A Road Less-Traveled: Cotton-Based Approaches to Wound Healing

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Introduction

Through many fruitful collaborations, the road of cotton textile research and development has led me to a long-term interest in biomaterial properties for wound healing and hygiene. However, cotton fabrics are present throughout recorded history and a proven textile in modern times. Thus, the "road less-traveled" is work that has sought to make the whole cotton fiber applicable to wound healing in the twenty-first century.

Southern Regional Research Center: A Home to Cotton Utilization Research Since the 1940s

I joined the Southern Regional Research Center (SRRC) in the mid-1990s following the very fruitful work established by several generations of cotton textile scientists who had performed post-harvest utilization research since the early 1940s. In the mid-twentieth century, King Cotton was challenged by the advent of synthetic fibers. Research on permanent press and flame retardant cotton helped restore cotton's place in the market. Moreover, in 2004, the SRRC was bestowed with an American Chemical Society Historical Landmark award for work on flame retardant and permanent press research.[1] Interestingly, stretch gauze was invented at SRRC in the mid-1940s at the close of WWII by the collaboration of a textile chemist, Charles F. Goldthwait (Olney Medalist 1962) with a local surgeon. Stretch cotton gauze later became a household product.[2] Olney medal recipients from SRRC's Cotton Chemistry Utilization Unit span three generations of cotton textile chemists since Dr. Goldthwait, and include Ty Vigo (2000), Beth Andrews (1992), Stanley Roland (1985), George Drake (1976), Harold Lundgen (1968), and Wilson Reeves (1966).

From the Past to the Present and Looking Forward

Similarly, today two of the most important things in cotton utilization research are increasing domestic consumption of cotton fibers grown by US farmers and unmet consumer needs. Nonwoven postharvest utilization to promote domestic consumption has been an important part of recent SRRC research and development. A reflection of progress in this regard is that cotton's share of the nonwoven market continues to grow today.[3]

A focus and commitment of my research has been to address unmet consumer needs. These include chronic wound and hemorrhage control in patients. Two and a half million people in US hospitals and nursing homes suffer from chronic wounds, which have been estimated to increase dramatically in this year of Covid-19.[4] Moreover, pressure ulcers cost US$9.1–11.6 billion per year.[5] Half of all deaths on the battlefield are caused by uncontrolled hemorrhaging.[6] In addition, 25 million people in the United States and 200 million worldwide suffer from incontinence.[7] The development of new prototypes to address unmet patient needs brings wound healing and biomaterial science concepts to cotton.

Properties and Functionality for Healing and Hygiene

Acute insults to the skin result in the initiation of wound healing, which is a complex process with many unsolved problems. As shown in Fig. 1, the overlapping phases from hemostasis to remodeling takes about 21 days to reach completion. The wound healing process may be divided into four major stages: hemostasis, inflammatory, proliferative, and remodeling, with each phase having a well-defined period of onset and completion, yet overlapping. Much of modern day wound dressing design takes into consideration disruption of at least one of these phases.[8] We have developed cotton-based products for hemostasis and the inflammatory phase.[9,10]

To design and develop wound healing and skin contacting cotton fabrics where do we start? Historically, work on post-harvest utilization that improved the functional properties of cotton was with bleached

