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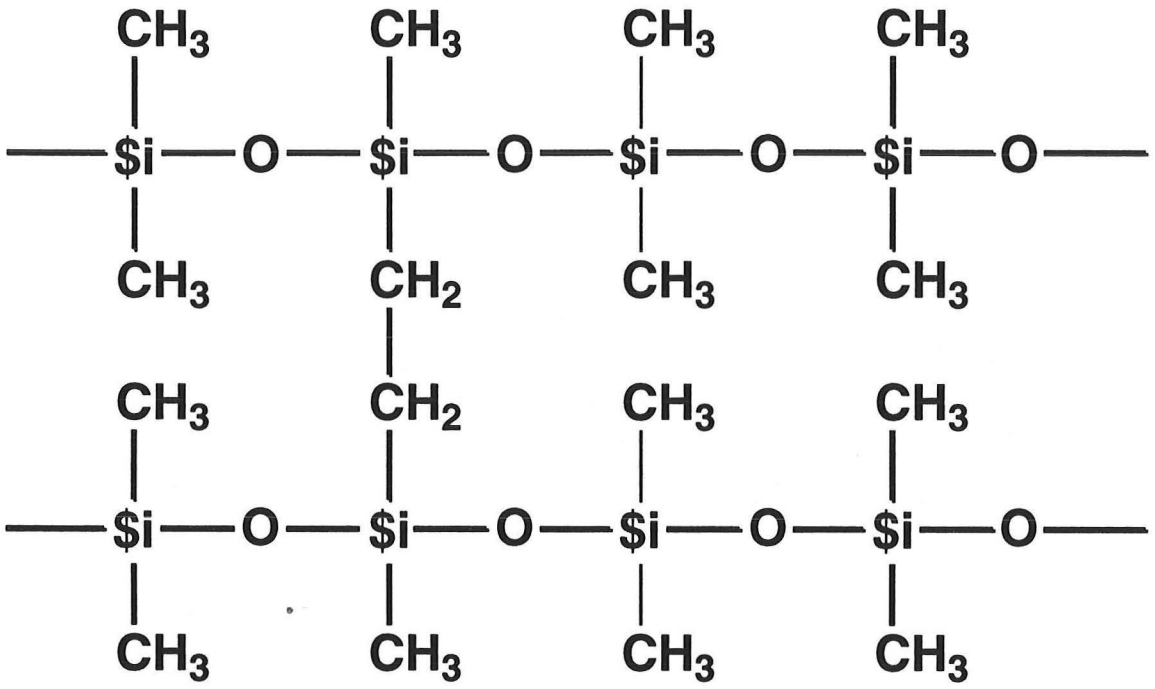

Silicone and Autoimmunity

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Dr. Karp has not testified or consulted for parties involved in breast implant litigation.

Introduction

In April, 1992, then FDA Commissioner Dr. David Kessler announced that silicone gel breast implants would no longer be generally available. This decision was the focal point for intense discussion within the medical community, litigation, media hyperbole, and the bankruptcy of a major US corporation, not to mention the anxiety of hundreds of thousands of patients with breast implants and other silicone-containing devices. In the five years since that announcement, a considerable amount of data has been accumulated concerning the safety of silicone implants. The issue seems far from resolved, however.

History

Augmentation mammoplasty has been performed for over 100 years (1). Following World War II the injection of various substances including paraffin wax, petroleum jelly, beeswax, and vegetable oils directly into the breast was tried (2). Most of these substances caused intense local inflammatory reactions and could lead to infection and scarring. Silicone gel was also injected under the assumption that it was biologically inert. However, the injection of large volumes of gel into the breast generally caused scarring and fibrosis. The gel did not stay in place, leaving the woman with painful, fibrotic lumps.

In 1961, two Houston plastic surgeons, Thomas Cronin and Frank Gerow, approached the Dow Corning Corporation with the idea to encapsulate silicone gel within an envelope of silicone elastomer (3). This shell would prevent the gel from migrating and facilitate the sub-glandular placement of the implant. The use of silicone gel implants became immediately popular, both for cosmetic surgery and for reconstruction following mastectomy. The true number of women with implants is not precisely known, but 1 to 2 million, or 1% of American women are frequently used estimates (4). White women made up 94.6% of implant recipients. Women in the southern US had the highest rates of implant prevalence. Texas, in particular, had a prevalence of implants in 22/1000 when estimated in 1989 (5). During the period from 1979 to 1992, 100,000 to 150,000 women annually had implant surgery at a cost of $300 million to $450 million in toady's dollars (6). Approximately 70% of implants were for cosmetic reasons.

Although silicone breast implants had been on the market since 1962, they did not come under FDA regulation until Congress passed the 1976 Medical Device Amendment to the Food, Drug, and Cosmetic Act. This amendment allowed the FDA to require manufacturers of new medical devices to submit animal and human data on effectiveness and safety, much as is done for new drug applications. Devices on the market prior to 1976 were "grandfathered" - including breast implants. In 1982, the FDA proposed and in 1988, required implant manufacturers to submit data for pre-marketing approval, as if they were new devices. This was done following anecdotal reports, primarily in the rheumatology and plastic surgery literature, of connective tissue disease in women who had silicone gel implants (2,7-12).

