UNDERSTANDING AND APPROACH TO TREATMENT OF SCARS AND ADHESIONS
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Introduction
The modern education system for manual therapy, including massage therapy, physiotherapy, osteopathy, and chiropractic works on the acceptance that manipulation of tissues for scars and adhesions is of therapeutic value. Manual therapy in its various forms is now being introduced in a growing number of integrated health clinics, and is accepted by many to be a valuable addition to allopathic care. Much of the manual therapy literature is innately conceptual, sometimes for lack of data, often using outdated concepts that may have been dispelled by modern science's ability to accurately measure and observe cellular level mechanisms. Manual therapy education splits systems and practices into various camps, including central versus peripheral nervous system, visceral work, and connective tissue/fascia manipulation. There are various conjectures as to how mechanical forces affect these different systems of anatomy, despite almost no directly relevant science. The manipulation of fascia as a technique is relatively recent in manual therapy history, and has been separated out by various schools of thought. Patients seem to receive benefit from the treatments they receive. Interest in the mechanisms at the cellular level that govern wound healing and understanding the mechanisms of pain are critical to the practice and diagnostic reasoning of tissue manipulation for scars and adhesions.

Fascia is generally defined as connective tissue composed of irregularly arranged collagen fibers, in contrast to the regularly arranged collagen fibers seen in tendons, ligaments or aponeurotic sheets. The irregular arrangement of collagen fibers allows fascia to fulfill a role as packing tissue and resist tensional forces universally (Willard et al., 2012). Conversely, tendons, ligaments and aponeuroses have a pronounced regular arrangement of collagen fibers equipping them to resist maximal force in a limited number of planes, while rendering them vulnerable to tensional or shear forces in other directions.

In 1939, an article appeared in the *Journal of the American Medical Association* written by Mennell called ‘The science and art of joint manipulation’ (Mennell, 1939). The author states; ‘It is not an easy task to present a subject as controversial as is the question of manipulative surgery to the circle of a critical profession.’ His critics later comment on Mennell's ability to apply his hypothesis on manipulations by stating that in view of the ‘careful restraint with which he handles physiologic and anatomic facts as a background for his indications, there is no tendency to admit any fantastic or forced theories into his field of reasoning’ (JAMA, 1951).

These comments are relevant to an understanding of the science in manual therapy. Manual therapy and its effect on tissues has been weakly understood. There is a growing skepticism amongst allopathic practitioners due to claims made outside of evidence, and anatomic facts that are not held to reason. This chapter will follow biological mechanisms of healing, and present the up-to-date scientific knowledge that may be relevant to the formation of adhesions and scar tissue and the potential role of manual therapy.

Scars and adhesions
The formation of scars and adhesions is a ubiquitous and naturally occurring process that most often, is not pathological. As a profession, manual therapists have long held the belief that local restrictions in tissue movements can result in a more global
dysfunction. There is little support for this concept. There are little data available that would suggest the validity of applying manual treatment to existing scar tissue. In addition, the innervation of fascia is poorly understood, with obvious clinical implications for local pain and presumed pathology.

In this chapter, we will explore the healing mechanism as it relates to different types of tissue, and the best treatment protocols and outcomes based on current published evidence for tissue manipulation and manual therapy.

Scarring is a multifactorial process with different clinical presentations that affects over 40 million people worldwide (Bloemen et al., 2009). Scars can be categorized either as pathological or nonpathological. Understanding the difference between a scar and an adhesion is essential to the diagnostic reasoning necessary to designing a manual therapy treatment protocol and assessing possible outcomes. Treatment of scars or fibrotic thickening of tissue after a wound presenting as a consistent pathology may not be supported by peer-reviewed literature. The availability of information online has made this important distinction more difficult, with case reports on scar reduction flourishing in the manual therapy education system. Understanding the difference between pathological adhesion formations, innervated versus noninnervated structures, and how and where adhesions are formed compared to the formation of a scar is critical to devising an evidence-based approach to treatments.

An adhesion is an attachment of tissues at unusual nonanatomic sites, which can be flimsy or dense, vascular or avascular, innervated or not innervated (Epstein et al., 2006). A scar is a mark left on the skin or within body tissues where a wound, burn, or sore has not healed completely by primary intention, and fibrous connective tissue has developed. There is still poor understanding of the complex mechanisms surrounding scarring and wound contraction (Gauglitz et al., 2011). Sensory nerve fibers have been found in adhesive tissue samples (Sulaiman et al., 2001a) although the relationship to pain or pathology is yet to be established.