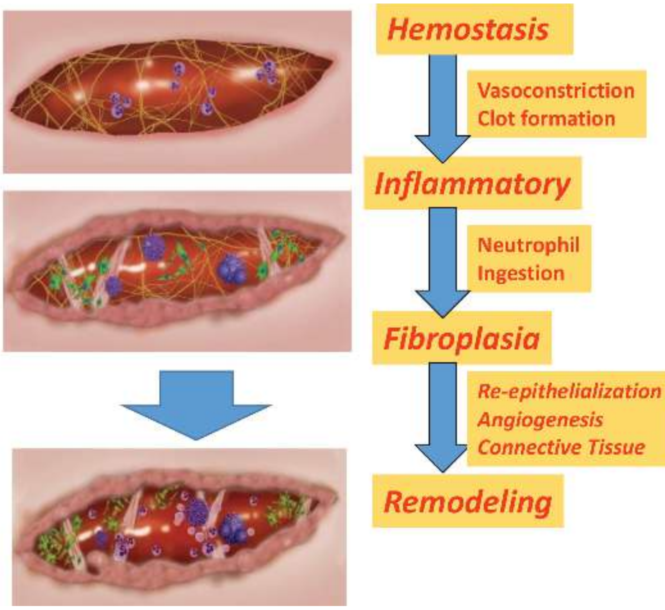

Fig. 1. Wound healing is a complex cascade of molecular and cellular events. During the coagulation phase following injury, platelets initiate healing through the release of growth factors. Growth factors are responsible for the activation of immune cells and cell proliferation. Neutrophils clear the wound of bacteria and cellular debris. The arrival of neutrophils marks the onset of the inflammatory phase of wound healing, and under acute healing conditions last only a few days. However, in a chronic wound, the period of growing neutrophil population is extended indefinitely. An overabundance of neutrophils in a prolonged inflammatory phase has a negative influence on healing, and a source of destructive protease activity. Granulation tissue forms in five days. Fibroplasia is the last restorative stage of healing. Fibroplasia involves the combined effect of re-epithelialization, angiogenesis, and connective tissue growth. In a healthy person, healing occurs in 21 days, and the remodeling phase consisting of scar transformation based on collagen synthesis continues for months following injury.

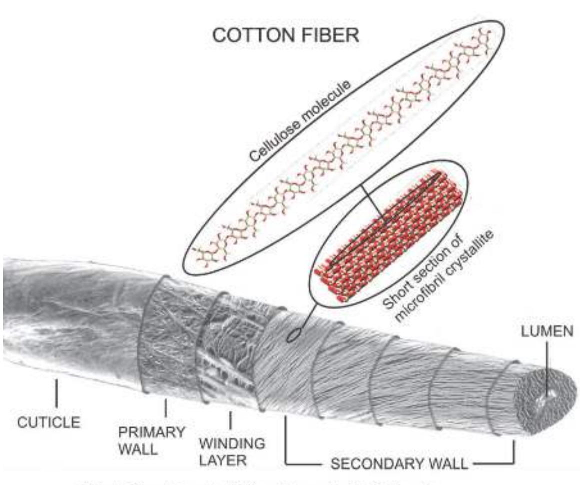

Fig. 2. A diagram of cotton fiber sections constructed from individual transmission electron micrographs (TEMs) and scanning electron micrographs (SEMs) of the fiber. These give an overview of the layered structures of the fiber. The fiber cuticle and primary and secondary cell walls are at different magnifications to better visualize structures and fiber layers from the surface to the lumen.

and scoured cotton. A fiber perspective, as shown in Fig. 2, demonstrates overlapping electron micrographs of the cotton fiber, and helps illustrate how improved functional properties are derived from the cotton fiber. For example, the outermost part of the cotton fiber contains a waxy cuticle thought to play a role in accelerating hemostasis and promoting non-adherence to the wound bed. Pectin, proteins, and small molecules residing near the primary cell wall are a source of hydrogen peroxide.[11] Cellulose not only affords an absorbent function, and a scaffold for chemical modification, it also is a source of nanocellulose—an important component in sensor design.[12] Nonwoven, unbleached cotton retains the cuticle lipids present on the outermost part of the cotton fiber, which confer a hydrophobic character presented as a thin waxy layer deposited across the fabric surface. This occurs because the lipid-containing layer is loosened from the cellulosic primary cell wall during the hydroentanglement process. In the process of creating a spunlace nonwoven, the cotton fiber cuticle is lifted, exposing the absorbent cellulosic primary and secondary cell wall, which are the hydrophilic portions of the cotton fiber that confer wettability and absorbency. Published models that may be used for product development have been highlighted and dedicated to marketing unbleached cotton in product development for wound care and hygiene.[13]

Trauma Dressing Innovation through De Novo Design

Historically, greige cotton played an important role in times of battle, as in the American Civil War. During that period, the production of cotton dressing derivatives, referred to as charpie, was a national effort. Charpie was a type of high surface area cotton lint obtained by scraping homemade fabrics (i.e., quilts). Producing charpie was a national effort that occupied many homes and aid societies at that time to supply badly needed dressing materials to field hospitals.[14]

