SPECIAL ARTICLE

SHATTUCK LECTURE — EVALUATING THE HEALTH RISKS OF BREAST IMPLANTS: THE INTERPLAY OF MEDICAL SCIENCE, THE LAW, AND PUBLIC OPINION

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THIS is the story of the controversy over the safety of silicone-gel–filled breast implants — a controversy that has raged in this country for nearly a decade and is still not resolved. It is a story fascinating in itself, but one particularly worth telling here because of the insights it affords into how contemporary American society deals with the problems of evaluating health risks. The breast-implant story illustrates better than almost any other event in recent times how litigation, fear, bias, and greed can interfere with scientific efforts to answer an important public health question. Perhaps most troubling of all, it clearly shows that in deciding about health risks, our courts and a substantial segment of the American public seem comfortable with methods that can only be described as antiscientific and irrational. Yet, like it or not, science and the rules of evidence and reason are the only reliable tools we have to investigate risks to human health. If we want to develop effective public policies to deal with health risks, we dare not abandon science.

Americans want very much to know about hazards to their health from the things they do or are exposed to in their everyday lives. Theoretically, it should be fairly straightforward to deal with their concerns. All we need are scientific studies to determine whether a possible exposure is risky and what the likely risk is. (Then we can make explicit decisions about whether the benefits are worth the risks.) In practice, however, assessment of risks is not so simple. Direct experimentation in the laboratory or in randomized, controlled trials is often impossible or unethical. Instead we need to rely on observational epidemiologic studies to gain information about risk factors. These studies are difficult to mount and fraught with pitfalls in design and interpretation. Confounding variables are almost always present, but not always adequately accounted for or even appreciated. The *Journal* reviews many observational epidemiologic studies dealing with health risks. A professional staff of 17, with the help of a great many expert peer reviewers, attempts to evaluate the validity of such studies, but still uncertainties remain. Some of the uncertainty reflects the limitations of the methods, but it is in the nature of medical research in general to be full of uncertainties and to advance in tentative, incremental steps. However, advance it does, on the basis of the gradual accumulation of evidence. Unless there are impediments, knowledge so gained is transmitted to doctors in medical journals and to the public by the media, and is ultimately translated into better public safety and health care.

But medical research does not occur in a vacuum. It occurs in a complex social context that greatly influences how it is understood. Particularly in the case of the risks of everyday life, the impediments to the orderly scientific process described above are formidable. The public is not accustomed to thinking in terms of uncertainties and probabilities. To many people, a health risk is an all-or-nothing matter. They expect certainties, and to them scientific studies carry the weight of revelations. (These people are greatly frustrated by news of conflicting research results.) Many people also believe they should be able to avoid risks altogether, even though that is impossible. Given these expectations, the tentativeness that marks most medical research is difficult to convey. In addition, the widespread and growing cynicism about government and business leads people to assume the worst; they are only too ready to believe that they are knowingly subjected to health risks, which, they may believe, were deliberately minimized or covered up. There is also cynicism about scientists and the scientific method itself. There can be little doubt that we are now experiencing a groundswell of antiscience feeling, which leads many people to discount scientific evidence, often in favor of anecdotes, irrational theories, or "other ways of knowing." When mass lawsuits are involved, the impediments to public acceptance of the scientific process become virtually insurmountable. Courts may find health hazards even when there is no good evidence. The public's alarm then takes on a life of its own, driven often by the huge amounts of money at stake in product-liability suits. Thus, the path from medical evidence to public action is by no means direct or smooth. The breast-implant controversy well illustrates these impediments to public understanding of health risks. Because the implications are so important, it is worth telling the story in some detail.

THE BREAST-IMPLANT STORY

Although breast implants first came on the market in the early 1960s, it was not until 1976 that they came under the purview of the Food and Drug Administration (FDA).[1,2] That year the Medical Device Amendment to the Food, Drug, and Cosmetic Act extended the FDA's authority to cover devices, as well as food, drugs, and cosmetics. Under this amendment, manufacturers of new devices could, at the discretion of the FDA, be required to submit an application for premarketing approval. Applications were to include data on safety and

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effectiveness from animal and human studies. Until FDA approval was obtained, new devices that required premarketing approval could not be sold. Since breast implants were already on the market, they were "grandfathered," at least for the time being. Given their long track record, they were presumed reasonably safe, although there was no evidence on this point. In 1988, however, the FDA announced that breast-implant manufacturers would have to submit evidence of safety.[1] In accordance with law, they were given at least 30 months to produce their data.

