endothelial cells are capable of undergoing proliferation, migration, and enlargement.

Remodeling

Remodeling is a dynamic process of maturation within healed tissue that is based on maintenance of collagen homeostasis through balancing synthesis and degradation as well as the response of tissue to mechanical stress.³⁵ When remodeling begins at approximately 3 weeks following injury, the tensile strength of the wound is only 15% of that compared with normal tissue despite the presence of similar amounts of collagen. As collagen within the ECM cross-links in an intra- and intermolecular fashion, the wound tensile strength increases, reaching 80 to 90% that of normal skin. During this phase, the ratio of type I:III increases to 4:1, reverting to that within normal skin. Angiogenesis has ceased by the latter part of remodeling. Ultimately, remodeling can continue for 12 to 18 months after injury during which time characteristics of the scar are dynamic. Wound contraction occurs via centripetal movement of components of the open wound on its periphery. When this occurs over a large surface area leading to functional impairment, this is termed a contracture. Fibroblasts play a central role in the contraction of open wounds by interacting with the ECM and by retracting the collagen fibrils as these cells migrate through matrix. Contraction of collagen within the matrix is inevitable, but is less marked when wounds are closed via skin grafting; a point made most evident in the management of burns. The greater quantity of dermis in full-thickness skin grafts lend to less contraction than split-thickness grafted wounds.

Wound Healing Specific to the Gastrointestinal Tract

Similar to skin, the gastrointestinal tract is provided with a strength layer made predominantly of collagen, the submucosa. The submucosa, similar to dermis, consists of coarse collagen fibers, elastin, and a lymphatic and vascular supply.

The collagen in the bowel submucosa consists of predominantly type I (68%), type III (20%), and unique to bowel, type V (12%).³⁶ The mucosa is repaired by epithelial cell hyperplasia and migration, covering the granulation tissue produced during proliferation within 3 days of injury if layers are accurately apposed.³⁷

Serosa, consisting of connective tissue and an outer layer of peritoneal mesothelial cells, when apposed, provides protection from anastomotic leakage. Interestingly, within the hollow viscera, both fibroblasts and smooth muscle cells produce collagen present in the submucosa; fibroblasts alone are involved in this process in skin.³⁸ Injury (iatrogenic or traumatic) results in a similar process of healing as outlined earlier. There are a few nuances in addition to those noted above specific to intestinal healing that are important to elucidate (►Table 2). After the creation of an intestinal anastomosis, collagen degradation specifically of mature collagen begins, predominating for the first 4 days.³⁹ Some reports describe a massive loss of mature collagen after anastomotic construction due to degradation unbalanced by synthesis.^{40–42} Collagen content, as measured by hydroxyproline concentration, is decreased by 30% within a fresh colonic anastomosis by 24 hours, with a nadir in content by the end of the 2nd postoperative day.⁴³ By the 3rd day, collagen synthesis has escalated and overtaken the amount of degradation within the healing bowel submucosa. With all other factors being normal (oxygen delivery, technical experience, tension-free construction, etc.), some authors hypothesize that anastomotic leakage is related to this process of collagen lysis within the fresh anastomosis; with some patients potentially having a predisposition to leak.⁴⁴ Collagen content is stable within the anastomosis at the 5th or 6th week with turnover remaining extensive during this period. Translated to resilience, bursting strength increases rapidly during the early postoperative period attaining 60% of the strength of the surrounding bowel by day 3 postinjury.⁴⁵ 3 to 5 days after injury, the bursting strength at the anastomosis is equal to that of the surrounding, noninjured bowel.⁴³ Interestingly, when comparing small and large bowel healing, ileal anastomoses demonstrate a similar pattern of hydroxyproline degradation to colon in the early postoperative period.⁴³ The ileal collagen loss is quantitatively less than colon and recovers more quickly. However, colonic anastomotic bursting strength recovers more quickly than ileum; suggesting that structure (such as cross-linking) and type (I vs. III) are of greater importance than quantity.⁴³ One report described a lower ratio of type I:III collagen in the bowel wall of patients who developed anastomotic leak.⁴⁶ Similar findings have been demonstrated in the skin and fascia of patients who develop recurrent hernia.⁴⁴ MMP levels obtained from peritoneal drain fluid may present a unique biomarker for determination of healing and outcome.⁴⁷ Overexpression of MMP-1 has been correlated with delayed wound healing in an animal model.⁴⁸ MMP-1, 2, and 9 have increased expression in the bowel wall of patients who develop anastomotic leak.⁴⁴ These findings suggest that there is an at-risk population with abnormal collagen metabolism that adversely affects wound healing and portends a higher risk of anastomotic leak.

