

Editor's Note: Most chefs don't get involved in the clean-up process. Bon Appétit!!

## Ideal Wound Healing Is Not a Stretch

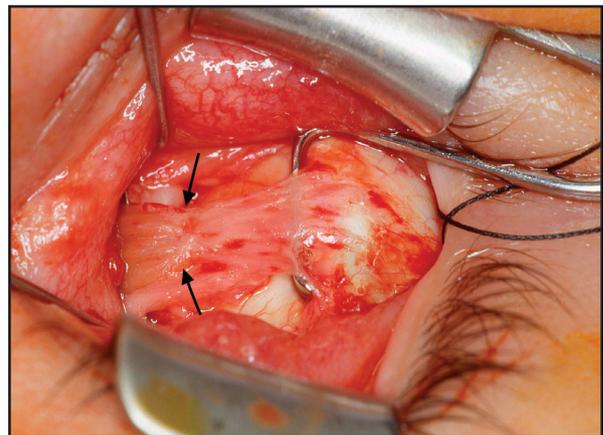
Irene H. Ludwig, MD; Robert S. Reiffel, MD; Frederick M. Wang, MD

**Y**ou cut the medial rectus off of the eye and, with your usual precise suturing technique, sew it back to the globe exactly where the measurements of the strabismic deviation would indicate. Case finished. . . Not so fast! The body must now heal the tendon to the globe in a strong and predictable manner.

Actually, wound healing began the moment you cut the muscle off of the globe. The first step toward wound healing is hemostasis. Immediate vasospasm, shortly followed by platelet aggregation, occludes the walls of the small cut vessels. Circulating clotting factors attach to the platelet plug and, through a complex cascade, form a fibrin net that strengthens the plug. Various signaling molecules called cytokines are released, indicating the presence and site of the wound. Cytokines include growth factors that act as wound healing hormones. Some are synthesized by cells distant to the target, some by adjacent cells, and some by the target cells themselves. Cytokines regulate cell proliferation, enhance cell migration to the site of the wound, and stimulate cells to produce substances necessary for healing.

Inflammatory cells, beginning with polymorphonuclear leukocytes (PMNs), migrate to the site of injury after being summoned by the cytokines, especially facilitated by transforming growth factor beta (TGF- $\beta$ ). The PMNs begin to clean up cellular debris and any contaminating pathogens that may have entered the wound. Sharper and less traumatic surgery (eg, less cautery) shortens the clean-up phase.

Beginning approximately 48 hours later, the PMNs are gradually replaced with macrophages. They have the dual role of finishing the clean-up of cellular



**Figure 1.** Medial rectus reoperation in a patient with consecutive exotropia, showing stretched scar segment (arrows).

debris and secreting cytokines. These cytokines, such as platelet-derived growth factor and TGF- $\beta$ , call in fibroblasts for the next phase of wound healing: the reparative phase. The reparative phase will not begin if the clean-up phase is incomplete.

Fibroblasts migrate to the wound by approximately the third day. They synthesize and secrete an extracellular matrix, which is a complex structure, to repair the wound. Repair often begins with the production of fibronectin, a large glycoprotein, that acts as a scaffold to which both cells and other structural proteins of the extracellular matrix attach.

The major structural component of repair is collagen. This protein is produced in the fibroblasts and secreted as the fibrillary protein procollagen into the extracellular matrix. Proteolytic enzymes cleave the procollagen into units that then coalesce into much larger collagen fibrils. A typical collagen molecule is a long, triple-stranded ( $\alpha$ -chains), rope-like helix.

