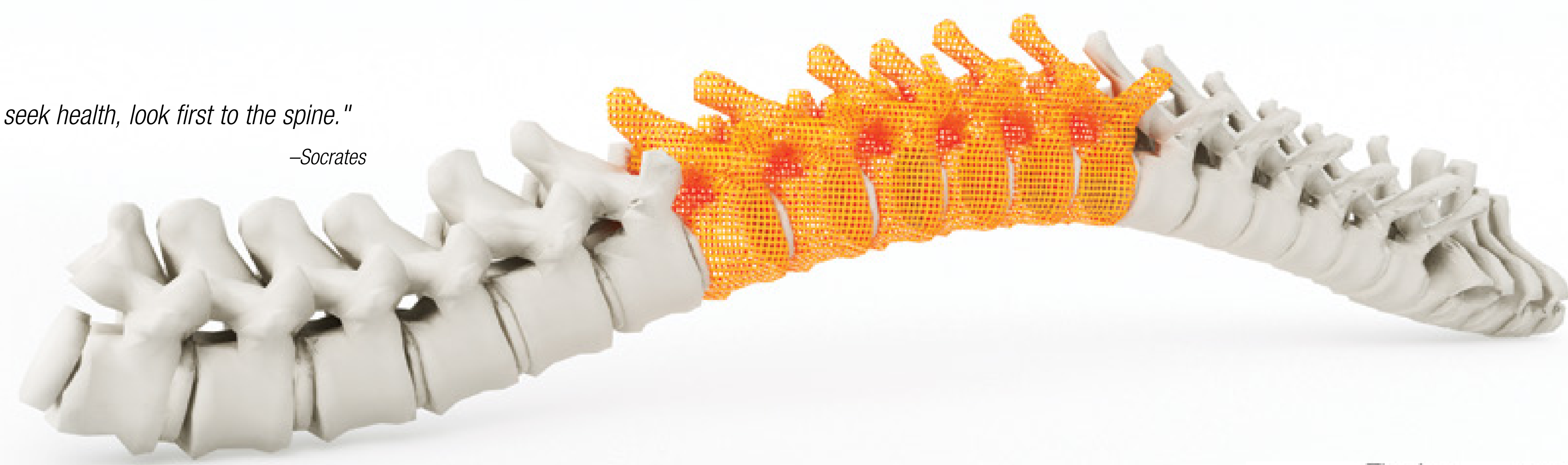


"If you would seek health, look first to the spine."

–Socrates

Silicon nitride—A ceramic surgical implant material

By Don Bray

Silicon nitride is used in many industries. For the healthcare industry, it is a relatively new adoption—but one with a lot of potential.

Little did materials scientist Ashok Khandkar and orthopedic surgeon Aaron Hoffman realize the impact that a ceramic material—silicon nitride—would have on the quality of life for many people with spine disease. Today, SINTX Technologies, the company they helped establish, is making silicon nitride spinal fusion implants and exploring many new applications for the material.

Background

Silicon nitride is an inorganic and nonmetallic material made of silicon and nitrogen, two elements that are essential in biologic systems. It is made by mixing highly refined raw powders that are formed into desired shapes. The final product is finished in furnaces under high pressure and heat. Dense silicon nitride is a very hard, abrasion- and corrosion-resistant solid. Unlike familiar ceramics such as porcelain or glass, silicon nitride has very high strength with the highest fracture resistance of any advanced ceramic.

Silicon nitride was first synthesized in 1857 and was commercialized in the 1950s. Later, research funded by the United States, European Union, and Japanese governments helped further development and reduced manufacturing costs. Because of its advantages, silicon nitride was soon adopted in many industries, particularly ones in which extreme conditions precluded the use of other metal, plastic, or composite materials.

Khandkar and Hoffman initially worked to develop a silicon nitride ball bearing for artificial hips. At the time, the news was filled with reports of some patients reacting to toxic metal wear particles due to higher wear rates of metal bearings in hips, thus leading to the search for new bearing materials. The company also submitted an FDA 510K approval for a product for spinal fusion based on animal data showing rapid healing of silicon nitride to bone.

The company received approval for the spinal fusion device and deferred a clinical trial of the hip bearing. Starting in 2015, the company invested heavily in the basic research and development related to silicon nitride and discovered additional properties, such as surface resistance to bacterial colonization. SINTX Technologies is now a materials technology company focused on developing new products based on its silicon nitride platform.

Advantages of silicon nitride

An ideal biomaterial

Existing biomaterials have limitations—metal implants fret and corrode, plastics oxidize, and allograft bone never fully heals. Toxic metal wear led to a recall of all-metal hip bearings, while fretting corrosion is a new concern in artificial hips. Metal allergies to total knee implants remain an unsolved clinical problem.

