Derived from the Greek word *plastikos*, meaning “to mold or give form,” plastic surgery has a long-standing history of creativity and innovation for the purpose of reshaping traumatized, congenitally-malformed, or aesthetically-displeasing abnormalities. The methods and techniques employed for this purpose have varied over the years, including autologous and alloplastic options. As our understanding of wound healing, tissue biology, and manufacturing/materials science has progressed in recent decades, the substrates available to the surgeon for application in a multitude of procedures have expanded rapidly. While synthetic materials are helpful in a variety of surgical settings, permanent prostheses suffer by nature of their inability to become completely incorporated into the human form—a permanent synthetic implant is always at risk for infection, extrusion, and invasion into surrounding tissue. Biological implants, however, carry the unique ability to become integrated into the native tissue, which aids in wound strength and offers a more biocompatible solution. Specifically, acellular dermal matrix (ADM) has revolutionized our approach to difficult clinical scenarios, including head and neck, breast, abdominal wall, and extremity surgery. In this introduction to the supplement “Acellular Dermal Matrix: Fundamentals and Expanding Applications in Plastic Surgery,” we review the basic science behind, general principles about, and applications of ADM in plastic surgery. Subsequent articles detail indications and describe techniques to illustrate the breadth of ADM application in plastic surgery.

**WOUND HEALING**

To fully understand the structure and function of ADM, one must first become familiar with the wound healing process. Whether the injury is a result of surgery or trauma, before the healing process may begin, the body’s initial response is one of hemostasis. This is achieved via platelet activation in response to endothelial injury, exposed collagen, and thrombin; it is aided by initiation of the coagulation cascade. In addition, local blood flow is slowed via prostaglandin- and catecholamine-induced vasoconstriction.

From the Division of Plastic Surgery, University of Pennsylvania Health System, Philadelphia, Pennsylvania.

**Corresponding Author:**
Dr. Joshua Fosnot, MD, Division of Plastic Surgery, University of Pennsylvania Health System, 10 Penn Tower, 3400 Spruce Street, Philadelphia, PA 19104, USA.
E-mail: joshua.fosnot@uphs.upenn.edu
Platelet aggregation in turn causes release of a whole host of cytokines (including adenosine diphosphate, serotonin, and thromboxane A2), which ultimately increases hemostasis and vasoconstriction.\(^1\) While vasoconstriction initially controls blood loss, inflammatory mediators such as kinins, histamines, prostaglandins, and leukotrienes soon cause local vasodilation, allowing for the influx of inflammatory cells necessary for the healing process to begin.\(^2,3\) Within eight hours of injury, polymorphonuclear cells begin cleaning the wound and preventing infection. This process continues for the first three days following injury and is augmented by the infiltration of macrophages, which help to remove debris. This orchestration is directed by cytokines, including TGF, PDGF, FGF, IL-1, and TNF.\(^7,3\)

Following completion of the inflammatory stage of wound healing, the next phase begins, characterized by proliferation. By Days 5 through 7, fibroblasts become the primary cell of interest, with an overall goal of collagen synthesis. Type III collagen predominates in early production but is replaced in the long term by Type I collagen for maturation of the scar (Figure 1). This collagen framework is embedded in a milieu of fibronectin and glycosaminoglycans, including heparan sulfate, hyaluronic acid, chondroitin sulfate, and keratan sulfate, which all aid in the creation of a matrix for wound structure.\(^3\) Overall, this matrix is ultimately responsible for wound structure and the reestablishment of wound continuity—characteristics that make it ideal for a biological implant. Fibroblasts also secrete matrix metalloproteinases, which help shape the surrounding matrix to allow for fibroblast migration.\(^3\) The resultant matrix structure also provides a framework for angiogenesis by providing a support network for budding vessels, stimulated by HIF-1, FGF, PDGF, TGF-β, TNF-α, and VEGF.\(^4\) Superficially, the wound is simultaneously being covered by epithelial cells where appropriate. This process occurs via rapid mitosis of epithelial cells from the periphery of the wound and adnexal structures. Once all key components of the wound are in place, the final phase of wound maturation and remodeling begins. Collagen is degraded and reformed to render a more uniform and balanced structural array, which maximizes wound strength. The overall quantity of collagen does not change; however, Type III collagen is replaced by Type I collagen, which is stronger and more durable. Overall, wound strength continues to improve until approximately 12 weeks, at which point the wound has reached its final strength. Overall wound strength reaches approximately 80% of its initial strength but never regains its original function.\(^3\) Elastin, another structural protein, provides for elasticity and stretching within native tissue and healing wounds. Myofibroblasts aid in wound contraction, especially in open wounds healing by secondary intention.\(^3\)

