Scientific and experimental research is necessary to investigate for possible side effects due to an increased number of implanted bioprostheses. Would the diseased aortic valve remnant after transcatheter aortic valve replacement be an additional degenerative threat to the bioprosthesis containing alpha-gal compared with a procedure including complete excision and revision of the inflammatory aortic valve? The association of alpha-gal immunoreactivity with xenograft calcification remains enigmatic, since the grafts are usually imbedded in glutaraldehyde. On the other hand, homografts without alpha-gal antigens also degrade. Although decellularization intends to eliminate alpha-gal antigens, a process including glutaraldehyde fixation may trigger the onset of tissue degeneration as well.⁶

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Commentary: Alpha-gal syndrome and cardiac implant durability

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Recent studies have increased our understanding of the downstream effects of an underappreciated food allergy known as alpha-gal syndrome (AGS). This delayed hypersensitivity, first described by Platts-Mills in 2007 as a red meat allergy, is manifested by chronic vague gastroenteritis, malaise, and even anaphylaxis when IgE-sensitized patients are exposed to the alpha-gal antigen.^{1,2} Alpha-gal is a cell membrane carbohydrate ubiquitously expressed in all mammals except humans and primates, making it the most common cause of food allergy in endemic regions, such as the southeastern United States.³ In this issue of the *Journal*,

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CENTRAL MESSAGE

A new study demonstrates immunoreactivity to animal-derived implants in patients with a common food allergy. Less immunogenic materials may extend implant longevity.

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Kuravi and colleagues⁴ demonstrate that serum from patients with AGS has high immunoreactivity against commercially available animal-derived products, including commonly used cardiac implants, such as decellularized bovine pericardium, porcine bioprosthetic valves, and bovine pericardial valves in vitro. They hypothesize that this immune reaction may lead to chronic inflammation that negatively impacts the durability of implants that carry the alpha-gal antigen. If this is so, then development of implants that specifically lack the antigen may improve longevity in vivo.

In the last decade, there has been a growing trend toward increased utilization of bioprostheses for valve replacement (both transcatheter and surgical) rather than mechanical valves. Despite rigorous decellularization methods, alpha-gal remains present in these materials.^{5,6} Kuravi and colleagues propose that the subclinical inflammatory state caused by permanent alpha-gal exposure in a sensitized individual may be responsible for some instances of early valve failure. Although plausible, this hypothesis takes a big leap from the in vitro analyses of immunoreactivity performed in this study. Follow-up studies are needed to evaluate the biological effects of this phenomenon in vivo.

The authors are careful to point out that although some published case reports have implicated AGS as a cause of premature valve degeneration, no large-scale observational data are available at present.^{7,8} Comparison of valve longevity in cohorts with and without IgE reactivity to alpha-gal will be of particular interest. If a causal relationship can be defined, this may herald the beginning of a new era of surgery in which products containing alpha-gal are phased out and future implanted products must adhere to strict immunologic guidelines.

Consequently, it may become critical to develop less immunogenic products for sensitized patients. The sponsoring company for the study of Kuravi and colleagues, Revivicor (Blacksburg, Va), has genetically engineered an alpha-gal knockout pig and has received Food and Drug Administration approval for the use of this model to develop human therapeutics.⁹ Kuravi and colleagues

demonstrate that cardiac tissue from the knockout pigs lack antigenicity when exposed to serum from AGS patients. Therefore, the introduction of less immunogenic alpha-gal-negative implant material is a breakthrough that will be followed with much interest by cardiac surgeons and their patients.

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