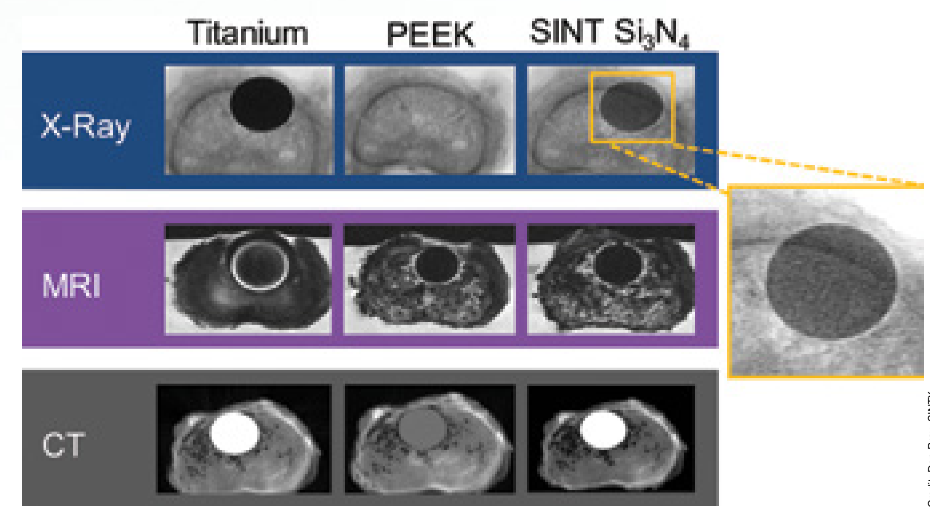


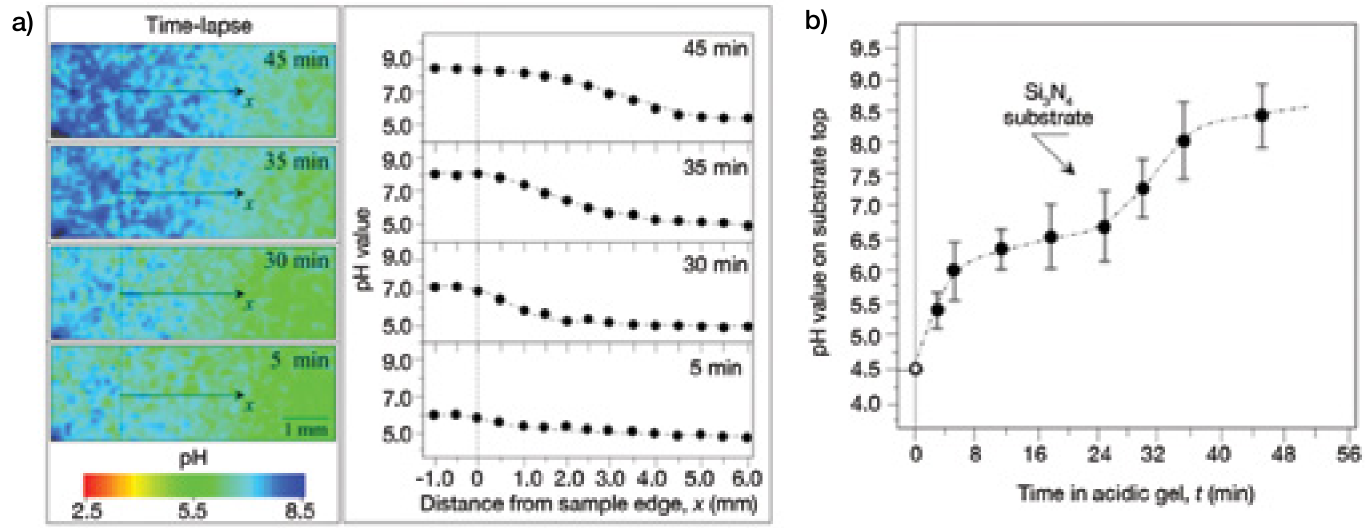
Figure 1. Comparison of implant visibility during medical imaging.

Silicon nitride has none of these concerns. Its wear rate is extremely low, and the wear particles are soluble and can be cleared from the body. Silicon nitride is chemically resistant, and it has a high dielectric constant, which confers resistance to fretting corrosion. Clinical data proves its efficacy—with more than 35,000 human spine implantations over 10 years and fewer than 30 FDA-reported adverse events, silicon nitride has an exceptional safety record.

In addition to spinal fusion implants, silicon nitride can be polished to a smooth and wear-resistant surface for hip and knee replacement bearings. Because of its inherent resistance to bacterial adhesion, silicon nitride is also suitable as a dental implant material, an application SINTX is actively pursuing.