**The Clinical Dilemma**

With any surgical wound, the goal is rapid healing with a minimal scar that will have a long-term natural contour and provide lasting tensile strength. Wound healing is ideally begun with primary wound closure. The body provides the natural substrate for healing and offers the best chance for positive results. However, tension is often too great for primary closure, and additional tissue is needed to complete the repair. Local flaps—pedicle or free flaps—can be utilized in these cases to provide additional soft tissue coverage and the necessary ingredients for wound healing. Unfortunately, autologous tissue is neither always available nor free of donor morbidity. While synthetic materials such as Marlex mesh, polytetrafluoroethylene, titanium implants, or methylmethacrylate have been useful for implantation and structural support, they all suffer from several limitations. They do not bring any of the basic wound healing units (eg, glycosaminoglycans, fibronectin) into the field to amplify the wound healing process. In addition, they become only minimally integrated in the final wound. Although scar tissue may adhere to the implant, it is never truly an integrated implant. Finally, because they are permanent foreign bodies, they are all subject to infection and extrusion. Therefore, an ideal prosthesis is one that augments the body’s natural efforts, provides structural support, allows for ingrowth, and is eventually replaced or fully integrated. Many of these characteristics are found in ADM.

**Acellular Dermal Matrices**

The dermis is a layer of the body rich with wound matrix, composed of collagen, elastin, fibrillin, and glycosaminoglycans. It provides a semirigid yet elastic support system to ward off injury from trauma as well as provide structural and nutritional support to the epidermis above. While the dermis is composed primarily of a matrix for structural
support of the skin, it serves a major role in thermoregulation through vasoconstriction, dilation, and evaporation via sweat glands.

Also within the dermis lie multiple nerve endings designed for special functions, such as temperature sensation and proprioception. Thus, although the dermis is full of the necessary elements for wound healing, the cells within this layer (eg, sweat glands, nerve endings) are rich in antigenic material, making routine allotransplantation or xenotransplantation impossible without rapid rejection. Multiple proprietary methods have been devised to strip the dermis of its cellular components after harvest from human cadaver, porcine, or bovine in origin. In the case of human donors, the tissue is screened for infectious diseases such as HIV and hepatitis. The tissue is run through a series of steps, with each company having its own proprietary process. AlloDerm (LifeCell Corp., Branchburg, New Jersey), one of the most ubiquitous products on the market, has a manufacturing process that begins by immersing the tissue in a buffered salt solution to separate and eliminate the dermis. Next, a series of mild detergents are applied to eliminate all cellular elements from the tissue. The tissue is extensively tested for any contamination to ensure a sterile product, then freeze-dried to prevent crystallization and allow for stable packaging and storage.

