BY AMY PATUREL

Unraveling the Power of Silk

HEALERS HAVE TREATED THEIR PATIENTS WITH SILK THROUGHOUT HISTORY. NOW THEY'RE HARNESSING ITS STRENGTH, BIOCOMPATIBILITY, AND BIODEGRADABILITY IN INNOVATIVE NEW WAYS.

David Kaplan has been working with silk for decades, molding and shaping it into scaffolds, sponges, and films. His lab, the Kaplan Lab, is strewn with the substance, stacked with cases of silk cocoons and wads of silk from around the world, all awaiting their transformation into new forms.

Kaplan, a biomedical engineer at Tufts University, has studied silk since the 1990s, uncovering ways to build bodily tissues from its fibers. But centuries before Kaplan was born, healers turned to silk to solve medicine's most pressing problems.

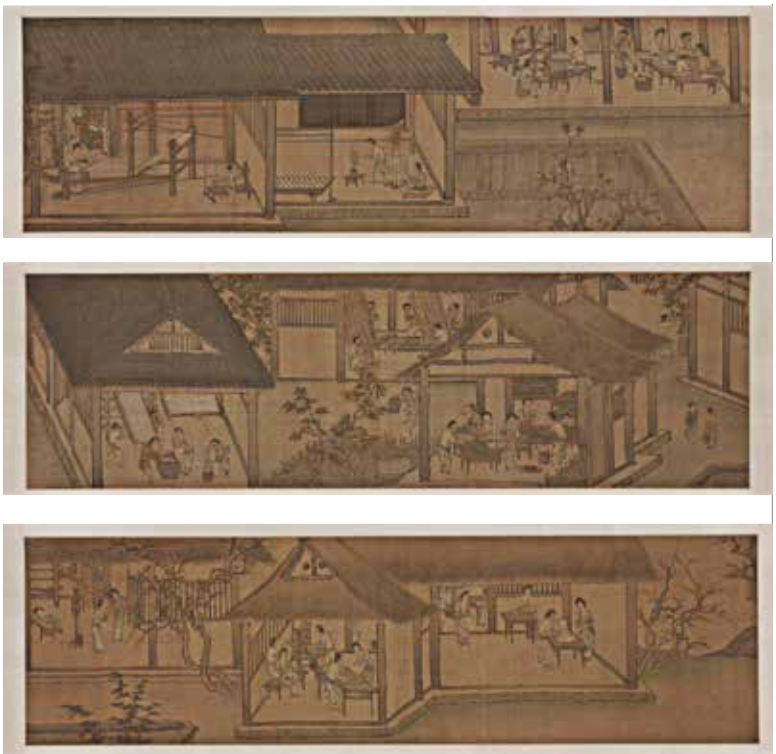
With strength that rivals steel and unique compatibility with the human body, silk is an ideal material for everything from wound closure to drug delivery. Today, scientists are still taking advantage of silk's abilities, positioning the ancient fiber to play a role in modern medicine as a multipurpose biomedical material.

SILK COCOONS **(above) become silk-based biomaterials at the Kaplan Lab. But David Kaplan (below) is only one of the latest in a long line of individuals who have used silk to help humans heal.**

THE STORY of silk begins in China, where it was supposedly woven into the fabric of society around 2700 B.C.E. According to ancient Chinese lore, the wife of the Yellow Emperor was sipping hot tea under a mulberry tree when the cocoon of a silkworm, the larva of a silk moth, fell into her cup. The hot liquid dissolved the cocoon's sticky coating, causing the cocoon to unravel into a strand of silk. Soon after, the woman began breeding silkworms and weaving their silk strands together, fashioning what were said to be the world's first silk fabrics.

Today, some scientists see a thread of truth in this legendary tale. Biologist Aarathi Prasad, author of *Silk: A World History*, says that, taken together, genetic traces and archaeological finds suggest that the domestication of silkworms likely began between 4,000 and 5,000 years ago, though artisans may have woven wild silk, sourced from wild silkworms, before then. In fact, in 2016, Chinese archaeologists announced that they'd found traces of silk in the soil beneath buried bodies in the tombs of Jiahu, in Central China, from around 8,500 years ago. Though the strands likely came from wild silkworms, they may have been woven into silk fabrics, as weaving tools were also found at the site.

CLOCKWISE FROM TOP LEFT: KUNGFU01/SHUTTERSTOCK; MYKOLA IVASHCHENKO/SHUTTERSTOCK; MATTHEW HEALY, TUFTS UNIVERSITY



THE TRADITION of sericulture, or silk cultivation, took shape in China, where silkworm cocoons were collected, soaked, and wound into threads for weaving.