Beginning in 1984, concern over the safety of silicone breast implants increased due to a number of product liability lawsuits and media publicity. Plaintiffs won several multi-million dollar judgments against implant manufacturers (see below), claiming that their implants had caused a variety of collagen vascular diseases. Consumer advocacy groups such as Public Citizen pressured the FDA to ban implants. In one famous 1990 television show, journalist Connie Chung

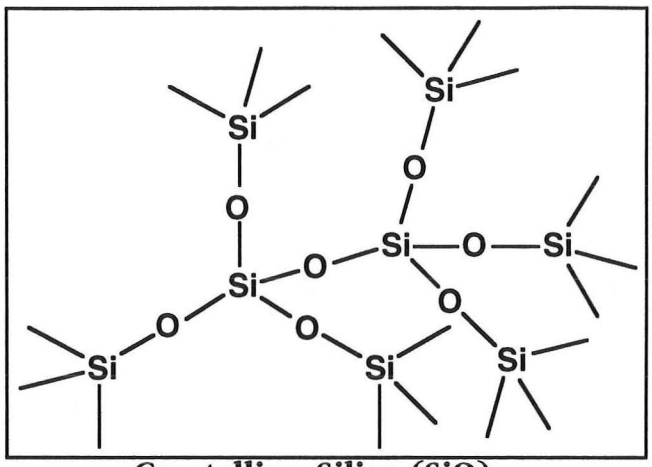
interviewed women who claimed their symptoms of autoimmune disease were due to their implants and implied that the FDA was to blame. In April of 1991, the FDA demanded that formal pre-marking approval data be provided by July of that year. In November, 1991, an advisory panel was convened to study this data as well as public testimony. They decided that the data were not adequate, but recommended that implants remain on the market during this time. In December, 1991, internal Dow Corning research documents were released in the wake of a $7.34 million jury verdict against the company. In January 1992, the FDA called for a moratorium on the use of silicone gel implants while these and other company documents were studied. Another advisory panel met a month later and recommended a virtual ban on the use of silicone gel implants, pending further research. Dr. Kessler accepted this recommendation on April 16, 1992.

The FDA decision left silicone gel-filled implants available only to women with breast cancer requiring reconstruction post-mastectomy, and women in limited clinical trials. Saline-filled implants which still have a silicone elastomer shell as well as other implanted devices made from silicone remained on the market, subject to FDA review. In an essay in *The New England Journal of Medicine*, Dr. Kessler stated that the FDA had no choice but to ban silicone gel implants under Federal law (13). This view has been questioned by some, including Dr. Marcia Angell, Executive Editor of the *Journal*, who has chronicled the debate over breast implants in both editorial and book form (6,14). The Council on Scientific Affairs of the American Medical Association also criticized the FDA after a review of the breast implant literature in 1992 (15). Dr. Kessler responded, saying that no public health need existed for cosmetic breast implants, and that uncertainty over their safety necessitated the ban on unregulated use. Furthermore, he felt that the AMA had failed in their role to further quality medical care (16).

Despite the ban on silicone gel-filled implants, saline-filled implants continue to be used. It is estimated that 40,000 are implanted per year. The limitations of the FDA ban have resulted in a decrease in the use of gel-filled implants to 22,000 per year (6).

Silicon and Silicone Chemistry

Silicon makes up 28% of the Earth's crust, making it the second most abundant element after oxygen at 45%. Together, they comprise 75% of the crust in the forms of silica, silicates, glass, and sand. Silica refers to silicon dioxide, SiO_2, a basic component of concrete, ceramics, and glass. In most cases, it exists in an ordered, cyrstalline state with the oxygen atoms forming tetrahedral links to other silicon atoms:

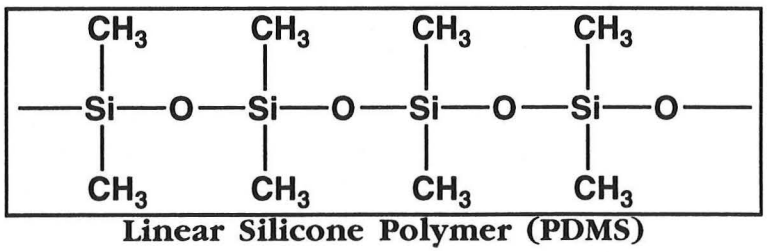


Crystalline Silica $(SiO)_{4/2}$

Silicas are generally insoluble in water, and are chemically inert at usual temperatures. As drying agents and fillers, they are added to both human and animal foodstuffs. Silica dust, however, is highly toxic when inhaled, leading to silicosis. This is one of the most common occupational lung diseases, characterized by the formation of fibrotic peri-brochiolar nodules, hilar lympadenopathy with non-caseating granulomas, and interstitial fibrosis. It is also associated with increased risk of pulmonary tuberculosis (17).

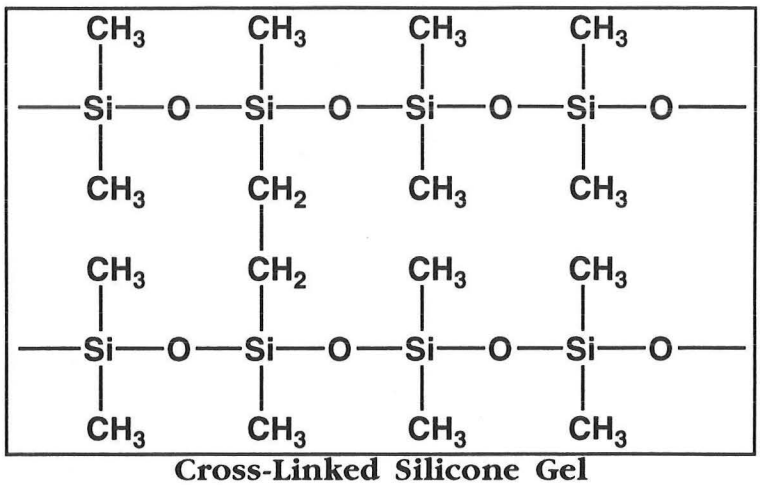
A non-crystalline, or amorphous, form of silica can be generated by heating the crystalline form to several hundred degrees centigrade. This 'fumed' silica exists as 7 to 22 micron particles that form spontaneous aggregates. It is typically added to silicone elastomer as a reinforcing agent. In this case, the SiOH groups are modified with organosilicon groups to make them less chemically reactive. Crystalline silica is not used in the manufacture of silicone-containing medical devices (18).