The literature suggesting that massage following burns leads to reduced scarring seems promising (Roques, 2002; Roh et al., 2007; Hallam et al., 2009; Cho et al., 2014) but is largely anecdotal. More experiments are required in order to make sound recommendations (Shin & Bordeaux, 2012). Elucidating the contribution of inflammatory pathways and hypoxia may lead to a deeper understanding of the effect that manual therapy can have in affecting scars and adhesions.

**Wound healing**

Humans desire wound healing through complete regeneration of damaged tissue. However, the reality is that after tissue maturation, humans do not heal by regeneration, but via wound healing or repair, which leaves scars or forms adhesions. Healing involves a complicated process that takes place in the extracellular matrix. Healing proceeds through four overlapping stages: hemostasis, inflammation, proliferation, and remodeling (Olczyk et al., 2014). All soft tissue injuries require wound healing. This involves in part, the coagulation and fibrinolytic pathways. The extracellular matrix orchestrates molecular interactions, and is where wound healing takes place. Morphogenic changes such as angiogenesis, fibrinolysis and neural sprouting (Tonnesen et al., 2000) contribute to the appropriateness of any wound repair, and are the factors that determine whether cellular differentiation of a less specialized cell type into a more specialized cell type takes place. The most relevant molecules to wound healing and repair may be the fibroblast growth factors. Studies suggest a basic antiscarring effect of fibroblast growth factors during wound healing, the mechanisms of which are still poorly understood (Shi et al., 2013).

Mesenchymal stem cells reside within the extracellular matrix. These cells are pluripotent in their respective tissues, and have similar sensitivities and functions. Fibroblasts, chondrocytes, osteocytes and adipocytes are derived from these cells. The contents of the extracellular matrix mediate the inflammatory response, as well as growth factors that control proliferation, differentiation and metabolism of cells involved in the healing process.

Fibroblasts and fibrocytes create and maintain the extracellular matrix (Bellini & Mattoli, 2007). These cells show some response to mechanical strain. Manual therapists apply mechanical stress to tissues. This is the common denominator in all professions that use tissue manipulation to achieve the goal of
affecting sensitivity or pain perception. There is little scientific evidence to support the hypothesis that fibroblasts communicate with each other. A differentiation must be made between meaningful communications such as transmission of information between cells via protein receptors, versus having an effect on cellular neighbors via neural connections. There is no evidence that such communication occurs between fibrocytes.

The changes of a fibrocyte to a fibroblast, and from a fibroblast to a myofibroblast are called differentiation. There are various factors that play a role in this process, such as physiological changes in the extracellular matrix, changes in gene expression and upregulation of genes, which lead to cell differentiation in the extracellular matrix (Parker et al., 2014).

In humans, wound healing is complete with the formation of a permanent scar consisting of collagen fibers, fibroblasts and small blood vessels. During granulation tissue formation, fibroblasts undergo extensive changes. Some fibroblasts start to express smooth muscle cell markers such as smooth muscle actin resulting in a phenotype referred to as myofibroblasts (Shephard et al., 2004). Myofibroblasts acquire morphological and biochemical features of contractile cells. They are responsible for contraction of granulation tissue to assist wound closure (Desmouliere et al., 1995). Although the contractile nature of myofibroblasts shows many similarities to smooth muscle cells, they fail to express the full repertoire of smooth muscle cell markers (Darby et al., 2014). Smooth muscle cells are organized to perform a contractile function under the influence of (primarily) neural control, whereas myofibroblasts are not under similar control. The difference is fundamental; the cells are not linked or coordinated. The relevance of differentiation of fibroblasts into myofibroblasts is not understood when it comes to manual therapy for wound healing and scar formation. It is unclear as to whether stimulation or mechanical strain may lead to further differentiation due to an increase in inflammatory response dependent on dose and timing of intervention. It is believed that differentiation into myofibroblasts happens within the extracellular matrix, with gene expression causing differentiation from fibroblasts into myofibroblasts that deposit fibrin (Sassoli et al., 2012; Parker et al., 2014). There is little understanding of the precursor cells and the interrelationships between phenotypes when it comes to the myofibroblast/fibroblast relationship. Once a wound is repaired, most myofibroblasts and cells that cause fibrosis disappear. Fibroblasts are viewed as being in a resting state in normal skin, but become active during tissue repair. They proliferate during wound repair, and synthesize new connective tissue. What has been established through in vitro studies is that mechanical forces do affect fibrocytes (Pietramaggiore et al., 2007). What we can glean from the literature on fibroblasts that may be relevant to manual therapy is that there has been a measurable response to mechanical stimuli (Klotzsch et al., 2015), and that fibroblasts respond to stretch (Abbott et al., 2013). This response has been observed in vitro, but not measured in humans. Other interesting responses that have been examined are the tissue growth factors such as transforming growth factor-β1 (TGFβ-1) for scarring and TGFβ-3 for regeneration (Campbell et al., 2004). Mechanical stimulation effects COX-2, MMP-1 and PGE-2 which are important markers for the modulation of the inflammatory response.