Factors Affecting Wound Healing

Corticosteroids

Corticosteroids represent classic examples of exogenous (systemically administered as medication) or endogenous (Cushing disease) factors that can impair healing. Corticosteroids are lipophilic, diffuse into the cell, bind and activate the glucocorticoid receptor, ultimately dimerizing and diffusing into the nucleus where the result is an increase or inhibition of gene transcription by binding to glucocorticoid response elements present in the promoter region of target genes.⁴⁹ During the inflammatory phase of healing, corticosteroids, specifically dexamethasone, decrease the expression of TGF- β 1, PDGF, TNF- α , and IL-1 in wounded tissue decreasing the chemotactic and mitogenic stimulus for other inflammatory cells.^{50,51} Steroids also down-regulate endothelial cell expression of intracellular adhesion molecule-1 specifically in colonic anastomoses which leads to attenuated granulocyte adhesion and migration.⁵² Steroids ultimately reduce macrophage infiltration into the wound; one of the vital cell types involved in this phase. During the proliferative phase, specifically the process of re-epithelialization, MMPs and plasmin are involved with digestion of the forward edge of the fibrin clot, a process inhibited by corticosteroids.⁵³ TGF- β and KGF production and expression, respectively, are decreased with a resultant attenuation of fibroblast proliferation.⁵⁴ Steroids are involved in impairment of collagen turnover, negatively impact the interaction of the dermal-epidermal junction, and decrease the tensile strength of the healing wound by a reduction in collagen content.^{55–57} This decrease in cutaneous wound tensile strength is in a dose-response fashion by a level of 30 to 40% depending on the process involved (Cushing syndrome; dose of corticosteroid).^{49,58,59} Despite the above findings, corticosteroid use, especially for short courses (typically defined as 10 days or less), is not associated with deleterious clinical effects.⁴⁹ Some reports describe no significant increase in wound complications in patients with inflammatory bowel disease on chronic corticosteroids; however, some studies describe a higher risk of wound infection, intra-abdominal abscess, sepsis, and anastomotic leak with preoperative use.^{60–65} Animal studies support that corticosteroids have no effect on tensile strength of cutaneous wounds if dosed 3 or more days after incision.⁶⁶ Although wound complications, specifically dehiscence are reported in patients on steroids, the typical regimens used in clinical practice do not generally result in marked impairment of wound healing.⁴⁹ Helpful for the clinician in practice are the facts that methylprednisolone may have less inhibitory effects on healing than other corticosteroids and vitamin A has been shown to reverse healing impairment in animal models, although these results have yet to be validated in humans.^{67,68}

Inflammatory Bowel Disease

Crohn disease results in impaired collagen metabolism within the bowel wall. During acute inflammation such as an active flare of Crohn, there is a significant increase in collagen content within bowel wall.⁶⁹ There is typically a lower

content of type I and similar content of type III collagen compared with normal bowel wall; thus, a lower type I:III ratio in Crohn disease.⁷⁰ This lower content is speculated to be a result of increased degradation of the type I collagen. Several MMPs have increased expression and production in active Crohn disease.⁷⁰ All these findings in active Crohn disease may reflect acute tissue damage rather than healing, the process representing suboptimal ECM remodeling.⁴⁴