Silicones are synthetic polymers consisting of the Si-O backbone to which organic groups are attached to the silicon atom by silicon-carbon bonds. The most common silicone is polydimethylsiloxane (PDMS):



Linear Silicone Polymer (PDMS)

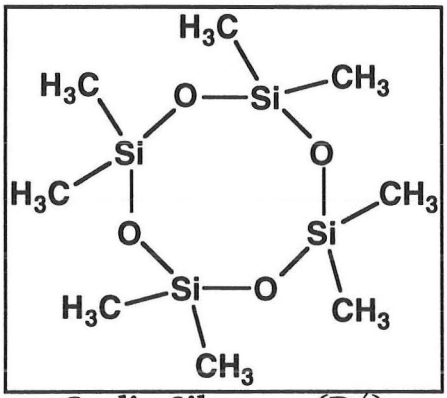
Depending on the degree of cross-linking or branching, PDMS can take the form of a liquid, gel, or elastomer. Silicone fluid is insoluble in water and available in different viscosities depending on the length of the PDMS chain. When PDMS is cross-linked by vinyl groups, a silicone gel is created:



Cross-Linked Silicone Gel

Silicone gel polymers are blended with silicone fliuds to create amorphous materials having the desired consistency and resiliency. Further cross-linking of the PDMS polymer results in the formation of an elastomer that can contain little silicone fluid. This elastomer forms the shell of silicone breast implants. Fumed silica is added to the elastomer to enhance its physical strength. In addition, the elastomer is often modified to contain other organic substitutions other than methyl groups. These phenyl or trifluoropropyl groups decrease the solubility of PDMS fluid in the elastomer matrix and prevent leakage known as "gel bleed".

The chemical precursor of linear silicone polymers is octamethyl-cyclotetrasiloxane (D4):



Cyclic Siloxane (D4)

D4 is removed by a process known as vacuum stripping. This process does not remove all the cyclic compounds. These low molecular weight substances may make up to 10% of the silicone gel of the implant (19). They are more likely to diffuse through the silicone elastomer of the implant shell.

In various forms, silicones are found in many medical applications. In addition to silicone breast implants, silicone is used in intravenous tubing (including indwelling catheters), prosthetic cardiac valves, intracerebral shunts, small and large joint prostheses, and intraocular lens implants. Silicone fluid is used to repair retinal detachments and to lubricate hypodermic needles. It is estimated that the average diabetic injects several grams of PDMS fluid over their lifetime.

Silicone Immunology

In contrast to the well-described inflammatory response to crystalline silica, it has been difficult to document a specific immune response to silicon or silicone-containing compounds (20). A large number of studies have been performed that are designed to quantify the either the presence of antibodies to silicone, or self-proteins modified by silicone, or the activation and proliferation of lymphocytes in response to silicone. In many of these studies, results with patient samples (symptomatic women with implants) are significantly different from results with controls or asymptomatic implant recipients. However, each of these studies is subject to some general criticisms. The very nature of silicone makes it difficult to work with as an immunogen or antigen. Silicones are highly hydrophobic, causing proteins and proteolipids to adsorb to them non-specifically. This makes traditional assays such as ELISAs difficult to perform and control. Silicones with unprotected hydroxyl groups can form covalent bonds with proteins, further complicating the analysis.

Inflammatory Responses to Silicon/Silicone

Silicosis

Crystalline silica is known to stimulate macrophages and T lymphocytes. As noted above, the inhalation of silica dust is associated with pulmonary fibrosis, characterized by histiocytic inflammation and non-caseating granuloma formation. Gold and coal miners are the primary occupations affected, although silicosis is also seen in sand-blasters, foundry, cement and pottery factory workers (21). In addition to silicosis, workers exposed to silica are at risk for the development of systemic sclerosis (scleroderma) (21-23). The calculated incidence of scleroderma in these workers was over 20-times the normal population. They have Raynaud's phenomenon, dermal sclerosis, esophageal dysmotility and pulmonary fibrosis, but rarely renal disease. The etiology of silica-induced scleroderma is presumably similar to silicosis. Macrophages ingest crystalline silica and become activated. They are also able to transport silica crystals to other cells including endothelial cells. Endothelial cell activation and damage results in characteristic vascular damage. Patients with silica-induced scleroderma exhibit many of the same immunologic and vascular markers of idiopathic scleroderma such as antibodies to Scl-70, anti-nuclear antibodies, and elevated von Willebrand Factor (23). Some of these findings are also seen in healthy, silica-exposed co-workers, suggesting that immunologic activation and vascular damage are primary, pathologic events. Experiments that exposed rats to silica support an immunologic mechanism. Their macrophages become activated and secrete cytokines including IL-1, and there is an increase in MHC class II antigen presenting cells in the lung (24).

Silicone Synovitis

Silicone elastomer has been used in small and large joint orthoses in hundreds of thousands of patients. The most common implants are metcarpalphangeal joints in patients with rheumatoid arthritis, followed by implants for carpal joints destroyed by arthritis, trauma, and osteonecrosis. These implants can degrade through constant movement and shearing by adjacent bones. Microfragments of silicone can produce clinically significant foreign body reactions, even from radiographically intact prostheses. One of the more striking presentations is a synovitis occurring at the site of a silastic joint prosthesis (25,26). Osteolysis and cartilage erosion can occur with a hypertrophic villous synovitis (27,28). Silicone particles are often found microscopically within the pannus. Regional lymphadenitis with the appearance of silicone in the lymph node has been documented (29-31).