TGFβ is central to many of the mechanisms of pathological scarring and fibrosis. Platelets are a major source of TGFβ-1 and in a wound event, cause coagulation and enable wound repair. In early stages of a wound, TGFβ-1 is deposited but not activated. TGFβ may cause chemotaxis with inflammation, but is not in itself chemotactic. This cellular response to a stimulus may only be in response to inflammation (Sato et al., 2000), which is important to understanding its role in the immune response to injury. Research shows that fibroblasts in both dense connective tissue and stiff cross-linked gels did not exhibit cytoskeletal remodeling in response to tissue stretch (Abbott et al., 2013). However, a loosely arranged compliant collagen matrix, characteristic of areolar connective tissue promoted fibroblast cytoskeletal remodeling in response to stretch regardless of the fibroblast’s tissue of origin. This finding by Abbott et al. shows that with pathological healing processes that increase cross-linkage of collagen such as fibrosis, the fibroblast loses its responsiveness in connective tissue.
TGFβ-1 is a potent regulator of extracellular matrix production, wound healing, differentiation, and immune response, and is implicated in the progression of fibrotic diseases (Venkatraman et al., 2012). Platelets are a major source of TGFβ-1 and in wound events cause coagulation and enable wound repair. The platelets deposit TGFβ in the extracellular matrix which may act as a reservoir to store growth factor necessary in later stages of wound repair (Blakytny et al., 2004). In early stages of a wound, TGFβ-1 is deposited but not activated.

It has been shown that when there is tissue pathology from impaired wound healing states (such as venous or diabetic ulcers) that TGFβ-1 expression is reduced. When administered topically, TGFβ-1 can assist healing through stimulation of wound contraction and increasing wound strength (Brunner & Blakytny, 2004). Embryonic wounds that heal without a scar have low levels of TGFβ-1 and TGFβ-2, low levels of platelet-derived growth factor and high levels of TGFβ-3 (Ferguson & O’Kane, 2004). The functional and evolutionary differences between TGFβ-1, TGFβ-2 and TGFβ-3 have been demonstrated in experiments where topical treatments were applied. TGFβ-1 and TGFβ-2 showed more extracellular matrix deposition but no difference between wound treatments at long-term outcomes. The addition of the TGFα-3 peptide leads to reductions in monocyte and macrophage profile, fibronectin, collagen I and collagen III deposition in the early stages of wound healing and marked improvement of the architecture of the neodermis and reduced scarring (Shah et al., 1995).

It is important to keep in mind that our understanding of the effects of mechanical stimulation on the behavior of cells has come from studies performed in vitro. Case studies on outcomes of treatments are prolific, but they fail to address the specific effects of the various interventions. There is much work to be done in better developing clinical experiments. In manual therapy science, there is little understanding of what cells are affected, or what pathways are forged, broken or encouraged. There are no long-term controlled outcomes of treatment to scars or adhesions in humans. Much literature is based on case studies, with little attention paid to dose, timing, techniques, or mechanisms.

At the cellular level, responses to trauma can be simple or complex (Fig. 51.1). Manual therapy entails use of external shearing or other forces on palpable tissue. The most relevant response to wound repair may be the treatment of interfaces, and the effect these forces have on the wound-healing cascade and extracellular matrix while healing is taking place.

Skin wounds heal by first intention, or by granulation. If a skin injury is a laceration without any tissue loss, then first intention healing takes place. If there is a loss of tissue such as in burns, ulcers or with infections, the tissue will heal by granulation, in which case a scar will be formed.