There were several important developments during the 1980s that changed the FDA's relaxed attitude toward breast implants. First, a number of anecdotes began appearing in the medical literature linking breast augmentation with systemic disease — most often connective-tissue disease.[3-5] The anecdotes originated in postwar Japan, and concerned not silicone breast implants, but rather direct injections of liquid paraffin or silicone into the breasts of Japanese prostitutes trying to satisfy the American taste for large breasts. But in 1982, there appeared a report from Australia of connective-tissue disease in three women who had silicone-gel–filled implants.[6] The same year, in San Francisco, the first multimillion-dollar lawsuit alleging that silicone implants caused systemic disease was filed.[7] These events set off a steady drumbeat of concern. Anecdotes in the medical literature multiplied,[8] and there were several more multimillion-dollar verdicts in the courts.[9]

Perhaps the most important event to bring the growing unease about breast implants to the attention of the public was TV reporter Connie Chung's sensational treatment of the matter in 1990.[10] On her CBS television show, *Face to Face with Connie Chung,* she interviewed women who claimed to have autoimmune disease caused by their breast implants, and she conveyed the clear message that implants were dangerous devices foisted on unsuspecting women. Without questioning the presumed link between the implants and the illness, Chung implicitly blamed the FDA for permitting hazardous devices to be sold. At about the same time, the late congressman Ted Weiss (D-N.Y.) held public hearings,[11] also marked by tacit acceptance of the view that breast implants were risky. In the meantime, consumer and advocacy groups were actively involved in spreading the alarm. Ralph Nader's organization, Public Citizen, through its Health Research Group, headed by Dr. Sidney Wolfe, helped to publicize the issue and press the case in the courts.[9]

In late 1991 and early 1992, all the activity came to a head. First, FDA Commissioner David Kessler notified the manufacturers that they had 90 days to produce evidence of the implants' safety.[1] When the evidence proved inadequate, an FDA advisory panel was convened to advise the FDA on what action to take. At about the same time, a jury in San Francisco awarded $7.34 million, the largest amount to date, to a woman who claimed that her breast implants, manufactured by Dow Corning, had caused her to have mixed connective-tissue disease.[12] That trial was marked by allusions to Dow Corning documents that were purported to show that the company was aware of the dangers of breast implants and suppressed the evidence. Kessler reviewed the documents (which were later released to the public) and called for a moratorium on the sale of silicone-gel–filled breast implants.[13]

On April 16, 1992, after impassioned public hearings before the advisory panel and in accord with the panel's recommendation, Kessler banned the implants altogether, except for use in clinical trials of breast reconstruction after cancer surgery.[14] (Saline-filled implants were permitted to remain on the market for the time being, while their manufacturers gathered data on safety.) The ban, Kessler was careful to point out, was not because implants had been found dangerous, but because they had not been proved safe. As he explained, it is the responsibility of manufacturers to show medical devices are safe, not the FDA's responsibility to show they are not. The breast-implant manufacturers had simply not fulfilled their obligation to produce evidence of safety.

Immediate Consequences of the FDA Ban

The fallout from the ban was swift and unsettling. Although Kessler tried to reassure the million or so women who already had implants that there was no evidence of danger, the reassurances fell on deaf ears. It did not seem logical that the FDA would take so drastic an action unless there was a substantial risk. Many women with implants returned to their plastic surgeons to have the implants removed. And the trickle of lawsuits became a flood. Dow Corning, the major manufacturer of breast implants, claimed to be the target of 20,000 lawsuits filed in the first two years after the ban.[15] Most of the cases were settled out of court, but a few large jury verdicts raised the stakes higher. The largest was a $25 million verdict awarded to a Houston woman who claimed that the silicone from a ruptured implant had caused a variety of nonspecific illnesses, such as recurrent respiratory and bladder infections.[16] Bristol-Myers Squibb, the defendant in the case, suggested that her symptoms might be caused by her cigarette habit instead of the breast implants, but the jury decided otherwise.

