Breast Implant Fears Put Focus on Biomaterials

Researchers are pushing a $250-million-a-year initiative to develop materials for long-term residence in the human body

THE RECENT NEWS THAT THE POLYURETHANE coating on some breast implants may break down in the body, perhaps augmenting cancer risks along with bustlines, caught tens of thousands of women and their physicians completely by surprise. But it was not particularly shocking to a number of materials scientists familiar with the foam-covered silicone sacs. Indeed, according to several clinicians and biomaterials researchers, the instability of polyurethane foam in the body was entirely predictable, and the production of carcinogenic byproducts from the breakdown of the material has been documented in the scientific literature for a year and a half (see box).

Moreover, to anybody who has followed the tortured history of attempts to craft materials for long-term residence in the human body, there's another reason why the breast implant controversy is unsurprising: Virtually every so-called biocompatible compound ever developed has proven more troublesome than anticipated when placed in the hostile environment of the body. Indeed, many scientists argue that whatever the outcome of the current (if inadvertent) clinical trial of breast implants, the episode highlights the lack of a national research focus on biocompatible materials at a time when this specialty science is growing in medical and economic importance. Clinical specialists in such diverse areas as cardiovascular surgery, dentistry, and ophthalmology are demanding biocompatible materials for use in bypass grafts, heart valves, drug delivery matrices, extracorporeal filters, joint replacements, tooth substitutes, and artificial ocular lenses.

The need for truly biocompatible materials is considered so pressing that the White House is currently mulling over a proposal for a $250-million-a-year biomaterials program as part of a broad materials research initiative being readied for inclusion in the Administration's 1993 federal budget request (*Science*, 5 April, p. 19). Backers of the proposal argue that such an effort is needed because biomaterials research has traditionally fallen through a crack between the physical and biological disciplines.

"We need to understand a lot more about what the body wants," says Edward Mueller, deputy director of the Food and Drug Administration's Division of Mechanics and Materials Science. "Until now, we've taken materials developed for other purposes, like aerospace alloys, popular for their corrosion resistance and their strength. But if we were designing materials specifically for the body, they'd probably be different." The polyurethane foam used in the breast implants, for example, was designed mostly for use in furniture, bedding, and carpet underlays, not for any long-term role in the body.

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"Biomaterials science is a fledgling, embryonic, interdisciplinary brat," agrees Sumner A. Barenberg, vice president and chief technology officer of the Packaging Corporation of America, who has worked with Mueller to craft the biomaterials research proposal. "Nobody has ever had the long-term funding to take a systematic approach to biomaterials development. The net result has been disjointed research, even though intelligent design of biomaterials could save lots of money in health care costs." To buttress his point, Barenberg cites calculations done this year at Baxter Health Care in Deerfield, Illinois, indicating that development of an implantable artificial pancreas could cut $2 billion to $4 billion from the current annual $20 billion cost of diabetes in this country.

The proposed initiative would cost $2.5 billion over 10 years, half of which would go to selected regional centers and half to various principal investigators, universities, research institutes, and companies. The program would stress rapid commercialization of new discoveries, with hopes that within 10 years 80% of ongoing research would be funded by royalties and licensing fees.

Perhaps most important, Mueller says, the program would encourage and incorporate new thinking about the ideal nature of biomaterials. "Years ago, so-called biocompatible materials were thought to be inert," he explains. "Now we believe that nothing is really inert." Today, he contends, it's time for biomaterials scientists to accept—and even exploit—this biological reality.

Medical history is certainly littered with failed attempts to design implants immune to biological degradation. Robert Baier, a materials scientist at the State University of New York at Buffalo, points out that the nation's single largest effort to develop biocompatible materials—the National Heart, Lung, and Blood Institute's program to develop an artificial heart and artificial replacement parts for living hearts—has seen many promising materials fall by the wayside. For example, a special hydrophilic plastic, or hydrogel, developed as a lining for the artificial heart proved sufficiently flexible and gas permeable for the job but eroded too quickly. (On the bright side, a close relative of this material found eventual application in soft contact lenses.)

Then there was the promising Dacron-covered heart valve, Baier recalls. The valve was implanted in thousands of patients, sometimes in mitral and sometimes in aortic positions. But in the aortic position, Baier says, "the valve door was slamming against the cloth, and Dacron fragments were going into the blood," causing problems.

Elsewhere in the body, attempts in years past to use certain "inert" metals such as nickel-steel alloys in joint replacements caused such high levels of toxicity that these metals are today used as positive controls against which the toxicity of other metals can be compared. And the first total hip replacement, which used a Teflon coating to reduce friction, proved similarly inappropriate for the task at hand. Tiny particles of the nonstick coating abraded, causing violent, local inflammatory reactions. Today's joints use polyethylene plastics, which are relatively trouble-free but still last only about 15 to 20 years, requiring eventual replacement in younger patients.

The reactive history of such a wide range of implants suggests that researchers would be better off using materials specifically designed to interact with the body in predictable ways, Mueller says. "The body constantly rebuilds and remodels," he says. "Implants can't do this, but ideally we'd like to have 'self-healing' materials—synthetic scaffolds that allow the body to provide some

Implants: How Big a Risk?

According to several biomaterials researchers, the polyurethane coating on some types of breast implants provides a clear-cut case of a material unsuited to the rigors of long-term residence in the human body. Recent evidence that the coating can break down, possibly releasing small amounts of a carcinogen, has physicians scrambling to determine the level of risks associated with the implants. Preliminary assessments by the Food and Drug Administration (FDA) suggest that the risk is small, but the episode seems to provide a classic example of biomaterial ambition gone awry.