Experiments have shown that with a subcutaneous injury, adding short stretch decreases the fibrotic response, which causes less collagen deposition and reduced tissue adhesions (Bouffard et al., 2008). Tissue stretch to skin after injury reduced the amount of TGFβ-1 inflammation and reduced macrophage expression in subcutaneous tissue (Corey et al., 2012).
Fibroblasts in both dense connective tissue and stiff cross-linked gels did not exhibit cytoskeletal remodeling in response to tissue stretch. However, a loosely arranged compliant collagen matrix, characteristic of areolar connective tissue, promoted fibroblast cytoskeletal remodeling in response to stretch regardless of the fibroblast’s tissue of origin. Mouse tissue loaded in a dish showed increased TGF-β1 but with stretch added, the levels were reduced. Fibroblasts in connective tissue have shown extensive changes in response to stretch (Langevin et al., 2013). As in all wound healing the control of inflammation may be the key to reduced fibrotic tissue deposition (Fig. 51.2).

**Figure 51.2**

Proposed model for healing of connective tissue injury in the absence (A, C, E) and presence (B, D, F) of tissue stretch. In this model, brief stretching of tissue beyond the habitual range of motion reduces soluble TGF-β1 levels (D) causing a decrease in the fibrotic response, less collagen deposition, and reduced tissue adhesion (F) compared with no stretch (E). Black lines represent newly formed collagen. From Bouffard et al. (2008) Tissue stretch decreases soluble TGF-beta1 and type-I procollagen in mouse subcutaneous connective tissue: evidence from ex vivo and in vivo models. J Cell Physiol 214:389–395. Reproduced with permission from John Wiley and Sons Publishing

**Angiogenesis**

Angiogenesis is a response of blood vessels to both pathological and normal physiology. Examples of normal angiogenesis can be seen in the female reproductive system during ovulation, menstruation and formation of the placenta. Examples of pathological blood vessel formation can be seen in rheumatoid arthritis, tumor growth, and diabetes. Angiogenesis restores blood circulation where damage has occurred, and prevents the development of ischemic necrosis whilst stimulating the tissue repair process (Olczyk et al., 2014). Angiogenesis is stimulated by local environment such as low pH, or high lactic acid concentrations (Gurtner et al., 2008). Inflammation and pathologies such as tumorigenesis typically lead to angiogenesis. During angiogenesis, endothelial cells migrate to the wound matrix, where they create a network of tubular structures (Schultz et al., 2011). When persistent inflammation or injury to tissue occurs, one of the hallmarks is vascular permeability. The inflammatory response increases capillary permeability and induces endothelial activation, which,
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when persistent, results in capillary sprouting (Arroyo & Iruela-Arispe, 2010). In the presence of newly formed blood vessels, fibroblasts proliferate and synthesize extracellular matrix components. This contributes to ‘closing’ wound surfaces.

The parallels between angiogenesis and other types of tissue development are numerous. In normal and pathological tissue development, angiogenesis is integral and has been suggested as an organizing principle underlying wound healing, tumor formation and selected other conditions (Schultz et al., 2011). The presence of vascular endothelial growth factor (VEGF) can increase the efficiency of skeletal muscle repair by increasing angiogenesis and, at the same time, reducing the accumulation of fibrosis (Figs 51.3 and 51.4).

Several studies have shown that vascular endothelial growth factor increases angiogenesis in tissues that have been exposed to mechanical strain (Pietramaggiori et al., 2007). When cyclic stretch was applied to bladder tissue in vitro, the capillary bed showed increased density in formation of blood vessels (Yang et al., 2008). This finding, that under cyclical or stretch conditions angiogenesis is increased, shows that inflammation can lead to more vascularization. In the reverse situation, it may be that increased tension causes more inflammation, and therefore more permeability of the capillaries, perhaps prolonging an inflammatory state. There has been no relationship attributed directly to manual therapy.