Silicone as an Adjuvant

Adjuvants are substances designed to increase the potency of immunogens. The function of an adjuvant is to create a depot of antigen, prolonging clearance from the tissue. In most cases, it is also designed to create an inflammatory response, activating antigen presenting cells such as dendritic cells or macrophages that can take up antigen, process it, and carry it to draining lymph nodes for presentation to helper T cells and deposition within germinal centers. Typical adjuvants for human use include alumna and talc. For decades, the most common adjuvant used to induce antibodies in laboratory animals was complete Freund's adjuvant (CFA). This is a mixture of mineral oil and heat-killed mycobacteria. The response to this agent is so strong that it could not be used for humans and is now only rarely used in animal studies.

In susceptible strains of experimental animals (particularly Lewis rats), the repeated administration of adjuvants such as CFA leads to the induction of synovitis resembling rheumatoid arthritis (32,33). Administration of other bacterial products such as streptococcal cell walls in oily vehicle will also produce adjuvant arthritis. The pathogenesis of adjuvant arthritis is presumed to be a T cell mediated delayed type hypersensitivity reaction to cross-reactive self proteins, particularly heat-shock proteins. The earliest reports of musculoskeletal symptoms following breast augmentation were felt to be reminiscent of adjuvant arthritis in rats and given the term "Human Adjuvant Disease" (8,34). These patients usually had direct subcutaneous injection of paraffin or silicone gel. After a brief popularity, this term has fallen to disfavor due to the lack of sufficiently specific classification criteria.

Silicone satisfies one of the criteria of an adjuvant, in that some preparations are intensely inflammatory. The local response to breast implant components has been tested in a number of animal systems. Picha and Goldstein implanted fumed silica, silicone oil, silicone gel, and silicone elastomer subcutaneously in Lewis rats (35). Histology of explanted specimens was performed at time periods between 7 and 90 days. Fibroblasts, eosinophils, lymphocytes and macrophages were present at the surface of silica-containing silicone elastomer at 7 days. Over time the fibrous capsule became more organized and less cellular. Elastomer without silica elicited less of a reaction. Silicone oil and gel also caused modest cellular responses that diminished over time. The strongest responses were to fumed silica itself, a compound not found free in manufactured implants, and the dried residue of a xylene extract of elastomer shells. The latter compound likely reflects non-silicone materials remaining from the manufacturing process.

Nearly all the components of silicone breast implants have been shown to enhance immunogenicity of foreign proteins in experimental animals. This includes both crystalline and fumed silica, silicone gel, silicone oil, and D4, the precursor of linear PDMS. In a rat model of rheumatoid arthritis, animals were injected with bovine type II collagen in association with different adjuvants (36).

Adjuvant	6 μg Bovine cII	125 μg Bovine cII
PBS	0%	0%
IFA	90%	100%
Silicone Gel	40%	60%
Silicone Oil	ND	20%
D4	ND	0%
Silicone Oil/D4	ND	10%

Development of collagen-induced arthritis in DA rats immunized with The indicated amounts of bovine type II collagen (cII) in different adjuvants. the percentage of animals with arthritis at 90 days is shown. ND: not determined. Adapted from (36).

These animals also developed antibodies to bovine collagen:

Adjuvant	6 μg Bovine cII	125 μg Bovine cII
PBS	0	0
IFA	11±32	439±142
Silicone Gel	59±74	144±49
Silicone Oil	ND	17±5
D4	ND	8±2
Silicone Oil/D4	ND	10±4

Titer of anti-bovine collagen antibodies in DA rats immunized with the indicated amounts of bovine type II collagen (cII) in different adjuvants. ND: not determined. Adapted from (36).

It is important to emphasize that the animals did not develop arthritis or antibodies when injected with the silicones alone. These substances were acting as adjuvants for foreign proteins, not self-proteins.

In another study, rats immunized with rat thyroglobulin emulsified with silicone gel produced low-titer autoantibodies but no throiditis, compared to animals immunized with complete Freund's adjuvant that developed disease (20). Lastly, the cyclic precursor of PDMS, D4 has been shown to be the most inflammatory substance found in breast implants when injected into mice as well as rats and to augment antibody production to foreign antigens (37).

Effects of Silicone on Cytokines

Given that some silicones can promote inflammation, it is a reasonable hypothesis that substances leaking or bleeding through the elastomer shell cause local tissue reactions that result in increased levels of pro-inflammatory cytokines. Cytokines such as IL-1, IL-2, IL-6 or TNF would be expected to cause sympotms of fatigue, arthralgia, fever, etc., as they do in infectious diseases. Several studies have looked at cytokines produced by peri-implant connective tissues in sympotmatic patients undergoing explant. One study found increased levels of IL-6 and TNF, but not IL-2 or PGE_2 in ten women whose implants were taken out (38). The controls included breast scar tissue from asympotmatic women and synovium. An increased

level of tissue macrophages was also seen. The investigators were unable to correlate symptoms to cytokine levels within the implant group. Another small study was unable to find IL-6, but noted increased levels of IL-2 in peri-implant tissue (39). Finally, a recent study suggested that circulating IL-1 is higher in a subset of breast implant patients (40). These studies are small and un-blinded. They do provide verifiable measurements that can be made in larger, population-based studies of silicone exposure and atypical or subjective symptoms.

Silicone and Autoantibodies in Humans

It is clear that silicone in different chemical forms is capable of augmenting antibody responses to foreign antigen. There is probably nothing special about this property, though, and would be seen with alumna or other adjuvants currently used for human vaccines. The data is less clear on whether silicone increases the prevalence or titer of autoantibodies. Most case series on the association of breast implants and connective tissue diseases document increased numbers of patients with positive anti-nuclear antibody (ANA) tests. The frequency ranges from 20-80% (7,41-44). These studies are generally subject to ascertainment bias, as the subjects are patients referred to rheumatology practices. Another problem is the lack of uniformity in the determination of a positive ANA. Currently most laboratories test sera on human epithelial carcinoma (Hep-2) cells. Approximately 5% of adults with no signs or symptoms of disease will have titers of 1:40 on this substrate. This is often used as the cut-off for a "positive" result, although patients with defined connective tissue diseases will have titers of 1:160 or more. This "gray-zone" fills both rheumatologists waiting rooms for "ANA consults" and rheumatology journals with "possible" disease associations.