Still, as Kessler pointed out,[14] there was no good scientific evidence for or against a link between breast implants and systemic disease of any kind. What we saw in the courtroom and in much of the media, at least at the time of the ban, were judgments based on anecdote and speculation. In the wake of the ban and the attendant publicity, large numbers of women with breast implants came forward complaining of a variety of illnesses. A small group of doctors and scientists were quick to concoct theories explaining how breast implants affected the immune system, without any evidence that they do. Some of the theories were ingenious, some were fanciful, but none were proved. Nevertheless, plaintiffs' attorneys made good use of the theoreticians as expert witnesses in court. Finally, in 1994, the breast-implant manufacturers, desperate to limit their losses,

agreed to the largest class-action settlement in history.[17,18] According to its terms,[19] $4.25 billion would be set aside for all women with breast implants. One billion dollars was earmarked for the lawyers, $1.2 billion for women claiming current implant-related illness, and the rest for apparently healthy women with implants who became ill over the next thirty years. Although those claiming current illness were required to submit medical records and possibly a doctor's diagnosis, there would be no further effort to verify the illness, much less that it had been caused by implants. Plaintiffs' attorneys sometimes referred clients to clinicians whose practice consisted largely of such patients and whose fees were paid by the attorneys. Perhaps not surprisingly, given the broadness of the terms, nearly half of all women with breast implants registered for the settlement, and half of those claimed to be currently suffering from implant-related illnesses.[20] With so many women registered, not even $4.25 billion could cover all the claims at the promised rate. Dow Corning filed for bankruptcy protection,[21] and the settlement collapsed a year after it was crafted.[22] The remaining three large manufacturers — Baxter, Bristol-Myers Squibb, and 3M — agreed to another settlement with slightly more stringent terms.[23] Whether this new agreement will hold together remains to be seen.

The Scientific Evidence

After the ban, under Kessler's prodding, the breast-implant manufacturers began to do what they should have done years earlier: they began to fund serious studies of the safety of breast implants. Since about 1 percent of American women have breast implants and about 1 percent have connective-tissue diseases, we could expect that by coincidence alone 10,000 would have both (assuming roughly 100 million adult women in the United States). The only way to show a link between implants and connective-tissue disease, then, would be to show a higher prevalence of the disease among women with implants. Doing so required observational epidemiologic studies. The first such study was a retrospective cohort study from the Mayo Clinic, published in the *Journal* in June 1994[24] — two years after the FDA ban and two months after the original global settlement was announced. It found no association between breast implants and 12 connective-tissue diseases and a variety of signs and symptoms of such diseases. The relative risk of any connective-tissue disease in women with implants, as compared with age-matched controls without implants, was 1.06. Because of the small size of the study, however, the 95 percent confidence interval was fairly wide, 0.34 to 2.97. Assuming no bias in study design, this interval is 95 percent likely to contain the true relative risk. Thus, although the best estimate is 1.06, there is nearly a 5 percent chance that the relative risk is increased or decreased by a factor of three or more.

Since the publication of the Mayo Clinic study, several other epidemiologic studies have also failed to find a connection between breast implants and connective-tissue diseases or related signs and symptoms. The largest of these was the Nurses' Health Study, also a retrospective cohort study, which was published in the *Journal* in June 1995.[25] The relative risk of documented connective-tissue disease was 0.6 (95 percent confidence interval, 0.2 to 2.0). Among those self-reporting connective-tissue disease, the relative risk of having any of 41 documented signs, symptoms, or laboratory features of connective-tissue disease was 0.7 (95 percent confidence interval, 0.3 to 1.6). Other studies, most with a case–control design, focused on particular connective-tissue diseases, including scleroderma, rheumatoid arthritis, and systemic lupus erythematosus.[26-29] These, too, failed to find an association with breast implants.