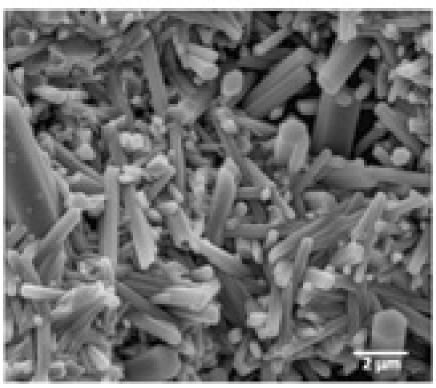
Favorable imaging

On X-ray images, plastic implants are invisible while metals obscure the visibility of bone. CT scans and MRI images are also distorted by metal implants. Here again, silicon nitride shows its advantages. Implants made of silicon nitride are visible on X-ray images without obscuring the underlying bone details (Figure 1). Also, silicon nitride implants allow for distortion- and artifact-free MRI and CT images, thus giving a clear assessment of the implant-



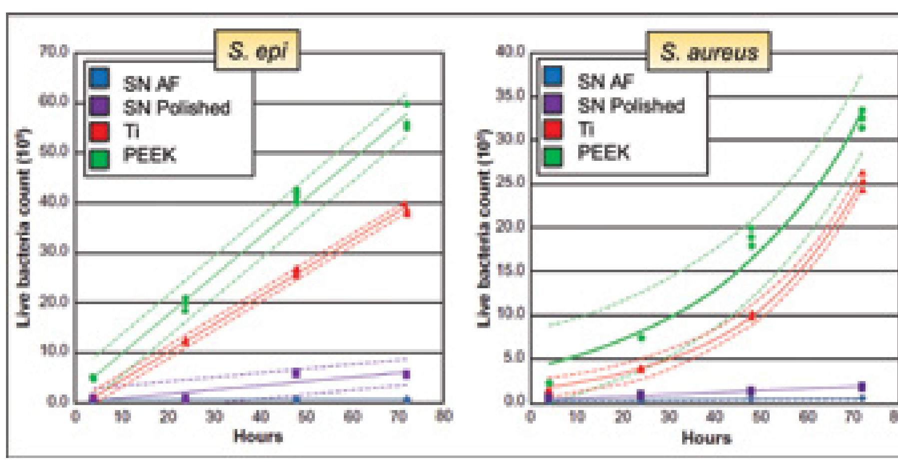
Credit: Don Bray, SINTX

Figure 2. a) Evolution of pH near a silicon nitride surface when placed in an acidic gel; b) average surface pH over time for same experiment.



Credit: Don Bray, SINTX

Figure 3. Surface microstructure of bioactive Si_3N_4.



Credit: Don Bray, SINTX

Figure 4. Counts of living bacteria (*y*-axis) versus incubation time (*x*-axis) for the bacteria *S. Epidermidis* and *S. Aureus*.

tissue interface and visualization of adjacent anatomy.

Versatile surface chemistry

Surface chemistry is a major factor in the success of any implantable device. Compared to the polymer polyetheretherketone (PEEK) or titanium, silicon nitride is hydrophilic, i.e., it attracts body fluids containing proteins and bone-forming cells that are critical to bone healing. Simple manufacturing variations, such as glazing or heating in a nitrogen or oxidizing atmosphere, can modify implant surface chemistry, which allows tailoring of implant chemistry to specific biomedical applications.

At the surface level, silicon nitride hydrolyzes, resulting in local, microscopic release of silicic acid and ammonia, according to the reaction shown below. Silicic acid enhances osteogenic processes near the material surface, and the ammonia creates an environment that discourages bacterial growth. This dual effect is highly desirable in any bone fusion implant.

$$Si_3N_4 + 12H_2O(l) = 3Si(OH)_4 + 4NH_3\,(aq)$$

Silicon nitride + Water = Silicic Acid + Ammonia

Figure 2a shows the evolution of pH near a silicon nitride surface when placed in an acidic gel. Dissolution of ammonia causes a local increase of near-surface pH over time. Figure 2b shows the average surface pH over time from the same experiment.

Silicon nitride's surface topography is equally supportive of bone healing. The surface of as-fired silicon nitride consists of anisotropic grains that are typically 1 µm up to 10 µm with individual features (e.g., asperities, sharp corners, points, pits, pockets, and grain intersections) that can range in size from less than 100 nm to 1 µm. While this structure is morphologically different from surface functionalized titanium, it has some common features (e.g., sharp corners, points, and pockets). Research shows that this type of surface microstructure is important in resisting bacterial attachment while concurrently promoting mammalian cell adhesion and proliferation (Figure 3).