Of note, several materials in this category are not entirely biological. In particular, Integra (Integra LifeSciences Corp., Plainsboro, New Jersey), which is designed for superficial wounds, has an adherent layer of silicone sheeting on its outer surface that serves as an additional temporary barrier to bacterial infiltration and helps avoid desiccation by preventing evaporation from the wound. In

<table>
<thead>
<tr>
<th>Proprietary Name</th>
<th>Manufacturer</th>
<th>Origin</th>
<th>Unique Attributes</th>
</tr>
</thead>
<tbody>
<tr>
<td>AlloDerm, Repliform</td>
<td>LifeCell Corp.</td>
<td>Human dermis</td>
<td></td>
</tr>
<tr>
<td>Cymetra</td>
<td>LifeCell Corp.</td>
<td>Human dermis</td>
<td>Micronized for injection</td>
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<td>NeoForm</td>
<td>Mentor</td>
<td>Human dermis</td>
<td></td>
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<tr>
<td>Flex HD</td>
<td>Musculoskeletal Transplant Foundation and Ethicon</td>
<td>Human dermis</td>
<td>Prehydrated and ready for use</td>
</tr>
<tr>
<td>DermaMatrix</td>
<td>Musculoskeletal Transplant Foundation and Synthes</td>
<td>Human dermis</td>
<td></td>
</tr>
<tr>
<td>SureDerm</td>
<td>Hans Biomed Corp.</td>
<td>Human dermis</td>
<td></td>
</tr>
<tr>
<td>Glyaderm</td>
<td>Euros skinbank</td>
<td>Human dermis</td>
<td>Relatively inexpensive</td>
</tr>
<tr>
<td>Collamend</td>
<td>Bard</td>
<td>Porcine dermis</td>
<td></td>
</tr>
<tr>
<td>Permacol, Enduragen, Pelvicol, Zimmer Collagen</td>
<td>Tissue Science Laboratories</td>
<td>Porcine dermis</td>
<td>Available in large sheets for abdominal wall use (Permacol; crosslinked)</td>
</tr>
<tr>
<td>Strattice</td>
<td>LifeCell Corp.</td>
<td>Porcine dermis</td>
<td>Premade geometric shapes</td>
</tr>
<tr>
<td>SurgiGraft (SIS)</td>
<td>Cook Biomedical</td>
<td>Porcine intestinal submucosa</td>
<td>Variety of products for specific indications</td>
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<tr>
<td>Surgimend</td>
<td>TEI Biosciences</td>
<td>Bovine dermis</td>
<td></td>
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<tr>
<td>Veritas, Peri-Guard</td>
<td>Synovis</td>
<td>Bovine pericardium</td>
<td>Noncrosslinked</td>
</tr>
<tr>
<td>Integra</td>
<td>Integra LifeSciences Corp.</td>
<td>Bovine Achilles tendon and shark cartilage</td>
<td>Semipermeable silicone layer over matrix</td>
</tr>
<tr>
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<td>Skin and Healthcare</td>
<td>Bovine dermis</td>
<td>Designed for skin defects</td>
</tr>
<tr>
<td>Pelnac</td>
<td>Gunze Corp.</td>
<td>Bovine dermis</td>
<td>Designed for skin defects</td>
</tr>
<tr>
<td>Renoskin</td>
<td>Groupe Perouse Plastic</td>
<td>Bovine dermis</td>
<td>Silicone outer layer; designed for skin defects</td>
</tr>
</tbody>
</table>

aNot a true ADM.
essence, Integra mimics skin in that the silicone sheet acts as the epidermis while the matrix component serves as replacement dermis.

An attribute of certain ADM products involves crosslinking, whereby adjacent collagen is linked chemically. While crosslinking occurs within normal human tissue, the degree to which it occurs during preparation of ADM can be controlled. Theory and research suggest that noncrosslinked substrates suffer from faster degradation due to collagenases within the body, whereas too much crosslinking may lead to limitations in native tissue ingrowth with subsequent poor tissue integration. Agents such as glutaraldehyde or hexamethylene diisocyanate can be utilized to crosslink the collagen within the matrix. Due to the poor integration of noncrosslinked ADM, these implants may show promise in applications where adjacent adhesion formation is undesirable, such as with intra-abdominal placement adjacent to the bowel and when a temporary barrier is indicated. Additionally, in aesthetic surgery where softer contours and subtle results are needed, noncrosslinked agents are likely more appropriate due to increased pliability. In contrast, properly crosslinked matrices likely offer more lasting strength in applications such as abdominal wall reconstruction and hernia repair.