The only study to suggest a possible link was the most recent of this series of epidemiologic investigations, the Women's Health Cohort Study.[30] It found that women with breast implants had a relative risk of 1.24 of reporting connective-tissue disease (95 percent confidence interval, 1.08 to 1.41). Although this was by far the largest of the epidemiologic studies, there was, unfortunately, no attempt to verify the diagnoses. Given the fact that the questionnaires were sent to the women after the publicity surrounding the FDA ban, the findings could easily be explained by a reporting bias, as the authors acknowledged. They plan a follow-up study to verify the diagnoses. Even if the self-reports should prove to be accurate, the increase in risk is so small that women with breast implants should have found these latest results reassuring. However, many did not, in part because of recent assertions that the diseases caused by breast implants are not the "classic" connective-tissue diseases, but rather a new syndrome, described so far only in vague and nonspecific terms. Unfortunately, this assertion cannot be proved or disproved until the postulated syndrome is defined objectively enough to be studied. It is impossible to study the prevalence of a clinical condition without knowing how to identify it.

Future studies will certainly be increasingly plagued by the problem of reporting bias. Even attempts to validate self-reports by medical records will be subject to bias, because there are now a number of doctors whose patients are referred to them by plaintiffs' attorneys and who diagnose implant-related illness so often that their records would be highly suspect.[31] For this reason, to study whether breast implants are associated with systemic diseases, long-standing data bases that antedate the FDA ban are crucial. For now, however, we can say that the accumulated evidence shows that any link between breast implants and a variety of systemic diseases and symptoms is very small, if it exists at all.

The nonepidemiologic research on the breast-implant issue — animal studies, clinical case studies, and immunologic investigations — has generally been of inferior quality. Some of it has been performed by people who earn much of their income testifying or consulting for plaintiffs' attorneys. In 1994 the Medical Devices Agency of the British Department of Health issued a thorough review of the published studies of the immunologic

effects of breast implants, and pronounced the quality of most of the work "disappointingly poor."[32] The agency concluded that "there remains no scientific evidence from the literature of any increased risk of connective tissue disease associated with silicone gel breast implants."

The Law

While the scientific evidence was accumulating to show little or no connection between breast implants and a number of systemic diseases, the courts were continuing in their own direction. Many women chose to opt out of the attempted global settlements in favor of going to court on their own, where they expected to do better. After Dow Corning filed for bankruptcy, some women with implants made by Dow Corning targeted its enormous parent company, Dow Chemical, instead. Although Dow Chemical argued that it should not be held liable for products it had not designed or manufactured, some jurisdictions ruled differently. In late 1995, a jury in Reno, Nevada, awarded $14.1 million to a woman who sued Dow Chemical.[33] Her lawyers argued that even though the parent company had not designed or manufactured implants, it had early on been involved in the development of silicone itself.

This case exemplified the growing divergence between science and the law in the breast-implant story. The trial came well after publication of the results from the Mayo Clinic study and the Nurses' Health Study cohort. Dow Chemical in its defense cited these studies in detail, pointing out that neither of them had found a link between breast implants and disease. Many observers thought that unlike the earlier high-stakes cases, when there was little scientific evidence in either direction, this case, because of the preponderance of the evidence, would have to be decided in favor of the defendant. But it was not.