Antibacterial properties

Bacterial infection of any biomaterial implant is a serious clinical problem. Silicon nitride offers a potential easy solution—it is inherently resistant to bacterial colonization and biofilm formation. In addition, a recent study showed a

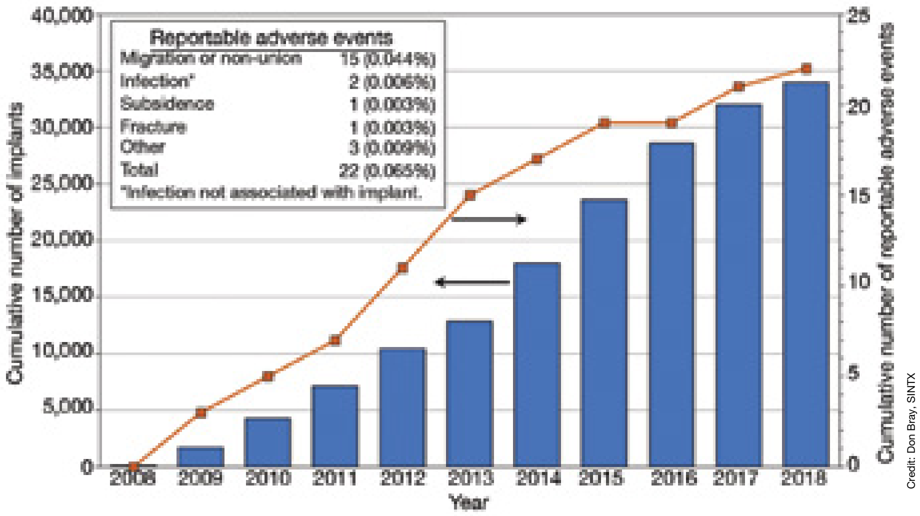


Figure 5. Silicon nitride in spinal applications: +33,000 implants in nine years.

direct bactericidal effect against an oral pathogen, *P. Gingivalis*. This property is probably multifactorial, reflecting the combined effects of surface chemistry, pH, texture, and charge. The ability to vary these surface properties for specific implants is an advantage of the material. In several studies, silicon nitride demonstrates significantly lower bacterial biofilm formation compared to polymers or metals. Independent studies performed outside SINTX corroborated these findings.

The graphs in Figure 4 are representative of in vitro tests done with several bacterial species. For simplicity, the graphs show results with *S. Epidermidis* and *S. Aureus*. Both common nosocomial pathogens are common causes of implant-associated infection. The graphs show counts of living bacteria (*y*-axis) versus incubation time (*x*-axis). In all cases, two forms of silicon nitride (as fired and polished) showed lower bacterial counts than either polymer or metal.

Promote bone growth

Silicon nitride stimulates osteoblasts (bone-forming cells) to form bone while suppressing osteoclasts (bone resorbing cells). A manufacturing change called "nitrogen-annealing" results in a near-200% increase in bone formation by cells exposed to silicon nitride. This finding has excellent implications for accelerating bone healing, bone fusion, and implant integration into the skeleton. Other data shows living cells adhere preferentially to silicon nitride over polymer or metal surfaces.

Cell adhesion promotes tissue development and enhances the bioactivity of materials. Cell adhesion to silicon nitride is a function of pH, chemical, and ionic changes at the material's surface. The surface chemistry and nanostructure topography of silicon nitride provide an optimal environment for the stimulation of bone growth. Silicon nitride implants demonstrate greater new bone formation at 3, 7, 14, and 90 days compared to polymer or metal implants. The amount of regenerated bone associated with silicon nitride implants is 2–3 times greater than polymer or metal implants three months after surgery.

Clinical studies

The first use of silicon nitride in spinal fusion was in a small Australian clinical trial in the mid-1980s. The implants used were anterior lumbar interbody fusion (ALIF) devices fashioned from a reaction-bonded silicon nitride. A 31-year follow-up of seven surviving patients was recently published, showing sustained implant stability, no subsidence, no migration, and excellent bone integration, even three decades after implantation. This study is the longest reported clinical history for a synthetic biomaterial used in spine. Cumulative silicon nitride implantations through 2018 total about 35,000. Of these, fewer than 30 FDA-reportable adverse events manifested, with no implant-related infections relative to an industry standard of 3–10% (Figure 5).

Future

With an expanding, ageing, and more active population, biomaterial innovations will lead to improved biomedical implant safety, higher-performance, and lifetime durability. Already well-proven in diverse industrial applications and currently used as intervertebral spinal fusion cages, silicon nitride has the foundational evidence to be applied likewise across a range of biomedical applications.

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