GENERAL APPLICATIONS

Due to the unique characteristics of biological implants and the variety of available products, ADM can be tremendously helpful in a range of applications within the field of plastic surgery. Although there are, to date, little if any prospective randomized data comparing ADM to the current standard of care in each field, there are several areas of plastic surgery that have yielded a significant amount of outcomes data, the results of which tend to be excellent. Despite numerous reports of novel ways of placing ADM in surgery, the following areas are the best studied.

Burns and Wounds

While grafting has long been a staple for the replacement of lost skin, ADM has become increasingly popular in these cases over the past 20 years for coverage of open soft tissue defects. While skin grafting is significantly less expensive, ADM placement can help prevent a painful and displeasing donor site. AlloDerm has been reported in the literature as a dermal substitute in full-thickness burn wounds. In addition, ADM has been used in conjunction with split-thickness grafts for treatment of full-thickness wounds. For significant full-thickness burns crossing the joint, ADM products are effective in wound coverage and allow for sufficient elasticity to prevent contracture over the joint. Aside from burn wounds, ADM has been shown to be effective in the treatment of diabetic foot ulcers, with one prospective randomized study demonstrating improved healing efficacy following coverage with dermal matrices. While the cost of ADM may limit widespread use, early results seem promising for many types of wound management.

Abdominal Wall Procedures

As many surgeons have found themselves operating in the abdomen with poor fascia for closure, combined with contamination from enteric sources, there has always been interest in an implant material that would add strength to the abdominal closure while resisting infection. Permanent mesh is unusable in these situations, and temporary synthetic meshes often do not provide adequate or lasting tensile strength to prevent hernia formation. ADM has been shown to be effective in decreasing hernia recurrence rates in infected fields when compared to primary closure without mesh. While AlloDerm (human ADM) was initially used for this application, many find its overall strength lacking; furthermore, its elasticity makes it prone to bulging over the long term. Therefore, its placement in the abdominal wall should be abandoned. More recently, porcine ADM products have been placed with success, preventing recurrence and providing for closure that is resistant to chronic infection.

For best results, these complex abdominal wall closures are coupled with component separation, which provides additional native coverage of the implant where there has otherwise been loss of sufficient fascia or even abdominal domain. Studies have shown an exceedingly high recurrence rate when the mesh serves as a bridge rather than a bolster. Overall, this highlights an important principle: ADM should be placed in a position that maximizes surface area contact with vascularized native tissue to facilitate wound healing and decrease hernia recurrence.

Similarly, in the setting of permanent mesh infection, removal of the infected implant often leaves a large defect in a contaminated operative field. Biological mesh provides an opportunity to bolster the closure without the risk of permanent infection requiring reoperation. Not all studies have had overwhelmingly positive results with ADM for abdominal wall reconstruction, due to high recurrence rates, extrusion, and infection. It is important to recognize that this material is in the early stages of use and that further prospective randomized studies are necessary to clearly delineate outcomes.

Reconstructive Breast Procedures

Reconstruction with tissue expanders and implants is a multistage process that can be exhausting to patients already coping with a difficult diagnosis. The limitation of immediate one-stage reconstruction has always been the inability to completely cover an implant with sufficient soft tissue to ensure a tension-free closure and avoid implant extrusion. Typically, with placement of a subpectoral expander, the taut muscle is the limiting factor for implant size and thus requires expansion. ADM has been increasingly used as an internal support and cover for single-stage operations. In this approach, the pectoralis major is allowed to “window-shade” upward,
and an AlloDerm sling is fixed from the inferior aspect of the pectoralis down to the inferior mammary fold (Figure 3). Thus, the implant is completely covered and supported by the AlloDerm. In many cases, this allows for single-stage reconstruction with placement of the final implant at the time of initial reconstruction.30-33 While few data exist directly comparing different products, at least one retrospective study did show similar side effect profiles between AlloDerm and DermaMatrix (Synthes, Inc., West Chester, Pennsylvania).34 However, there are some data suggesting that implant infection and extrusion rates in alloplastic reconstruction are higher with AlloDerm.35-37 Other ADM products have not been studied sufficiently to draw any similar conclusions. Overall, human-derived products with a high elastin content (such as AlloDerm) are desirable in this application, due to their ability to stretch.