Nerves

Any event that may compromise or disrupt the gliding movement of a nerve may result in epineu-
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Muscles

Muscle fibrosis may be irrelevant to the application of manual therapy, due to the delicate balance between strength and healing (Jarvinen et al., 2007). The treatment outcome following an injury to skeletal muscle without tendon involvement has mostly focused on reduction of inflammation. In sports medicine studies this has led to suboptimal outcomes in comparison with natural healing times (Jarvinen & Lehto, 1993). Most timelines for the application of manual therapy to a muscle tissue repair have not been studied. Manual therapy has been assessed on the outcome of muscle recovery times from post-exercise stress and showed some benefit within the same day, but had no affect after multiple days (Crawford et al., 2014). The treatment approach that has been alluded to is that the reduction in the development of a fibrous scar may be beneficial to the increase of muscle fiber regeneration, and reducing the inflammatory response of a trauma or laceration. Muscle injury may also cause denervation of the distal segments that will result in atrophy (Lim et al., 2006). The deposition of scar tissue in a muscle describes the extent to which a repair is functional, or leads to dystrophy. If the fibrotic tissue could be repaired and the dystrophic muscle be redirected toward regeneration thereby preserving muscle integrity, the health of the muscle tissue could be considerably improved (Mann et al., 2011). Nerve regrowth into muscle fibers does not seem to be inhibited by scarring; axon sprouts are able to penetrate scar tissue and are able to form new, functional neuromuscular junctions (Fig. 51.5) (Kaariainen et al., 2000).

Mechanical stimulation promotes growth, and this seems relevant to the healing of muscle fibers (Jarvinen et al., 2005). Gentle mobilization was shown to better align the developing fibers after a short period of immobilization allowed a firm scar to develop (Jarvinen & Lehto, 1993). The research showed that with mobility, the scaffolding of the repairing tissue loses strength. Muscle tissue requires a firm scar in order to maintain its strength and not tear with contraction. Tissue that had been mobilized early was much more prone to reinjury, where the new trauma

Figure 51.4
Heterogeneity in caliber of the vessels and increased curvature are early signs of vascular remodeling. These peculiar changes are characteristic of the casts collected after the application of continuous force, and cyclical stretch regimens were also able to induce similar initial signs of vascular remodeling. The bar on each image is equal to 100 µm. Pietramaggiori et al., 2007) From Pietramaggiori et al. (2007) Tensile forces stimulate vascular remodeling and epidermal cell proliferation in living skin. Ann Surg 246:896–902. Reproduced with permission from Wolters Kluwer Health
most often occurred in surrounding tissue, not in the initial wound repair (Jarvinen et al., 2000). One study performed muscle biopsy after manual therapy and did not observe any alterations in muscle glycogen levels nor in muscle lactate, suggesting that the acute effects of massage occur independent of glucose uptake, or lactate clearance (Crane et al., 2012). The ameliorative effects may be that when administered to skeletal muscle that has been acutely damaged through exercise, there appears to be a reduction in inflammation, and alterations in metabolites associated with mitochondrial biogenesis (Urakawa et al., 2015; Crane et al., 2012). This new literature supports the reduction of inflammation after exercise by manual therapy. The available data may not support utility of direct manual therapy to damaged or healing muscles until after the repair. Reduction in inflammatory mediators may inhibit muscle healing.

**Ligaments and tendons**

Ligaments and tendons are designed to transmit force. Although healing occurs to varying degrees, in general healing of repaired tendons follows the typical wound-healing course, including an early inflammatory phase, followed by proliferative and remodeling.
phases. Oxygen consumption by tendons and ligaments is 7.5 times lower than skeletal muscles (Sharma & Maffulli, 2006), which has advantages and disadvantages. Given that they have a low metabolic rate and well-developed anaerobic energy generation capacity, tendons are able to carry loads and maintain tension for long periods, whilst avoiding the risk of ischemia and subsequent necrosis. However, the low metabolic rate results in slow healing after injury. There has been considerably more literature on the effect of mechanical strain applied to tendons and ligaments after injury (Loghmani & Warden, 2009). The response of healing tendons to mechanical load or movement varies depending on anatomic location. Flexor tendons require motion to prevent adhesion formation between the sheath and the tendon surface. Excessive force results in gap formation and weakening of the repair (Killian et al., 2012). When damage occurs, cells from the intrasynovial sheath infiltrate to the repair site, leading to adhesions between the sheath and the tendon surface, which impairs tendon gliding, leading to a decrease in range of motion (Fig. 51.6).

Mobilization may decrease the amount of proinflammatory cytokines through movement of the extracellular matrix. Although an inflammatory response is essential for healing of a tendon to occur, high levels of inflammatory cytokines may result in collateral tissue damage and impaired tendon healing (Manning et al., 2014). In flexor tendon to bone repair, muscle loading across the repair site led to improved functional and biomechanical properties and was beneficial to healing. Complete removal of load by proximal transection resulted in tendon-to-bone repairs with less range of motion and lower biomechanical properties (Thomopoulos et al., 2008).