Let us fast forward to modern design principles. De novo design implies starting at a molecular level from what is known about the composition of the fibers and building on the relation of fiber and fabric properties for functional activity as understood based on the science of blood-contacting surfaces.[10] As shown in Fig. 2, we have used the whole cotton fiber to examine structure function relationships in this manner. Thus, to develop an improved hemostatic dressing, the

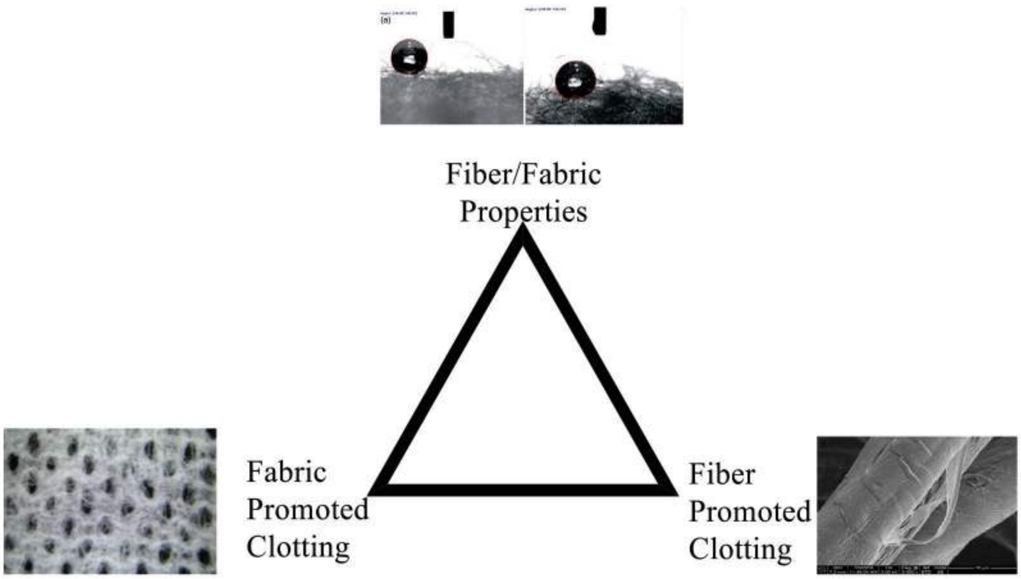

Fig. 3. A diagram of the three-point triangular approach, including fiber promoted clotting fabric clotting, contact angle, surface polarity, and absorption properties.

structure of fiber, fabric, and the inter-related influences on pro-coagulant properties are required. This process, as shown in Fig. 3, is triangular. The vertices of the triangle connect fiber-promoted and fabric-promoted clotting with fiber/fabric properties. Using this approach, the final factory-produced commercial prototype fabric demonstrated hyper-coagulopathy activity as determined by a thrombin generation assessment. The dressing was found to be 60% more absorbent, and accelerated clotting as compared with the standard bleached and scoured USP Type VII cotton gauze dressings.[15]

From the process outlined above, and through a tech transfer relation that involves cotton farmers, SRRC, and manufacturers, dressings are developed. The hemorrhage control prototype is based on formulation of a pro-coagulant recently reported in *Military Medicine*.[16] The rationale of the prolonged field care prototype is described below.

Dressings that Promote Wound Healing and Antimicrobial Activity through Hydrogen Peroxide Generation

With the one-hundred year anniversary of AATCC, we may reflect on some parallels of today with the 1921 founders. Perhaps one of the most visible icons shared is the donned facemask. Barrier textiles used during the three-year Spanish Flu pandemic of 1918-1921 consisted of multilayered gauze. Notably, little was known about the mechanism of microbial or virus transmission during that time (i.e., both the first identification of a viral particle and the discovery of penicillin were a decade or more away).[17] During this past year, many efforts have been undertaken to address the application of mechanism-based barrier fabrics in prevention of the spread of SARS-CoV-2.[18,19]

The development of antiviral fabrics has been part of this effort, and a continuation of work on cotton-based antimicrobial fabrics is described below. Notably, fabrics that release hydrogen peroxide at antiviral levels have been shown to be quite effective.