Why is science in the courtroom so disconnected from the scientific evidence? I have discussed elsewhere some of the reasons for the discrepancies in outcome.[34] The most important reason, in my view, is the use of expert witnesses in the courtroom. Witnesses are chosen by the adversaries' lawyers, paid by them, and rehearsed in advance. Despite the 1993 U.S. Supreme Court ruling, in *Daubert* v. *Merrell Dow,*[35] that requires federal judges to review expert testimony and admit it only if it is reliable and relevant, the criteria are only loosely applied. Witnesses are considered experts on the basis of very broadly defined credentials (for example, pathologists may be permitted to testify about epidemiologic questions), and they needn't produce evidence from the literature to buttress their opinions, even when there are relevant studies in peer-reviewed journals. In the courtroom, their opinions *are* the evidence. This is a far cry from the scientific method, which accepts no conclusions, no matter whose they are, without evidence. There are other reasons for science in the courtroom to produce seemingly capricious results, but space does not permit my discussing them in any detail here. They include: the contingency-fee system, which entices plaintiffs' attorneys to file multiple suits, knowing that one victory can subsidize many losses; the threat of large punitive damages in product-liability suits, which contributes to the desire of defendants to settle even weak cases out of court; and the use of juries in tort cases involving highly technical matters, which often leads to a "never mind the facts" sympathy verdict for an appealing plaintiff who is taking on a rich corporation. These features of the American tort system are virtually unknown outside the United States, where plaintiffs' attorneys are paid a flat fee and tort cases are almost always decided by judges.[36,37]

Since juries are drawn from the general public, the attitudes they bring with them to court can be expected to reflect public opinion. Although I am unaware of any systematic polls on the breast-implant controversy, a large segment of the public seems to accept the view that breast implants cause serious disease, despite the lack of evidence. I believe this has to do in large part with the difficulties many people have in thinking in terms of probabilities, or in acknowledging the possibility of coincidence. To them, nothing is — or should be — due to chance. They simply cannot accept the fact that if a woman falls ill after she gets implants, it may be coincidence. Given the concern about the risks of breast implants, people naturally assume that implants are the cause of any illness or symptoms that occur after they were inserted. Thus, the watchword of some women with implants, "We are the evidence," seems reasonable to many people, although it is logically meaningless. It is as though the rooster who crowed before dawn took credit for the sunrise, and thought the sequence of events was evidence enough.

Long-Term Consequences

The full effects of the breast-implant controversy are far-reaching, and will probably not be entirely felt for years. They certainly extend beyond the question of whether breast implants are safe, important though that question is. The narrow concern about whether breast implants cause autoimmune or connective-tissue disease is, in fact, largely settled. Taken altogether, the studies have failed to find an association, although they are not large enough to rule out some small effect. The 95 percent confidence interval of the Nurses' Health Study, for example, was 0.2 to 2.0. Nevertheless, for an individual woman with implants wondering about her risk, even a doubling of risk would mean that her chances of developing connective-tissue disease increased from 1 to only 2 percent (or, put another way, her chances of remaining free of connective-tissue disease dropped from 99 percent to 98 percent) — not a large chance to take. From a public health perspective, of course, a doubling of risk may matter, and it certainly would from the perspective of scientists interested in the pathogenesis of disease. Unfortunately, these three different perspectives — individual, public health, and pathogenetic — are often blurred when we think about risks, causing unwarranted alarm for individuals.

The broader effects of the controversy are far from

settled. Concern about groundless mass litigation threatens the medical-device industry, as well as patients dependent on it. Silicone is a component of a great variety of medical devices, some of them vital, including shunts, catheters, pacemakers, and artificial heart valves. Already, mass litigation has been launched against manufacturers of penile implants[38] and the Norplant contraceptive device,[39] both of which contain silicone. The principal threat is that suppliers of the raw materials will no longer sell to manufacturers of medical devices. Most of the suppliers can well afford to pull out of this market, since it accounts for only a trivial part of their revenues. Dupont, for example, will no longer supply medical manufacturers with Dacron polyester, which is used in vascular grafts.[40] In May 1994, Senator Joseph Lieberman (D-Conn.), then chairman of the Governmental Affairs Subcommittee on Regulation and Government Information, held hearings on the impact of product-liability suits on the availability of medical devices.[41] The father of a boy with hydrocephalus testified of his fear that hydrocephalus shunts, which contain silicone, may become unavailable. Also testifying was the president of Meadox Medicals, a manufacturer of vascular grafts and other devices. She said she had tried to contact 15 alternative suppliers of polyester yarn after Dupont announced it would no longer supply Dacron to her company. None of them, even foreign suppliers, would deal with American manufacturers because of the liability risks. Lieberman, arguing for reform of the product-liability system, said, "This is a public health time bomb, and the lives of real people are going to be lost if it explodes."