In one cross-sectional study, 150 women were tested (45). They included asymptomatic controls without implants, asymptomatic women with implants, women with implants and symptoms (myalgia, arthralgia, fatigue), and women with implants and definite connective tissue disease. They used an ANA titer of 1:256 or more on the Hep-2 cell as positive, and the degree of fluorescence graded as 1+ to 4+. Women with implants were significantly older than the controls, although this was said not to affect the results.

Group	N	# with ANA (%)	ANA Score
Control	19	0 (0%)	NA
Asymptomatic	38	7 (18%)	1.6
Symptomatic	82	21 (26%)	1.8
CTD	11	7 (64%)	2.9

Prevalence of anti-nuclear antibodies in 150 women. CTD-Connective tissue disease. The ANA score is the mean value to positive ANA's on a 1-4 scale. Adapted from (45).

Despite the potential for bias and the small sample size, there appears to be an increased prevalence of ANAs in women with implants, regardless of symptoms. No correlation was seen with type of implant, time since implantation and possibility of implant rupture. This study is notable for the inclusion of an asymptomatic implant group. Other cross-sectional studies that have shown increased prevalence of ANA in implant patients have not included this control, nor patients with similar symptoms without implants.

An increased occurrence of ANA in women with implants was not seen in a larger Mayo Clinic study designed to quantify the occurrence of connective tissue disease in implant recipients (46) (see below):

	Implant (N = 749)	No implant (N = 1498)
ANA	11	27
Incidence rate	18.8	21.8
Rate ratio	0.86	
95% CI	0.42-1.70	

Occurrence of positive ANA in cases and controls. Adapted from (46).

It must be noted that these data are from medical record reviews. Not all women had testing done. Unfortunately, like much of the research in the human immune response to silicone, accurate conclusions cannot be drawn unless large, prospective, studies are done.

Antibodies to Silicone Biomaterials

Early reports of the inert nature of silicones included the failure of animals to be immunized by them. In 1968, Nosanchuk evaluated the repeated subcutaneous injection of PDMS fluid mixed with complete Freund's adjuvant (CFA) into guinea pigs over a 15 week period (47). This study was not controlled by the injection of CFA alone. No antibody responses were detected, nor were there immediate or delayed type hypersensitivity reactions. However, there were severe granulomatous reactions at the injection site as well as evidence of migration of PDMS fluid to the liver, spleen and lung. Other investigators have also failed to demonstrate specific anti-silicone antibodies in immunized animals, with a variety of adjuvants, and under conditions where antibodies to other polymers (e.g., dextran and polyvinylpyrrolidone) were easily demonstrated (48).

More recently, Wolf, et al. used a mixture of bovine serum albumin (BSA) and low molecular weight silicone fluid to coat ELISA plates (the BSA is needed to get silicone to stick to the plastic plate) (49). Sera from patients with ruptured implants, asymptomatic patients, diabetics exposed to silicone as a lubricant for hypodermic needles and controls were tested in a blinded fashion. Although non-specific binding accounted for 30-50% of the observed reaction, the authors concluded that all women had antibodies to silicone, including non-exposed controls. They proposed that the antigen was simethicone contained in antacids, although no attempt was made to document such exposure. There was no difference between controls and diabetic patients. Women with ruptured implants had the highest level of reactivity in this assay, although no comment is made about their general condition and level of antibodies to other antigens. The techniques used in this study are novel, and have not been reproducible (50,51). Until specific antibodies are isolated, it is impossible to conclude that silicone is an immunogen.

Earlier this year, a study was published in the *Lancet* concerning an "anti-polymer antibody" assay (52). Some of the patients who attended a large rheumatology practice and had silicone breast implants were asked to participate. The authors do not state how they decided who would be chosen. Over two-thirds of the patients declined to be part of the study. Control subjects were employees of the investigators, or their friends. No comparison of the patients and controls is

made. The assay method has only been published in abstract form and is an immunoblot where the immobilized antigen was an empirically derived mixture of synthetic polymers. The assay was performed in a blinded fashion.

Category	N	APA+ (%)
SBI Exposed		
Limited	34	1 (3%)
Mild	26	2 (8%)
Moderate	16	7 (44%)
Advanced	19	13 (68%)
Classical Autoimmune disease	15	3 (20%)
Clinic controls	23	4 (17%)
Autoimmune disease without SBI	20	2 (10%)
Total	153	32 (21%)

Prevalence of anti-'polymer' antibodies (APA) in women with silicone breast implants. Adapted from (52)

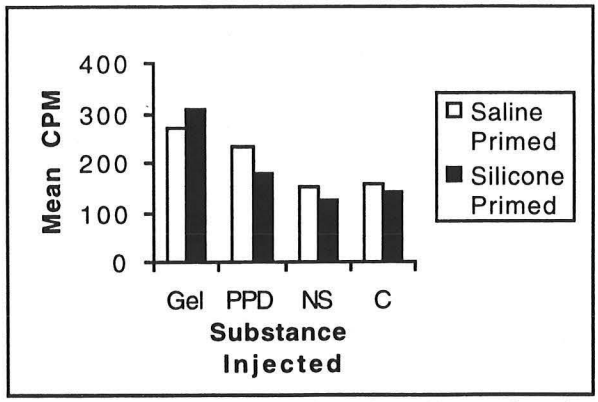
44% of patients with moderate symptoms (arthralgias, myalgias, poor sleep, cognitive dysfunction, etc.) had anti-polymer antibodies, as did 68% of implant recipients with "severe" symptoms. Antibodies were found in 17% of their clinic controls. This study characterizes the difficulty in assessing the immune response to silicone. It contains potential bias in patient/control selection, the clinical assessments are subjective (which is not to say that they are incorrect), and the assay cannot be correlated with any pathophysiological hypothesis. Nevertheless, the correlation of a serologic finding with symptomatology in these patients suggests that a larger, more formal investigation be done.