MANY CREATURES make cocoons out of silk to protect themselves against predators and disease, including myriad moth and spider species from around the world. But silk has historically been sourced from the domesticated *Bombyx mori* silkworm, which was relatively easy to domesticate. "It's not that it was a better silk, but it was a more usable silk," Prasad says. While the fibers spun by spiders are stronger than those spun by silkworms, spiders tend to eat each other, posing a tremendous domestication barrier.

Centuries of selective breeding have created *B. mori* moths that are blind and bright white, so they can't see or blend in with their surroundings. Their wings are so stubby they can't fly. And the females are engorged with hundreds of eggs waiting to be fertilized. "They can't go very far," Prasad says, discussing the domestic silk moth's suitability as a source of silk. "They have to be fed by humans and bred by humans."

Silk has historically been sourced from the domesticated *Bombyx mori* silkworm.

Once laid, *B. mori* eggs hatch into teeny larvae that feed on huge amounts of mulberry leaves until they're so fat they can barely move. That's when the silkworms begin to spin cocoons to shield themselves from harm as they transform into moths.

To make silk, *B. mori* produce a composite strand of two proteins — fibroin and sericin. Fibroin serves as the silk's structural core, while sericin serves as the silk's sticky coating, causing the silk to adhere to itself and allowing the cocoon to stick together. While the proteins are stored as a liquid gel inside the silkworm's silk glands, it's the process of being stretched and spun through a nozzle near the worm's jaws that transform the proteins into a solid, structured fiber.

B. mori silkworms spin threads that are thinner and stronger than a strand of human hair, with a single cocoon containing as many as 5,000 feet of continuous, composite thread. Silk's remarkably repetitive molecular structure gives the material its tensile strength, while the molecules themselves grant its biocompatibility and biodegradability. In fact, by boiling the cocoons in an alkaline solution and removing the sticky sericin, sericulturists, or silk producers, untangle threads that are compatible with the body, and capable of breaking down slowly.

JUST AS SILK protects silkworms, it helps humans heal, and has done so for thousands of years. In ancient Greece and Rome, for instance, healers had already recognized a role for silk, both spider and silkworm, in covering and closing wounds. Not only did ancient Greeks and Romans bundle up bunches of spider silk to serve as bandages; they also used silkworm silk as a suture material, thanks to its strength and slow breakdown in the body.

COUNTERCLOCKWISE: ATTRIBUTED TO LIANG KAI. SERICULTURE (THE PROCESS OF MAKING SILK), EARLY 1200S. HANDSCROLL; INK AND COLOR ON SILK. THE CLEVELAND MUSEUM OF ART. JOHN L. SEVERANCE COLLECTION 1977.5; CRISTIAN ANDRES CASTRO/SHUTTERSTOCK; JOAQUIN CORBALAN P/SHUTTERSTOCK; HXDBZXY/SHUTTERSTOCK

GALEN **(top) treated injured gladiators in the 100s C.E., while Ambroise Paré treated injured soldiers in the 1500s. Both mended wounds with silk.**

Galen, in particular, used the material to stitch injured tendons in gladiators. "Let ligatures be of a material that does not rot easily," the Greek physician and philosopher wrote in his anthology of medical treatment, *De Methodo Medendi,* or "Method of Medicine," around 150 C.E. Centuries later, in the 1500s, the French surgeon Ambroise Paré used vascular ligatures made of silk to avoid cauterizing wounds with boiling oil. Even later, in the 1860s, the British surgeon Joseph Lister introduced the first sterile silk sutures, cleaned of contaminants using a solution of carbolic acid.

Silk's strength has made sterilized silk sutures popular in modern times, too. Known for their knot security and smooth passage through tissue, they're especially useful in ophthalmic, neurological, and cardiovascular procedures, where fine quality and precision are critical. Yet, sutures aren't the extent of silk's modern medical utility.

IN MUCH the same way that silk cocoons unravel, silk unravels, too, when rid of its sericin and transformed into an aqueous solution of pure fibroin fiber. Perfected by Kaplan in the 1990s, this process of reverse engineering, or "unspinning," silk unlocks its potential as a versatile building block, allowing the substance to be turned into gels, sponges, sheets, and inks — all sorts of things — all for the benefit of human health.

Molded into implants in Kaplan's lab, researchers reconstitute silk into structures that mimic the human body, supporting cell growth and tissue reformation. According to Kaplan, silk's compatibility with cells and customizable properties make it ideal for 3D scaffolds that help cells regenerate. Researchers can control the density, strength, and structure of the scaffolds by modifying the water content. "There's no limit to size and scale, and you can use almost any processing method — extrusion, 3D printing, casting, et cetera," Kaplan says.