The earliest versions of the coated implants were introduced in the late 1960s—nearly a decade before Congress gave the FDA authority to regulate medical devices—in an attempt to circumvent a common problem with uncoated models: The development around the implant of a uniform layer of scar tissue, which can harden and contract, causing pain and disfigurement. The felt-like coating of polyurethane fibers was designed to "confuse" scar-forming cells, sending the body's defensive regiments into disarray and so preventing any organized contraction of tissue.

The tactic seems to work, at least for a few years. But the foam itself appears to be highly vulnerable to attack within the breast. "It's basic, introductory chemistry," says Nir Kossovsky, an assistant professor of pathology and laboratory medicine at UCLA School of Medicine, who for 14 years has studied the interactions between body tissues and implants. Kossovsky notes that the kind of polyurethane foam coating the implants consists of isocyanate monomers strung into long chains with ester linkages—a chemical bond he calls "renowned" for its susceptibility to hydrolytic cleavage. "The body is extremely capable of hydrolyzing things, and many degradation enzymes are designed specifically to break ester linkages," Kossovsky says. "If you were picking a material to put in the body and you wanted it to break down, you could hardly come up with a better candidate."

Though Kossovsky and others believe the behavior of polyurethane in the body should have been predicted long ago, it was only recently that the material's behavior aroused widespread concern. The reason: In vitro studies have shown that one of the hydrolytic breakdown products of polyurethane foam is 2-toluene diamine (TDA), an amino-substituted version of the polyester monomer and a known carcinogen in animals. The first evidence of this came from research by Christopher Batich and others at the University of Florida in Gainesville, which was published in the *Journal of Biomedical Materials Research* in December 1989.

These reaction products have now been assayed directly in a few women who have the implants. Toxicologists Siu C. Chan and Claire Y. Gradeen and pathologist Dale Birdsell of the Foothills General Hospital in Calgary report in the 20 May issue of *Clinical Chemistry* that they detected about 0.5 nanograms of TDA per milliliter of urine and about 10,000 times that concentration, or about 6 micrograms per gram, in a breast tissue specimen from a patient undergoing surgical replacement of a polyurethane-coated implant. And T. Roderick Hester, a professor of plastic and reconstructive surgery at Emory University School of Medicine, reported at the annual meeting of the American Society for Aesthetic Plastic Surgery in New York City last month that he had found TDA in the urine of four women with the implants. TDA was detected at levels up to 35 nanograms per milliliter in urine during the first few days after implantation, he said, but it dropped to undetectable levels in all women within a month.

Such tests were prompted in part by a review of the safety of breast implants ordered by the FDA in 1988, at which time the agency gave manufacturers 30 months to prove their products are safe. The manufacturers themselves say that in vitro and in vivo data they are now submitting to FDA indicate the implants are safe, with TDA concentrations too low to carry any risk.

As *Science* went to press, the FDA had not released results of its own risk assessment of the implants. Agency investigators reportedly hold widely divergent views on the matter, with some predicting the implants confer a one in 50 chance of getting cancer. But in a letter circulated on 29 April, the deputy director of the FDA's Center for Devices and Radiological Health, Elizabeth D. Jacobson, stated that preliminary analysis of the agency's data suggests an added risk of less than one in a million—a risk she calls "too small to warrant alarm on the part of patients, and certainly too small to justify surgically removing the implants." ■ **R.W.**

living material." One such material, an implantable ligament, recently underwent testing in humans. It consisted of a carbon-fiber scaffolding covered with polylactic acid. Once it was inside the body, tissue enzymes gradually broke down the polylactic acid coating, allowing cells to migrate into the gaps, forming a "bio-synthetic" composite. Although the carbon fiber ultimately proved too weak to serve as a ligament, researchers are now taking similar approaches with stronger materials.

John Watson, chief of the heart institute's Devices and Technology Branch, which has overseen the artificial heart program, adds that new research must address a growing realization that materials compatible in one part of the body can prove troublesome in another, necessitating a careful customization of a material to its intended function. The most apparent and troublesome example of site-specificity, he says, is that even materials that appear relatively compatible in, say, breast tissue or bony environments sometimes prove thrombogenic, or clot-forming, if they come in contact with blood, precluding their use in the vascular system. Others note that metals that are reasonably useful and compatible as structural supports in some parts of the body often fail when applied as neural prostheses, which must retain appropriate and specific electrical properties for long periods within the body. "Ideally we'd like to fabricate materials for the specific anatomical and physiological conditions they will have to operate in," Watson concludes.

Developing such materials will not prove easy, says J. Paul Santerre, a biomaterials researcher at the University of Ottawa Heart Institute in Canada. Very little is known about the enzymatic pathways biomaterials are subjected to in the body, or about the role of phagocytes and other cells in the biodegradation and excretion of implanted materials. Santerre and his colleagues are developing in vitro culture systems and radiolabeled polymers that allow them to trace the fate of digested materials under physiological conditions. But he says scientists have a long way to go before they'll be able to predict accurately the biochemical denouement of implanted materials in various parts of the body. "There's been such a demand for biocompatible devices that manufacturers have gone in for short-term applications," Santerre says. "A lot of companies that think they've solved these problems are rushing to market, and we'll just have to wait and see whether they've really solved them or not." ■ **RICK WEISS**

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