**Cosmetic Breast Procedures**

Although ADM products have been utilized extensively in breast reconstruction, similar techniques have been applied in cosmetic breast surgery. ADM placement can yield a natural

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Figure 2. (A, B) This 45-year-old woman presented with loss of abdominal domain, in need of concomitant bowel surgery. (C) Component separation ventral hernia repair with the placement of ADM bolster (Permacol) in a retrorectus position. Note a small midline area that could not be covered entirely. (D) This 58-year-old man also presented with similar loss of domain and is shown undergoing a colostomy reversal. (E, F) Even with component separation, the ADM could not be covered in the patient featured in part D. (G, H) One year postoperatively, the patient in parts D, E, and F, with no evidence of hernia recurrence of bulge.
contour for significant irregularities. In addition, significant implant malposition can be corrected with the support of a sling to lift and hold an implant in proper position. \textsuperscript{38,39} Similar in concept, an internal support can be placed to help prevent bottoming out with inferior pedicle breast reduction. \textsuperscript{40} One significant deterrent from widespread application in cosmetic procedures is the need for patients to absorb the cost of the ADM. \textsuperscript{41}

**Head and Neck Procedures**

In eyelid and periorbital surgery, the surgeon is often in need of a biological construct that will provide enough structure for support while simultaneously offering an aesthetically natural, soft contour. ADM has been used successfully in these cases to bolster lid structure and fill volume deficits. \textsuperscript{42,43} Similarly, ADM can act as an off-the-shelf material for reconstructing the tarsal plate. \textsuperscript{44,45}

Secondary rhinoplasty is often plagued by insufficient structural support to establish the desired optimal cosmetic outcome. In these patients, many surgeons have found ADM useful for filling space while maintaining a soft contour in either saddle nose deformities or irregularities of the alar rim. \textsuperscript{46-48} In addition, nasal septal perforations have been successfully treated with ADM. \textsuperscript{49}

In children with cleft palate, there is often insufficient soft tissue to provide stable, tension-free closure. ADM has been useful for adding bulk to this closure, whether primarily, in revisional surgery, or for treatment of a fistula. \textsuperscript{50-53} In addition, ADM has been useful in the healing process of nasoalveolar bone grafting by providing additional nasal-oral mucosal lining where it is otherwise deficient. \textsuperscript{54} Similarly, ADM has been successfully placed to line the oral cavity following intraoral cancer extirpation with similar quality of life to split-thickness skin grafts, at a lower cost, and without donor defects. \textsuperscript{55}

Figure 3. (A) In this two-stage breast reconstruction, an AlloDerm sling has been placed for additional coverage of the implant. Note that the pectoralis major has been released inferiorly. (B) Upon expander exchange, the ADM is visible but has been incorporated into a healthy capsule for adequate implant coverage. (C) In sum, 240 cc was placed into the expander at the time of initial placement. Photos courtesy of Joseph J. Disa, MD—Memorial Sloan-Kettering Cancer Center.
CONCLUSIONS

The production of biological mesh for various surgical applications is an ever-burgeoning market with potential for great improvement in patient care. The ideal implant for surgical placement would be a biological replacement of lost native structure that, over time, is either replaced by normal human tissue or at least completely integrated. While there is no perfect ADM for all applications, there are many available products that work well with proper technique and patient selection. While there have been numerous publications on ADM, it does seem that the application of these materials has far outpaced the evidence in support of their use. That is not to say that no evidence exists; rather, we must recognize that these materials are very expensive and that just because they can be useful in a given situation does not mean that they always offer improved clinical results.

Disclosures

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