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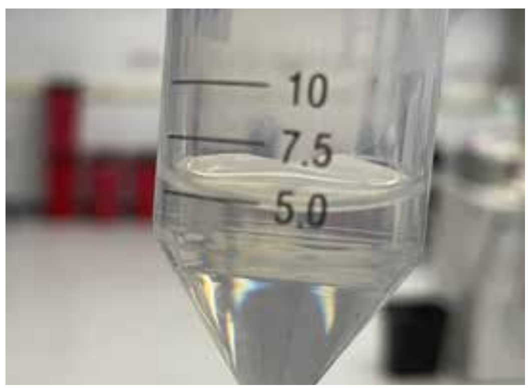
Once implanted, the silk stays the same size and shape until the body's tissues reform and replace it. "There's not a single part of the human body that hasn't been recreated in silk [from a] research perspective," says Chris Holland, a biomaterials scientist at the University of Sheffield, from "the covering of your eye through to your teeth, through to everything."

With the help of his colleague, Fiorenzo Omenetto, a fellow biomedical engineer at Tufts University and the director of the school's Silklab, Kaplan has even designed a silk scaffold for healing a human cornea. Thinner than a single, composite strand of *B. mori* silk, the transparent film gives corneal cells sufficient space to grow, while the tiny holes poked throughout the scaffold ensure that the growing cells get enough oxygen.

Other research from Kaplan turns to silk for bone and blood vessel repair, skin regeneration, and regrowth of cartilage, connective tissues, and ligaments. And similar treatments are already available to patients. SilkVoice, an injectable implant made from silk, augments damaged and deformed vocal cords, improving their production of sound. Tied to the Kaplan Lab, it was approved by the Food and Drug Administration in 2018.



SINCE ANCIENT times, healers have recognized silk's protective potential. Beyond bandages and sutures, silk was used in military uniforms, including the body armor of Mongol and Chinese soldiers in the Middle Ages, not only for its strength, but also for its ability to shield wounds, saving them

TOP TO BOTTOM: DEA / BIBLIOTECA AMBROSIANA/GETTY IMAGES; ZVONIMIR ATLETIC/SHUTTERSTOCK; DAVID KAPLAN

A SILK cell culture plate (top) and a thin sheet of silk foam show off fibroin's ability to take on complex shapes and structures. They are only two of the many forms that silk takes in David Kaplan's lab.

DAVID KAPLAN (2)

from further injury. If an arrow struck, the fabric would stick to the injury, protecting it, Prasad says, while also wrapping around the arrowhead, making it easier to remove.

In this way, silk serves its original purpose when transformed into a biomaterial, protecting the body without bothering the immune system. "Silk is pretty boring, and I mean that in a good way," Kaplan says. "That's what makes [it] so special." Once inside the body, the silk fibroin is inoffensive. There's no immune reaction to it, and it stays innocuous as it degrades. "It's the inherited chemistry and structure that is very quiet in the body," Kaplan adds.

Adding to silk's suitability as a biomedical material, scientists can also manipulate their silk solutions, modifying their shape and structure and adding substances to their mix to speed up or slow down silk's degradation. "We can control it," Kaplan says of the silk's breakdown, citing silk-based screws and plates that dissolve anywhere from a week to a year after implantation, depending on the amount of water or enzymes that scientists add into their silk-fibroin solutions. Some of these silk implants are even infused with antibiotics, allowing them to fend off infection as they degrade.

A natural preservative, silk even maintains the integrity of blood samples and vaccines for months at a time. Another offshoot of Kaplan's work is a sustained-release vaccination patch called MIMIX, which features silk-based microneedles. Molded from a vaccine-infused silk fibroin solution, the microneedles penetrate the skin and slowly dissolve, releasing the vaccine over a period of days to months, resulting in fewer side effects and enhanced immune response.

Silk's unique structure can help other drugs stay stable, too, adhering to drug molecules so they can't break down, protecting them from water and preventing their degradation until delivery.

WHEN KAPLAN became interested in the medical properties of silk, the research was relatively sparse, restricted to silk sutures. "There was almost no other research on [the] medical uses of silk, which was quite puzzling," he says.

Now there are thousands of studies on silk's medical potential, though they only scratch the surface of the material's modern promise. Even today, Kaplan is finding new uses for silk at the Kaplan Lab, testing the success of tiny silk particles as drug delivery systems and of transportable silk sprays as treatments for burns.

From ancient lands to modern operating rooms, silk's applications have changed over time, transforming alongside advances in medical technology. But the sources of silk, the silkworm cocoons and the silkworms themselves, have remained incredibly consistent — a result of many millennia of *B. mori* cultivation. "This is a tried and tested biomanufacturing system," Holland says, "optimized for 4,000 or 5,000 years through domestication."

Bridging the gap between ancient wisdom and modern science, *B. mori* silk is thus sewn into the tapestry of medical history. A blend of consistency, compatibility, and versatility, it reminds us that even the most modern solutions may be woven within the threads of the past. ◘

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