In a systematic review of rotator cuff repair by (Shen et al., 2014) it was shown that long-term outcomes for mobilization versus immobilization showed no significant difference in repairs at one year. In general, data supports that some controlled loading is essential for development, homeostasis and repair. However excessive loading will result in a negative effect and reduced healing (Killian et al., 2012) (Fig. 51.7).

Peritoneal cavity

Peritoneal adhesions are almost ubiquitous after surgery and can cause a number of complications. Peritoneal adhesions can lead to intestinal obstruction, infertility and chronic pain (Herrick et al., 2000a). As many as 97% of women who undergo surgery for gynecologic indications have been shown to develop postoperative adhesions (Yelian et al., 2010). Peritoneal adhesions are fibrous bands of tissue that have connected viscera together, or attached organs to the abdominal wall. Adhesions have been found to be highly vascular, innervated and cellular (Epstein et al., 2006). They are most often as a result of surgery, but can be formed from any defect that causes inflammatory exudate (Arung et al., 2011). Many approaches have been taken to resolve adhesion formation in the abdomen, but none offer reliable results (Alpay et al., 2008). Most often, patients are readmitted to hospital and require laparoscopic lysing of the fibrous bands that are causing pain, obstruction or infertility. Surgery to lyse adhesions often results in reformation of adhesions (Bolnick et al., 2014). It is important to note that adhesions cannot be imaged accurately (Ghonge & Ghonge, 2014), and can only be accurately
diagnosed upon reoperation by laparoscopy, which often leads to a reformation of adhesions (Mais, 2014).

Despite claims of modern practitioners of visceral massage to have ‘invented’ techniques, the practice of visceral massage has been documented since the 1800s. Procedures used to reduce the burden of adhesions in clinical practice have not shown clinical effectiveness, and have lacked scientific validity. A few clinically relevant case studies have been published by one group (Wurn et al., 2008) but no mechanism, control group or standardization was used.

Visceral massage has been documented since 1887, but the first text on the subject may be from (Fielder, 1955) who wrote The Science and Art of Manipulative Surgery. In his 1919 book called The Peritoneum, Hertzler described management of permanent adhesions: ‘Permanent adhesions require attention only when they limit the movement of a mobile organ or contract the lumen of a hollow one.’ His observation on the application of manual therapy in his clinic showed little effect: ‘Massage, particularly of the pelvic organs, once was in vogue but the results obtained were negligible.’

To date, there is little scientific evidence to confirm that there is any beneficial effect from the manipulation of viscera in relationship to pathological process.

In 1887, Symons Eccles a surgeon published his observations about his experience with atonic dyspepsia in the British Medical Journal. He noted that it occurred: ‘where the abdominal organs partake of the generally anaemic, feeble, pathetic condition which appears to pervade the whole system and personality of the patient to such an extent that the disorder of digestion is overshadowed by the nervous system.’ He noted: ‘I have found it useless to practice massage too frequently at first’ then, after bed rest, general corporeal massage including rapid effleurage to the limbs and trunk, then abdominal massage, the walls being vigorously rubbed and rolled between the hands, after which deeper kneading of the liver, stomach and intestines is carried out finishing with somewhat firm friction along the course of the colon. His prescription for massage was following treatment of two patients, and he noted that any increase from twice daily would retard as opposed to advance recovery. (Eccles, 1887). Negative effects from the treatment were recorded, which are lacking in current literature. These include; acute painful sensations during or after massage, skin modification, parietal hematomas, and functional digestive symptoms.

There is inconsistent evidence in the literature that manual stimulation of the abdomen can impact neurogenic bowel dysfunction. The mechanistic hypothesis is that manual stimulation of the digestive pathway may enhance propulsive peristalsis and has been shown in spinal cord patients (Ayas et al., 2006). In the Ayas et al. study, the group discusses the same limitations that confound much manual therapy literature: lack of a control group, a small sample size, and a poor study design. Despite these considerable flaws, they recommend that manual therapy be included in any spinal cord injury bowel program.