Lymphocyte Responses to Silicone

The hallmark of a specific immune response to silicone would be the demonstration of memory T lymphocytes activated by a silicone derived antigen. The majority of T cells recognize peptide fragments of immunogenic proteins that are bound to self-MHC structures. It is not likely that silicone polymer could replace peptide in this system. It is possible that silicone denatures self-proteins, making them more immunogenic. Also, a minority of T cells can recognize non-protein antigens such as mycolic acid or prenyl pyrophosphate (53). Low-molecular weight components of silicone manufacture may also be recognized in this manner. However, experimental proof of either of these hypotheses is lacking

Several studies have attempted to document lymphocyte responses to silicone. Rats injected with silicone gel mixed with complete Freund's adjuvant failed to show evidence of a specific lymphocyte response to silicone (54). No alteration in the relative proportion of different lymphocyte subset was seen. In another study, sheep were injected with saline, silicone gel, complete Freund's adjuvant, and a mixture of silicone and adjuvant. One month later, the efferent lymphatic from a draining lymph node was cannulated and lymph collected. Cells from the lymph were labeled with ^{111}Indium (55). To test for recall to specific antigens, the animals were then given intradermal injections of silicone gel, PPD, or saline. After 48 hr., the radiolabeled lymphocytes were injected intravenously into the same sheep. Three hours later, the skin overlying the injections was removed and analyzed for radioactivity. As expected, Freund's adjuvant had the greatest effect of priming a delayed-type hypersensitivity reaction to subsequent PPD challange. Much smaller

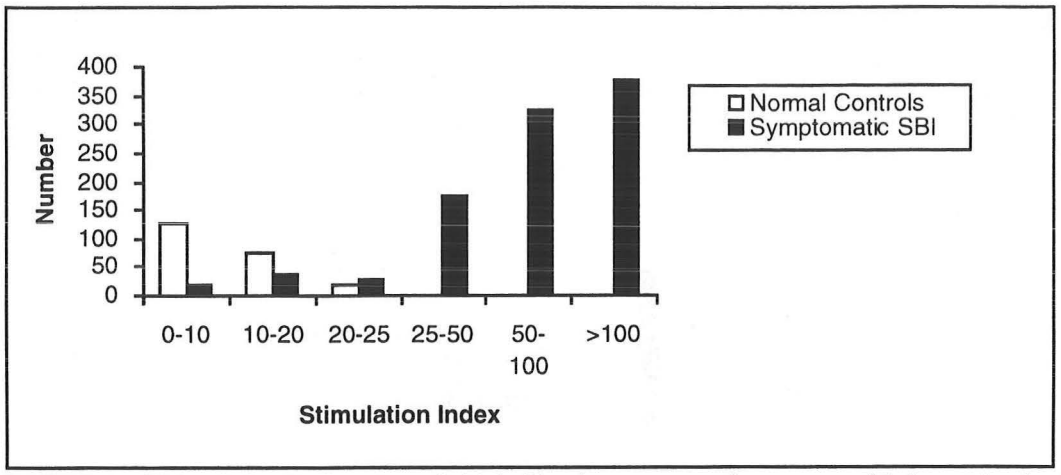
effects were seen in the other combinations. More cells accumulated at the site of silicone injections as well. This was statistically significant in the silicone primed animals when compared to saline injections. However, the silicone injections also caused DTH-like reactions in saline-primed animals.



Localization of radiolabeled lymph cells to intradermal injections of silicone gel (gel), PPD, normal saline (NS), or control skin (C). Adapted from (55)

Therefore, it is unclear whether this represents true immunological memory, or merely an inflammatory reaction to silicone gel. Although the efferent lymph contains mainly lymphocytes, no attempt was made to characterize or purify the cells further.

Another study has looked at the response of peripheral blood mononuclear cells (incorrectly designated lymphocytes in the paper) to a preparation of "colloidal pharmaceutical grade silicon dioxide (56)." Whether this represents crystalline silica found commonly in the environment but not in implanted silicone, or amorphous silica that is bound in silicone elastomer is not clear. Cells from symptomatic (fatigue, myalgia, arthralgia, Raynaud's phenomenon, etc.) women with implants, asymptomatic implant recipients, patients with rheumatic disease (primarily fibromyalgia), and controls were stimulated by the silica, pokeweed mitogen, phytohemagglutinin, and concanavalin A. Lymphocyte proliferation was assessed by tritiated thymidine incorporation and expressed as a stimulation index (SI), which is the ratio of stimulated to control counts per minute. 220 adults without implants had a mean SI of 10.0. 91.3% of 942 symptomatic implant patients had SI values greater than 25.



Distribution of Stimulation Indices to colloidal silica in symptomatic women with breast implants and normal controls. Adapted from (56).

The distribution of SI values for asymptomatic implant recipients was intermediate between controls and symptomatic patients. No difference was seen in the responses to traditional lymphocyte mitogens, nor was there any correlation with length of time since implantation or determination of implant rupture. The authors concluded that their results indicated migration of silicon dioxide out of mammary prostheses in nearly all women, with subsequent processing and presentation of this inorganic solid by macrophages to specific T lymphocytes.