This type of work began with an interest in developing affordable and effective hemostatic and antimicrobial wound dressings for prolonged field care (PFC) and has to do with treatment of traumatic wounds in remote and austere parts of the world where the Golden Hour of care does not apply.[20]

Research on an antimicrobial dressing based on a mechanism that generates hydrogen peroxide from greige cotton led to its development. From the start, we were interested in bridging that activity with the role that hydrogen peroxide plays in wound healing. Hydrogen peroxide is one of the most relevant small molecules in wound healing. In a healing wound, low levels of hydrogen peroxide are produced at the leading edge of migrating cells and increase from three minutes to an hour after injury.[21] While working with collaborators, we discovered that small amounts of ascorbic acid added to nonwovens under textile finishing conditions gave rise to robust antibacterial activity.[22] The pad dry cure finishing chemistry yielded fabrics with 99.99% inhibition of Gram negative and positive bacteria. This dressing approach to prolonged field care has been cited recently in the *Marine Corp Gazette*.[23]

Chronic Wound Protease Modulating Dressings

Wound healing does not always occur in a predictable fashion, as outlined in Fig. 1. Numerous local and systemic factors may influence the pattern and rate of healing, and can lead to a chronic, non-healing state. A chronic wound is one that fails to heal in a timely fashion due to one or more pathologies precipitated by the onset of conditions including infection, radiation damage, hypoxia, diabetes, venous insufficiency, malnutrition, or ingestion of pharmacological agents.

Although chronic wounds are a type of inflammatory disease, it was not until the late-1990s that potential treatment options were proposed. The studies were based on inhibition of destructive proteases thought to prolong the inflammatory response. An overabundance of proteases in chronic wounds arises from the induction of neutrophils during the stalled inflammatory phase of wound healing. Thus, through my collaboration with wound healing scientists and physicians, the application of protease inhibitors to lower pathologic levels of proteases in the chronic wounds was first proposed, and was based on a cotton formulated serine protease inhibitor.[24] Subsequently, the mechanism of protease inhibition applicable to chronic wound treatment was extended to include non-toxic inhibitors of human neutrophil elastase. This inhibitor was based on oleic acid, and a mechanism of action delineated with albumin as an inhibitor transfer-carrier protein.[25] Albumin, which is the most abundant protein in wounds, has been characterized as having 64 oleic acid storage binding sites. It was further elucidated that oleic acid's application to acute wounds accelerated healing.[26] The application of oleic acid and other fatty acids is now an approved treatment for chronic wound patients in some parts of the world.[27] It is interesting that oleic acid's activity aligns with folklore remedies where olive oil is attributed with wound healing properties.

Our development of the first protease modulating dressing (PMD) was based on modified textile fibers designed to bind and neutralize the destructive activity of human neutrophil elastase and matrix metalloprotease in chronic wound pathology.[28] Thus, a form of phosphorylated cotton was adopted as one of the first PMD prototypes and was developed for FDA approval in the early-2000s. Its mechanism of action is based on binding the cationic portion of serine proteases and the zinc-binding site of metalloproteases (Fig. 4). The PMD's commercialization was also founded on the principle of providing a low-cost