Diabetes Mellitus

Diabetes mellitus is another disease state associated with impaired healing. Tissue hypoxia plays an important role in these patients with nonhealing wounds as a result of decreased perfusion and inadequate angiogenesis.⁷¹ Decreased levels of VEGF are implicated in abnormal angiogenesis.⁷² Tissue hypoxia results in an amplified inflammatory response and increased levels of reactive oxygen species.⁷³ Markedly high levels of MMPs are noted, especially in chronic, nonhealing wounds.⁷⁴ Multiple cell lines demonstrate dysfunction leading to defects in immunity, inflammatory cell chemotaxis, phagocytosis, and bactericidal activity.⁷⁴ These patients have been noted to have thickening of the basement membrane of capillaries and arterioles which provides an anatomic barrier to cellular migration.⁷⁵ Hyperglycemia directly inhibits wound healing via formation of advanced glycation end-products resulting in the production of inflammatory cytokines (TNF- α , IL-1) which impair collagen synthesis.⁷⁶

Radiation

Radiation therapy, necessary for tumor cell death, has unwanted short- and long-term effects on normal tissues. Radiation of hollow viscera can result in fibrosis and stricture formation, radiation enteritis, and ischemia due to obliteration of the local microvasculature.⁷⁷⁻⁷⁹ Clinically, anastomotic leak after irradiation has been described and is felt to occur more frequently than in nonirradiated bowel.⁸⁰ Animal models suggest that there is a reduction in perfusion at the seromuscular level which may contribute to this risk.⁸¹ It has been proposed that postoperative radiation dosed before macrophage arrival at the anastomosis may provide an abundant population of inflammatory cells thereby promoting normal healing to commence.⁸² Vitamin A may also be protective for healing when used after radiation.⁸³

Omental Wrapping

Omental wrapping of the anastomosis represents a beneficial technical procedure that may impact wound healing after an anastomosis.⁸⁴ Evidence exists that demonstrates omental wrapping assists with sealing the serosal closure at the suture line (especially helpful in everting type anastomoses), promotes angiogenesis and granulation (the proliferative phase of healing), and provides perianastomotic lymphatic drainage.⁸⁵ These benefits are only provided when pedicled, perfused omentum is used.⁸⁶

Healing Related to Bioprosthetic Materials

When considering the history of hernia surgery, synthetic meshes resulted in a dramatic decrease in hernia recurrence

rate. Despite efforts to make these products biocompatible, all synthetic meshes initiate a local tissue reaction initiating an inflammatory response, ultimately leading to permanent encapsulation of the mesh. These and other characteristics of the original synthetic products are associated with infection requiring explantation, visceral adhesion formation, and fistulization.⁸⁷⁻⁹⁰ Second-generation synthetic meshes incorporated antiadhesion barriers and were more lightweight resulting in a reduction but not elimination of complications. Biologic prosthetic meshes, termed bioprosthetics, were developed and introduced in the 1990s to provide a collagen scaffold for hernia repair.⁹¹ Bioprosthetics are developed from human or animal sources, and provide an option for the management of hernia repair/abdominal wall reconstruction in a contaminated field.⁹² Currently, dermis from humans and porcine sources, and porcine small intestinal submucosa are used as commercially available hernia repair bioprosthetic materials.⁹² After harvest, products undergo decellularization (physical, chemical, or enzymatic techniques), some undergo collagen cross-linking (the nonhuman collagen scaffolds only), and sterilization.⁹² Acellular human dermal meshes are typically not sterilized or collagen cross-linked. Characteristics of human dermis provide a matrix with abundant collagen, elastin, and an intact basement membrane. After use for hernia repair or fascia reinforcement, 80 to 85% of the graft will persist at 22 months after implantation in humans.⁹³ Cross-linked porcine dermis is enzymatically decellularized, sterilized via gamma irradiation, and cross-linked; persisting for up to 20 months after implantation.⁹⁴ Porcine small intestinal submucosa is also decellularized, laminated into four or eight layers (is not cross-linked) and sterilized; demonstrating full native tissue uptake at 6 months.⁹²