Of equal concern to the medical-research community is the encroachment by tort law on the conduct of research studies. The institutions and investigators involved in the major epidemiologic studies of breast implants received subpoenas from plaintiffs' attorneys requesting enormous amounts of primary data.[42] In the case of very large data bases, such as the Mayo Clinic's Rochester Epidemiology Project and the Nurses' Health Study, the lawyers' demands were intimidating. In addition, the necessity to protect patient confidentiality made compliance extremely difficult or impossible. If strict patient confidentiality were not maintained, clinicians who cooperate with these epidemiologic projects might be unwilling to continue to participate, thus threatening the very existence of the data bases. And, of course, the underlying, implied message was clear to both institutions and researchers. They knew that research on breast implants could easily cost them vast amounts of time and energy, as well as large legal fees. The National Institutes of Health is currently trying to initiate its own, very large epidemiologic study of breast implants. Its principal investigator found it necessary to confer with plaintiffs' attorneys to try to enlist their good will. In a form letter, she noted, "Plaintiffs' attorneys have been consulted on issues such as respondent confidentiality, and several of them have endorsed the study; however, interactions with attorneys have in no way threatened the study's objectivity" (Brinton LA: personal communication). This simultaneous deference and disclaimer is surely extraordinary in epidemiologic research.

In my view, the most important implication of the breast-implant story is its reflection of what appears to be a widespread distrust and misunderstanding of science in American society. In the long run, this feeling will cause more damage than any other aspect of the controversy. Several jurors who participated in implant decisions, as well as the head of a powerful advocacy group, have publicly said that the results of scientific studies did not matter to them. In their view, medical research was irrelevant.[43] All that mattered was what they believed, never mind why they believed it. Yet readers of the *Journal* know that medicine is replete with instances of convictions being proved wrong by rigorous research. Only a commitment to evidence can test the hopes and fears and biases that otherwise would have full sway. Science is not perfect, but it is the best method we have to answer questions about the material world and to evaluate the myriad alleged health risks that continually capture public attention.

The breast-implant controversy is not the only example of the problem. Over the past 20 years, the public's attention has been caught in rapid succession by asbestos, diethylstilbestrol (DES), Bendectin, the Dalkon shield, Agent Orange, Alar-treated apples, radon, and electromagnetic fields, among other real or alleged health hazards. Each engendered a mix of fear, recriminations, and denials. There were also mass lawsuits, Congressional hearings, and demands for tighter government regulation. The scientific evidence was highly variable.[44] Sometimes, as in the case of the connection between DES and vaginal cancer, it was solid. But in other cases, such as the alleged link between Bendectin and birth defects, the evidence was strongly against a connection. And in others, such as those of asbestos and radon, the risk was real but greatly exaggerated. The strength of the evidence seemed irrelevant to the public debate. Risks for which there was little evidence were taken as seriously as those for which there was good evidence, and small risks received as much attention as large ones.

Many people have become alienated from science and scientific habits of thought — at a time when we need science more than ever to help us find our way through an increasing number of serious and complicated questions involving risks to health and safety. To reverse the alienation we need a better public understanding of science, beginning with more and better science education in schools at all levels. That requires more than a field trip, a bug collection, and a computer. It also means attention to scientific thinking, including an understanding of the nature of evidence, the concepts of chance and error, and the value of skepticism. We also need better media reporting on scientific issues. The best science reporting is very good, but most stories about health risks fall far below that level. When reporters writing about science have little or no training for their task and their editors seem more interested

in entertaining or startling readers than in educating them, the public is not well served. Courts compound the problem by largely ignoring the rules of science and handing down verdicts that fly in the face of evidence. Given these conditions, it is no wonder that the public finds the scientific approach so foreign. And yet, without a better understanding of science, we stand to live out Carl Sagan's darkest vision: "It's a foreboding I have — maybe ill-placed — of an America in my children's generation, or my grandchildren's generation . . . when, clutching our horoscopes, our critical faculties in steep decline, unable to distinguish between what's true and what feels good, we slide, almost without noticing, into superstition and darkness."[45]

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