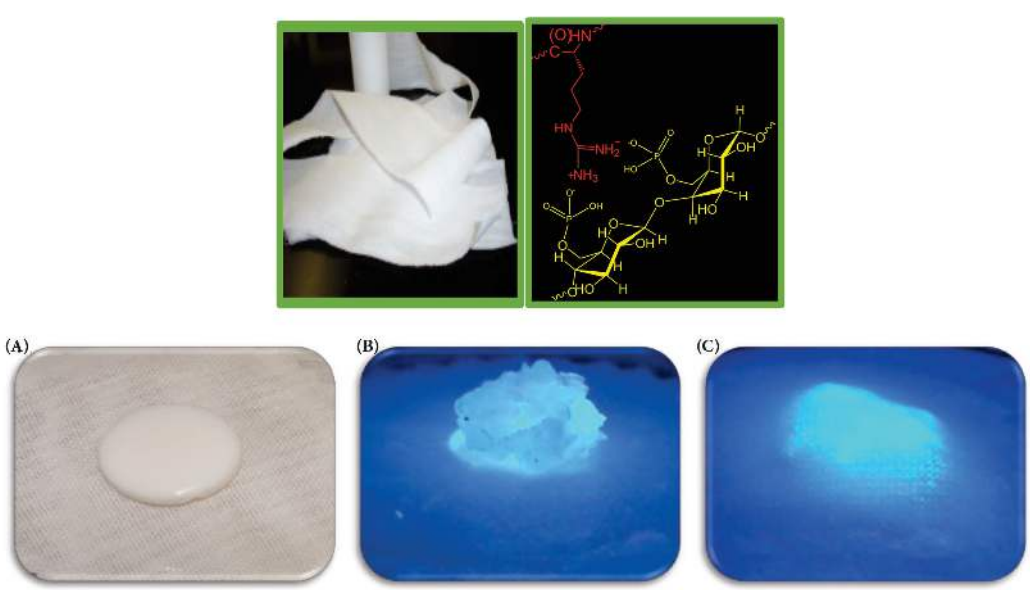

Fig. 4. Cotton-based protease modulating dressing. Structure of the ionic interaction between the phosphorylated cotton dressing and elastase (top right). A cotton-based aerogel (A), fluorescent signal upon detection of proteases (B), and sensor interface with a protease modulating dressing (C).

Medicare-reimbursable dressing for chronic wound treatment.[29] Subsequently, a variety of approaches to protease modulation have been proposed and commercial dressings developed for chronic wound treatment.[30]

Biosensors

The twenty-first century, as described by the National Science Foundation, is characterized by a New Biology that will provide us innovations in life sciences needed to meet challenges in food, climate, energy, and health. In addition, there will be increased interdisciplinary research between biology, chemistry, and engineering.[31] And, a recent assessment on PubMed reflects a significant growth in research on "intelligent textiles," with the goal to improve human health.[32]

The first reported "intelligent dressing" was based on the ability to sense and modulate the release of moisture from a wound bed.[33] Since then, advances in material properties, and most recently, in point of care diagnostics, holds the promise to revolutionize healthcare by assessing health status and disease onset using non-invasive methods. This is especially the case with sensors and imaging to promote wound healing, using biochemical and cellular markers. I took the approach of developing sensors that could be combined with protease modulating dressings to help guide treatment and dressing changes.[34] Protease biosensors incorporate two critical components: (1) a biomolecule (the protease substrate) and (2) a transducer surface (nanocellulose).[12] Conjugation of the substrate molecules with the transducer surface forms the apex of activation. Sensor activity is triggered by a biochemical event that gives rise to a detection signal. The interface of a biosensor with the protease modulating dressing described above is effective and sensitive in the detection of chronic wound proteases with both colorimetric and fluorescent approaches (Fig. 3). We have found that nanocellulose derived from cotton is effective in a variety of forms as a transducer surface for detection of clinically relevant levels of protease.[35]

As discussed in the next section, textiles incorporating pressure ulcer detection and sensor-based delivery devices are also being designed to combine prevention with treatment measuring the pressure and shear between a patient's body and the support surface. Pressure relief devices that ameliorate nodal stress at bony prominences is a growing area of prevention technology.[36]

Incontinence and Pressure Ulcer Prevention

The best cost-effective treatment for pressure ulcers is their prevention through optimal care. Patients are at high risk for pressure ulcer formation due to numerable intrinsic risk factors including mobility, age, nutrition, sensory perception, and disease. However, reduction of extrinsic risk factors related to the patient's support surfaces should coincide with decreased incidence of pressure ulcers. Risk factors fundamental to the interfacial forces include pressure, shear, and friction. These act on the bony prominence areas of the patient's body in contact with support surfaces.