Unlike synthetic meshes, bioprosthetics provide strength to the hernia defect only initially. Once implanted, bioprosthetics are incorporated into native tissue via host repopulation of the mesh by fibroblasts, endothelial cells, and other cells involved in the process of healing as outlined earlier. Angiogenesis assists with infection control by perfusing and supplying immunity proximate to the graft. Matrix degradation results in a potential period of weakness if remodeling is incomplete when no components of mesh persist.⁹⁵ In the event of infection, collagenase production can result in rapid prosthetic degradation and graft failure. Collagen cross-linking of xenograft bioprosthetic mesh has been proposed as protection from breakdown via collagenases but may result in unwanted effects such as decreased angiogenesis, encapsulation, and incomplete degradation, resulting in incomplete incorporation into the host tissue.^{91,92} The collagen matrix provided by the mesh is ultimately degraded by host cells, causing site-specific remodeling; resulting in a mature neofascia in the case of hernia repair.⁹⁶ In the case of porcine grafts, replacement by human collagen types I and III has been described.⁹⁴ The end result of bioprosthetic mesh use is healing via a regenerative or remodeling process contrary to scar formation and inflammation as is the case with synthetic mesh implantation.⁹⁴

The use of bioprosthetic meshes for hernia repair has been proven to be feasible; however, outcomes are widely variable. Bioprosthetic mesh is ideally suited for the management of hernia repair or complex abdominal wall reconstruction in the setting of a contaminated field (peritonitis, fistula, parastomal hernia, enterotomy, infected prosthetic mesh requiring removal). The mesh can be placed to bridge (with varying amounts of underlay) a fascial defect that is not able to be closed primarily, to reinforce primary fascial closure (via either an underlay, overlay, or sandwich method), or concomitant with components separation to facilitate primary fascial closure. Skin can be closed primarily or left open to prevent infection. In the event of very large fascial defects, multiple pieces of bioprosthetic mesh can be sewn together (running or interrupted, permanent monofilament suture) to construct a single piece to achieve the desired effect. When used for bridge or inlay repair, acellular human dermis is associated with diastasis, eventration and recurrent hernia development in 80 to 100% of patients.⁹⁷ Mesh elasticity increases over time with acellular human dermis.^{98,99} Some authors state that when acellular human dermis is used in a bridging fashion, it provides only a temporary restoration of abdominal wall integrity with no permanent durability and mandates future, elective herniorrhaphy; similar to outcomes when polyglactin 910 (Vicryl; Ethicon Endo-Surgery; Somerville, NJ) meshes are used.⁹⁷ Cross-linked porcine dermis has shown positive results in regard to good incorporation into native tissue and infrequent wound complications. Porcine small intestinal submucosa is associated with frequent seroma formation,⁹⁸ although this may be reduced with newer methods of processing and construction. Biomesh use and outcomes are optimized by achieving tissue closure over the mesh to promote angiogenesis which assists with infection prevention; hence their use as a bridge has been discouraged by some.^{100,101} This may potentially limit their widespread use in laparoscopic repair. Outcome data are limited due to lack of long-term follow-up. It is promising to note that hernia recurrence rates for bioprosthetic reinforcement of primary fascial closure in the setting of a contaminated field approach the results of uncomplicated synthetic prosthetic hernia repair.⁹⁷ The use of bioprosthetic mesh reinforcement of primary laparotomy incision closure (such as in an underlay fashion) may prove beneficial for the prevention of primary incisional hernias.⁹⁶ For patients who are at risk for inferior collagen production (corticosteroid use, diabetes mellitus, patients with abdominal aortic aneurysm) and incisional hernia, implantation of a bioprosthetic mesh scaffold may be useful.⁹⁶ Ultimately, it is recommended that use of these products be individualized and that they should not be thought of as interchangeable due to each material's unique properties and issues. Ansaloni et al have developed a European registry for bioprosthetic mesh use with the goal of providing long-term outcomes data to guide future recommendations for use.⁹⁶

Conclusion

This article provides a general review of wound healing from the perspective of cutaneous and intestinal injury and sur-

gery. The processes, while not identical, provide a framework for understanding this elegant process in the human body. Factors that adversely and positively affect wound healing have been described along with a review of how bioprosthetic materials are incorporated into tissue and some of the available short-term effects on their use; specifically for abdominal wall reconstruction/hernia repair. We hope this article will benefit surgeons by providing a concise resource to better understand wound healing and motivate scientists from all areas to explore areas to modulate and improve the process of healing in the future.

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