Much work has been done in order to understand the formation of adhesions in the abdomen. They are a result of an inflammatory process, often caused by infections, endometriosis, and most often by surgical trauma (Saed & Diamond, 2004). Injury to the peritoneal cavity causes a loss of mesothelial cells and decreased plasminogen activator activity (PAA), then, underlying fibroblasts are exposed and adhesions result between two adjacent surfaces (Braun & Diamond, 2014). Many studies suggest that the reduction in peritoneal fibrinolysis during an abdominal surgery is a local response to trauma, and is a cause of adhesion formation (Holmdahl & Eriksson, 1998). It has been recently recognized that tissue hypoxia from surgery or an inflammatory event leads to a coordinated series of molecular actions that promote an inflammatory response leading to enhanced tissue fibrosis. These events are; reduced plasminogen activator activity (PAA), extracellular matrix deposition, increased cytokine production, increased angiogenesis, and reduced apoptosis (programmed cell death) (Saed & Diamond, 2004).

The intrinsic protective fibrinolytic activity of fibroblasts is essential to the normal healing mechanism of the peritoneal cavity. The TPA/PAI-1 ratio has been shown to be 80% higher in normal peritoneal fibroblasts than in adhesion fibroblasts. Under hypoxic
conditions, this ratio significantly decreases in normal fibroblasts (90%), with an even more exaggerated decrease observed in adhesion fibroblasts (98%) (Alpay et al., 2008). Collagen deposition and angiogenesis further result from conditions of hypoxia, and are key components of the infrastructure for postoperative adhesion formation (Awonuga et al., 2014; Bolnick et al., 2014).

Mechanical stimulation or massage to the abdomen aiming to affect bowel dysfunction has been documented (Le Blanc-Louvry et al., 2002). There appears to be some effect in reduction of symptoms, however the mechanisms remain unclear. Reduction in intraperitoneal inflammation and inhibition of macrophage function has also been postulated as a possible key in reduction of intraperitoneal adhesion formation (Bauer, 2008; Wehner et al., 2007).

Intraperitoneal protein concentration and the number of inflammatory cells were reduced by visceral massage, indicating a dilution of the inflammatory milieu (Chapelle & Bove, 2013) in postsurgical animals, however both protein and leukocyte numbers increased in normal animals with visceral treatment, indicating a proinflammatory response in the absence of pathology. In a rat model, visceral massage immediately following surgery interfered with the formation of postoperative adhesions (Bove & Chapelle, 2012) but failed to significantly reduce already formed adhesions after one week.

It may be possible that manual therapy performed on the abdomen may prevent or reduce the formation of adhesions when performed immediately after abdominal surgery. Postoperative soft adhesions form as early as from 72 hours to two weeks. Twenty per cent of these adhesions form within one month, while 40% form within one year (Menzies, 1992). Once formed, adhesions are difficult or impossible to disrupt (Bove & Chapelle, 2012). Pain may be caused by nerve infiltration into the adhesions (Sulaiman et al., 2001a) however, the presence of sensory nerves can be found in all peritoneal adhesion formations and size is not indicative of perception of pain (Almeida & Val-Gallas, 1997). A possible hypothesis to be explored with manual therapy is prevention of adhesions through reduction of hypoxia, and to understand introduction of macrophage and TGFβ cells. Yet another path to explore is the interruption of the fibrinolytic cascade, and the deposition of fibrin, or the conversion of plasmin to plasminogen at an early stage to encourage lysing of fibrin (Heydrick et al., 2007).

The dose and timing of postoperative prevention of adhesions with manual therapy is in need of significantly more scientific literature and exploration. The effect of manual therapy on the fibrinolytic cascade; in particular, plasminogen and the lysing of fibrin before forming fibrous bands, the timing of interventions, the possibility of effecting hypoxia and vagal nerve involvement are all in need of basic science.

The role of innervation in scars and adhesions

For the most part, people seek care from manual therapists for pain relief. When a link is made between a treatment and pathology such as a scar or an adhesion, it may be presumed that there is also some connection between the pathology and the symptoms, and thus, neurology. Every injury also involves nerves of some caliber. Mastectomy surgery involves cutting many intercostal nerve branches, and even a small cut in the skin damages a few axons. These damaged axons remain alive, and immediately start to regenerate. For the most part, nerves regrow appropriately, but in many cases they do not, and can lead to persistent pain.

It has been shown that scars and adhesions become innervated with nerve fibers that have properties consistent with nociceptors (Herrick et al., 2000b; Sulaiman et al., 2000; Sulaiman et al., 2001b; Liang et al., 2004). Endometrioma, the lesions that occur from endometriosis, also can become innervated with similar fibers (Berkley et al., 2005). Intraoperative mechanical stimulation of adhesions has led to reports of pain (Almeida & Val-Gallas, 1997; Almeida, 2002), supporting that the innervation of adhesions is a functional response. While there may be anecdotal evidence that manual therapies reduce pain associated with scars and adhesions, we are unaware of
any study that shows any effect on the sensory supply to either.