Historically, cotton bed sheets and overlays have been less than ideal as an interface to prevent bedsores due to higher friction between the body and fabric. The uptake of increased moisture on the surface of the fabric increases the coefficient of friction with the patient's skin. However, the renewed application of greige cotton to bed sheets, incontinence pads/diapers, and prevention-based wound dressings is promising. This is based on recent findings demonstrating the ability of greige cotton nonwovens to mediate fluid transport, prevent rewet, and enhance strikethrough.[37]

Hydrophobic surfaces are associated with a reduced coefficient of friction.[38] Thus, the presence of fiber cuticle lipids at the skin-fabric interface contributes to lowering friction, Moreover, a roughness factor has been considered in our work with contact angle values for greige cotton nonwovens derived based on the work of Wenzel and Cassie-Baxter.[37] In addition, it is important to consider that the rapid removal of moisture from the skin-fabric interface, in conjunction with lubricant functionality, improves applications for pressure ulcer prevention.

We first identified that fiber surface polarity, moisture uptake, and swelling found in greige cotton nonwoven blends are similar to those found in incontinence topsheets (TS) and acquisition distribution layers (ADL) of commercial absorbent products. Considerations of material surface polarity are central to TS and ADL[39] The electrokinetic properties for TS and ADL are related to fluid transport of urine (strikethrough), transport within the layers of the absorbent product (fluid acquisition), and prevention of rewet. The mechanism is thought to be based on hydrophobic channels or interstitial spaces distributed randomly in the fabric and open to the absorbent cellulose.

Fabric Hand

Skin adopts a varied microclimate at the cutaneous-textile interface. Textiles and skin should ideally work in concert to act as a barrier to inflammation and infection and in concert with maintaining fluid balance, and thermoregulation, while providing comfort and healing. Nonwoven fabrics can be engineered to adapt to the cutaneous-textile microclimate and meet sensorial requirements. One of the goals of absorbent nonwoven product development is the improvement in fabric comfort while retaining functional performance. This includes improving methodologies for modeling friction, pressure, and shear at the skin-fabric interface with care sheets and incontinence pads.

Assessment of tactile comfort at the skin–fabric interface strives to improve the objective and subjective evaluations of fabric handle. The Leeds University Fabric Handle Evaluation System (LUFHES) mimics the multidimensional rubbing, squeezing, and stretching human interactions that plays a role in handle determination.[40] We have found that by using this approach in collaboration, there are identifiable indices of comfort conferred by greige cotton and synergistic with fluid management. For example, fabric formability (FMR) represents a fabric's ability to be conformed to a 3D shape; when combined with lower friction and increased smoothness, it is advantageous for bedsore prevention. The relative order of fabric formability observed was consistent with combining small amounts of polyester with greige cotton fibers (76%–90%).[41] This suggests that malleable hydrophobic materials, such as wax and polyester, may improve fabric formability. Enhanced formability occurs synergistically with optimal strikethrough, rewet, and fluid acquisition. The mechanics of fabric hand and fluid management function synergistically. This improves incontinence material leakage and promotes a more efficient retention of fluid in the absorbent.

Finally, enhanced softness of the greige cotton fabrics compared to polypropylene is due to the effect of hydration and swelling capacity. Notably as well, there is a significant change in the mechanical properties of microcrystalline cellulose when the moisture content exceeds 5%; ambient bound water molecules make cellulosic materials more easily deformable and imparts a soft hand.

Conclusion

It has been an exciting time to be involved in the application of wound healing science to dressing development. In this regard, I have summarized some of my involvement in research and development over the last quarter of a century. There are four areas where work on cotton textile fibers focuses for prevention and treatment of chronic, infected, and acute wounds: (1) improved trauma dressings that accelerate blood clotting, (2) chronic wound protease modulating dressings interfaced to point-of-care diagnostic (POC) sensors, (3) nonwoven greige cotton that generates hydrogen peroxide designed to stimulate cell proliferation, or antibacterial activity, in the wound bed, and (4) spunlace nonwovens with enhanced fabric hand designed to modulate polar surface properties at the skin-fabric interface for incontinence management and bedsore prevention. Based on these approaches, new product lines are being developed and promising fabric technologies that bridge bioactivity with sensor function are a topic of current research and development.

Disclaimer

Trade names are used solely to provide specific information. Mention of a trade name does not constitute a warranty or an endorsement of the product by US Department of Agriculture to the exclusion of other products not mentioned.

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