Although the Food and Drug Administration has not certified any test for the documentation of silicone immunology, this particular assay was marketed to detect cell-mediated immunity to products of silicone breast implants. The utility of the test was called into question by the results of an informal test by a prominent academic plastic surgeon (57). He sent blood samples from symptomatic patients and non-implanted controls for testing. For the control patients, a fabricated history of silicone breast implants was included along with non-existent symptoms. All blood samples had stimulation indices exceeding 2.5 times the mean values for normals described in the study above. Moreover, on repeat testing done 7 to 12 months later, the mean stimulation index of the true implant group fell, while that of the non-implant group rose. Overall, the mean index for the true control patients was eight times that of the laboratory control. The test was reported to cost $350 per sample and felt by the author to be either meaningless, or too sensitive to be practical.

HLA Associations

If exposure to silicone promotes autoimmunity, then it stands to reason that women with certain HLA types will be more likely to be affected than others. Although the associations are not completely understood, well-characterized disorders such as systemic lupus erythematosus, rheumatoid arthritis, insulin-dependent diabetes mellitus can be linked to certain HLA haplotypes. Presumably, this represents the recognition of certain disease-causing antigens presented by these HLA molecules. Other explanations, including modification of the T cell repertoire during development and the participation of HLA-linked genes (including complement proteins) are possible. To address this question, Young, et al. obtained HLA haplotypes on 199 women (58). Seventy-seven women in Group I had implants and symptoms of connective tissue disease such as arthralgias, myalgias, fatigue, and widespread pain. They did not meet criteria for defined disorders such as SLE or RA.

37 women in Group 2 had implants but did not have symptoms. They were matched with the first group in terms of age and duration of implants. 54 healthy women without implants served as controls in Group 3. A fourth group included 31 women with fibromyalgia who had symptoms similar to the first group, but did not have implants. All women received complete HLA typing as well as tests for autoantibodies to their own B cells. musculoskeletal exams were done on symptomatic patients.

	Group I	Group II	Group III	Group IV	p value (X^2)
DR1	18%	38%	15%	26%	0.048
DR4	44%	27%	31%	45%	0.188
DR7	34%	11%	20%	29%	0.046
DR53	**68%**	35%	52%	**65%**	0.007
Homozygote (DR4,7,53)	10%	35	2%	10%	0.143
Autoantibodies to B cells	**42%**	14%	2%	19%	<0.001

Frequency of HLA alleles and anti-B cell autoantibodies in symptomatic patients (Group I), asymptomatic patients (Group II), controls (Group III) and fibromyalgia patients (Group IV). Data from (58).

The most striking finding is the increased frequency of the DR53 allele in symptomatic breast implant and fibromyalgia patients. HLA-DR53 is the single product of the *DRB4* class II beta chain gene and the non-polymorphic alpha chain. It is in linkage dysequilibrium with the *DRB1*-coded beta chain alleles, DR4, DR7, and DR9. Due to its non-polymorphic nature, little is known about its role as an antigen presenting molecule. The authors postulated that its presence was associated with the production of anti-B cell autoantibodies as 81% of symptomatic women with implants and such antibodies were DR53 positive. The cause of fibromyalgia is unknown. It is possible that the same features that predispose women to develop idiopathic fibromyalgia also increase the likelihood that they will develop symptoms following breast implantation. This could be true regardless of any immune reaction to silicone itself. There are problems with this study such as its small size and the potential for enrollment bias. However, it suggests that traditional mechanisms of molecular immunology can and should be studied further to classify symptomatic patients and identify the pathogenesis of their problems.

Clinical Data

Case Reports and Series

The decision of the FDA to limit access to silicone gel implants was based on several reasons. Although they had been in use for thirty years, and the vast majority of patients were satisfied with their implants, the manufacturers were unable to present the FDA with adequate safety data. Under the law, Dr. Kessler argued, the FDA had no choice but to ban these devices. Influencing their decision were Dow Corning internal research documents made public at a 1991 lawsuit against the company. They documented incomplete corporate studies addressing the inflammatory nature of silicone gel that really did not add to or contradict what was already in the literature. However, they did show that the company did know about gel bleed - the slow leakage of lower molecular weight silicones and other substances through the elastomer - and instructed marketing personnel to conceal this fact from plastic surgeons. This was the basis for the jury's determination of fraud on the part of Dow Corning.

The FDA was also faced with a large number of case reports and case series describing autoimmune diseases in patients who had undergone augmentation mammoplasty. The earliest cases were Japanese women who had either paraffin wax or processed petroleum jelly injected directly in their breasts approximately 20 years previously (2,8,34,59). The case descriptions of these women fit the diagnosis of systemic sclerosis with Raynaud's phenomenon, diffuse scleroderma, and axillary lymphadenopathy. There followed approximately two dozen reports of connective tissue diseases or symptoms in nearly 300 patients. The reported patients usually came from rheumatologists known for their interest in silicone-related disorders, and who had often established relationships with plaintiff's attorneys. The cumulative data in these reports have been reviewed. The following summary is from two hundred and ninety-three cases reported from 1964 to 1993 (60):

Syndrome	Number of Cases Reported
Systemic Sclerosis	38
Rheumatoid Arthritis	9
Systemic Lupus	8
Myositis	5
Mixed CTD, overlaps, etc.	8
Rheumatic symptoms/Human Adjuvant Dis.	221

Data are from (60). Cases of definite and possible connective tissue diseases are combined.