*From Eye Center South, Dothan AL, and Eye Health Partners, Nashville, Tennessee (IHL); the Department of Surgery, Section of Plastic Surgery, White Plains Hospital, White Plains, New York (RSR); and the Department of Ophthalmology and Visual Science, Albert Einstein College of Medicine, Bronx, New York (FMW). The authors have no financial or proprietary interest in the materials presented herein.*

*Correspondence: Irene H. Ludwig, MD, 3215 Kinnard Springs Road, Franklin, TN 37064. E-mail: ihludwig@aol.com  
doi:10.3928/01913913-20180126-01*

This gives collagen its ability to resist tensile pulling forces. Cross-linking between strands through the formation of covalent bonds between lysine residues further strengthens the strands. There are approximately 25 types of  $\alpha$ -chains and mixing and matching produces the 20 or so clinically important collagens. Initially, tendons repair with collagen III, which is gradually replaced with the larger and stronger collagen I. Initial low wound strength is the result of the wound being composed of the smaller caliber collagen fibers. Gradually, over months to years, the smaller collagen fibers are replaced by larger ones. This remodeling is a complex equilibrium between breakdown and repair, which is mediated by proteases. These proteases cooperate to degrade matrix proteins such as collagen and fibronectin, allowing for the replacement by larger fibers. Remodeling continues until an equilibrium is established between collagen synthesis and breakdown. Wounds continue to gain strength in adults for more than 1 year and for as long as 2 years in children. It should be kept in mind that scar tissue never achieves the full strength of native collagen. Steroids profoundly inhibit collagen formation.

Elastin in the extracellular matrix consortium adds a little stretchability. Pure elastin is actually very stretchable, with approximately 6 times as much stretch as a rubber band.

The bulk fill of the extracellular matrix is composed of large glycosaminoglycans (GAGs), which are unbranched polysaccharide chains composed of repeating disaccharide units. The polysaccharide chains are too stiff to fold up and are extremely hydrophilic. These GAGs form a gel that associates with extracellular matrix proteins to produce tissue turgor. So, while the collagen fibers resist stretching forces, the GAGs resist compressive forces.

While wound repair is taking place, new vessels are needed to bring oxygen, nutrients, and building materials to the new tissues. Angiogenesis takes place through the interaction of growth factors such as VEGF and TGF- $\beta$  with endothelial cells and other components of the extracellular matrix.

Dysregulation of wound healing during the proliferative and maturation stages leads to excess fibroblast replication and collagen deposition, resulting in hypertrophic scars and keloid formation.

Importantly, mechanical factors affect wound healing. It is well known that mechanical

tension along the long axis of a wound produces hypertrophic scars. The body senses the need to strengthen a scar that is under lengthwise tension. Incisions made parallel to relaxed skin tension lines heal with much less exuberance than those placed at right angles to them. When incisions must be placed perpendicular to relaxed skin tension lines, the number of lines crossed should be minimized. Paper tape placed along the long axis of a skin incision for a few months helps prevent hypertrophic scarring when a wound is under lengthwise tension.

Tendons that have been cut and repositioned, such as those of extraocular muscles, are under tension. Fibronectin strands mechanically orient the matrix initially. Collagen fibers then align parallel to the length of the tendon. Even in cell cultures, cells line up in relation to mechanical stress on the matrix. Tension along the axis of the tendon fibers produces microbreaks in the collagen, resulting in lengthening until the scar is strong enough to resist these breaks.

A longer scar attaching an extraocular muscle to the globe after strabismus surgery has weakening effects on the muscle function. It lessens the mechanical transmission of the muscle force to the globe because it has some elasticity, and causes shortening of the muscle length. These “stretched” scars are not uncommon and are clinically relevant (**Figure 1**). They may represent a secondary effect of poor healing such that the tendon lengthened when the attachment was put under mechanical stress. Alternatively, they may be produced by a dysfunctional proliferative phase, allowing for the deposition of a lengthened scar segment.

Seems like the wound healing is actually the most complex part of the case. We should be glad the surgeon doesn't have to do it!

### TO LEARN MORE

[https://www.youtube.com/watch?v=24PtkXz\\_WIU](https://www.youtube.com/watch?v=24PtkXz_WIU)

### SEMINAL ARTICLE

Ludwig IH. Scar remodeling after strabismus surgery. *Tr Am Ophth Soc.* 1999;97:583-651.

### CLINICAL CORRELATE

Reiffel RS. Prevention of hypertrophic scars by long-term paper tape application. *Plast Reconstr Surg.* 1995;96:1715-1718.