A direction research may wish to explore is the possible effects on inflammation. There is some evidence that manual therapy may reduce some inflammatory mediators (Corey et al., 2012; Crane et al., 2012; Haas et al., 2013). If this is found to be true, the effects on pain may be surmised based on known axonal biology. Nerves pass through many structures, and may be exposed to inflammation or become mechanically compromised by compression or adhesion (Araki & Milbrandt, 1996). For instance, the median nerve passes between the flexor muscles in the forearm, and the visceral nerves pass within a thin mesentery to reach the intestines. Inflammation in these areas, independent of any condition at their end-organ, will induce changes in the nociceptor axons seen as ongoing activity (which may be perceived as spontaneous pain) and mechanical sensitivity, which would be perceived as pain coming from the end-organ (Bove et al., 2003; Dilley & Bove, 2008a). These changes are not permanent (Dilley & Bove, 2008b), resolving sometime after the stimulus is removed. If manual therapy reduces inflammation, it may also facilitate this recovery. These experiments have yet to be performed.

**Discussion**

While most of these examples of mechanical strain capture important aspects of tissue degeneration and the impact of injury, it is important to keep in mind that none captures the complete etiology of the injuries seen in human patients. Therefore, care must be taken in the choice and interpretation of the study model used to assess the impact of manual therapy on scars and adhesions. Further work is needed to validate the generalizability and translatability of basic science studies of healing mechanisms and the effect of mechanical strain in these models. Case studies and observation are important. Understanding basic cellular level function and response to mechanical strain are critical to the progression of manual therapy education and integration into the model of allopathic medicine.

It is important to recognize that regulated inflammation is largely beneficial to tissue repair, whereas excessive or persistent inflammation can be damaging. One consistent observation in all models and studies that include mechanical strain is that there is some effect on cell biology.

Whereas inflammatory cytokines attract fibroblasts to the repair site, excessive inflammation may lead to poor clinical outcome and an increase in fibrosis. Macrophages play essential roles in both promoting and resolving inflammation and in facilitating and moderating tissue repair. That a single cell type can serve opposing functions may seem counterintuitive, but dramatic phenotypic changes occur when macrophages respond to local stimuli. It has been shown that manual therapy evokes an immunomodulatory response to tissue, including an increase in macrophage activity (Crane et al., 2012; Waters-Banker et al., 2014a). By altering signaling pathways involved with the inflammatory process, manual therapy may decrease secondary injury, nerve sensitization, and collateral sprouting, resulting in more rapid recovery from damage and reduction or prevention of pain (Waters-Banker et al., 2014b).

The important role of the extracellular matrix in the formation of scars and adhesions cannot be overstated in this chapter. The interfaces in between the following are important:

- Skin to fascia,
- Epimysium to epimysium,
- Visceral peritoneum to visceral or parietal peritoneum,
- Nerve sheath to fascia, and
- Tendon to tendon sheath or fascia.

Interfaces may prove relevant and possible to attenuate with manual therapy. There have been studies examining the relationship of lumbar fascia to lumbar pain (Schilder et al., 2014) but the differentiation of tissues may be irrelevant to the application of the techniques of manual therapy since most tissues have been found to contain axons that are nociceptive. Clinical relevance may be the attenuation of inflammation to tissue healing cascades. Understanding the dose effect of pressure, techniques and applications to acute or chronic tissue injuries is work that still needs to be done.
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the Society for Investigative Dermatology, Inc. [and] European Society for Dermatological Research 5:40–46.


AUTHOR QUERIES

1. In 1887, Symons Eccles a surgeon published his observations about his experience with atonic dyspepsia in the British Medical Journal. He noted that it occurred: ‘where the abdominal organs partake of the generally anaemic, feeble, pathetic condition which appears to pervade the whole system and personality of the patient to such an extent that the disorder of digestion is overshadowed by the nervous system.’

2. Much work has been done in order to understand the formation of adhesions in the abdomen. They are a result of an inflammatory process, often caused by infections, endometriosis, and most often by surgical trauma (Saed & Diamond, 2004).

This had 'MD'. Changed to Saed & Diamond, 2004 as this seemed to be the reference, but please check.