Similar findings from nearly 400 more patients with rheumatic complaints have been documented by several other groups (61,62). Systemic sclerosis was the most common definite connective tissue disease described. This made some sense to investigators, as exposure to crystalline silica is associated with a sclerosing illness. Scleroderma is also the one collagen vascular disease most commonly associated with exposure to environmental and pharmaceutical agents (63). In addition to silica, it can be seen with bleomycin, cocaine, pentazocine, organic solvents (notably vinyl chloride), and adulterated food oils (Toxic Oil Syndrome). In 1989, a epidemic of cases with eosinophilia, myalgia, and scleroderma-like skin changes occurred in the US. Most cases of eosinophilia-myalgia syndrome were associated with ingestion of L-tryptophan food supplements containing manufacturing impurities. Thus it seemed reasonable to individual investigators, who could not estimate the referral bias in their studies, that they were seeing another example of environmental-induced scleroderma. When data from these un-controlled case reports were pooled, the occurrence of scleroderma in breast implant patients approaches the current population prevalence (60).

Most cases of rheumatic complaints in women with breast implants were of a subjective, atypical nature (64). Frequent complaints were fatigue, arthralgias, myalgias, cognitive difficulty, breathing difficulty, rash, and upper body pain (65). One of the largest groups of such patients was from the University of South Florida (43). One hundred and fifty-six patients referred for rheumatic complaints had detailed histories, physical exams, and laboratory studies.

Symptom or Finding	Patients with arthralgia/myalgia (n=95)	Patients with joint swelling on exam (n=32)
Fatigue	92%	94%
Sicca symptoms	13%	22%
Cognitive dysfunction	12%	16%
Pulmonary symptoms	8%	28%
Rash	4%	0%
Recurrent fever (>38°)	5%	0%
Lymphadenopathy	21%	0%

Adapted from (43).

These symptoms are common and difficult to quantify. They are very similar to the symptoms of fibromyalgia, a disorder seen in ~10% of general medicine patients and up to 25% of rheumatology practice patients. In some patients, the symptoms have abated following removal of their implants. In the context silicone breast implants (or other exposure to silicone), the terms "human adjuvant disease", "siliconosis", and lately, "systemic silicone related disease" have been coined.

In a follow-up study these researchers examined a cohort of breast implant patients compared to patients who had undergone other cosmetic surgery (66). Women with silicone gel breast implants were more likely to report swollen axillary lymph nodes (OR = 7.082; 95% CI = 1.129 - 44.439) or tender axillary lymph nodes (OR = 6.898; 955 CI = 1.752 - 27.154). No differences were seen in the other symptoms such as fatigue, myalgias, arthralgias, and skin rashes. This study also looked at defined diseases (see below) and found no differences between groups.

Epidemiological Studies

The data that the FDA wanted to see in 1992, and the breast implant manufacturers were unable to provide are contained in fifteen epidemiological studies published from 1992 to 1996. These consist of case-control studies, cohort studies, and population studies. The case control studies can be summarized as follows (67-72):

Study	Disease	Cases	Controls	OR (95% CI)
Dugowson	RA	349	1,456	0.41 (0.05-3.41)
Englert	SSc	251	289	0.9 (0.2-3.4)
Burns	SSc	274	1,184	0.72 (0.2-3.2)
Strom	SLE	195	143	NA
Hochberg	SSc	869	2,061	1.3 (0.6-2.5)
Sanchez-Guerrero	CTD	448	4480	0.94

RA - rheumatoid arthritis; SSc - Systemic sclerosis; SLE - systemic lupus erythematosus; CTD - connective tissue disease; OR - odds ratio; CI confidence interval. The number of case and control subjects in each study are shown.

The cohort studies had the following characteristics (46,66,73-78):

Study	Disease	Implants	No Implants	RR (95% CI)
Weisman	SSc	125	literature	0
Schusterman	CTD	250	353	1.1 (0.1-17.2)
Gabriel	CTD	749	1,498	1.1 (0.34-3.0)
Wells	Arthritis	826	310	1.2 (0.15-9.0)
McLaughlin	CTD	824	literature	2.72
Giltay	CTD	287	287	0.44
Williams	CTD	323	literature	1.15 (0.23-3.41)
Hennekens	CTD	10,830	384,713	1.24 (1.08-1.41)

Abbreviations as above; RR - relative risk. Number of subjects with and without implants is shown. Literature values for disease prevalence were used where indicated.

In addition, Goldman, et al. (79) performed a cross-sectional retrospective review of computerized medical charts in a single rheumatology/internal medicine practice. 721 patients had a defined connective tissue disease and 3,508 did not. There was no association with breast implants (OR, 0.45; CI, 0.22-0.90).

Several of the studies deserve separate discussion. Researchers at the Mayo Clinic in Rochester, MN are in a relatively unique position to do epidemiological studies. Nearly every resident of Olmsted County receives their medical care at the Clinic or one of its affiliates. Computerized databases are maintained on this care. Gabriel, et al., used these databases to identify all residents who had received breast implants between January, 1964 and December, 1991 (46). Two age-matched controls that had received medical care at the same time were chosen randomly for each case. 749 case subjects and 1,498 controls were included in the analysis. Clinical, laboratory, and radiographic data to support diagnoses of defined autoimmune diseases were abstracted from the charts. In addition to collagen vascular disease, Hashimoto's thyroiditis and primary biliary cirrhosis were looked for. Rheumatoid arthritis, lupus, or systemic sclerosis were not seen in the case subjects. Cox proportional hazard ratios adjusted for age and length of implant found a significant increase in the occurrence of morning stiffness in cases, as well as insignificant increases in arthritis and sicca symptoms. Serositis was seen only in the sub-group with implants after breast cancer.

Event	Hazard Ratio (95% CI) for all implants
Any connective tissue disease	1.10 (0.37 - 3.23)
Thyroiditis	1.00 (0.47 - 2.13)
Non-breast cancer	1.10 (0.56 - 2.16)
Arthritis	1.38 (0.84 - 2.28)
Morning stiffness	1.80 (1.10 - 2.93)
Sicca symptoms	1.42 (0.92 - 2.21)

Data adapted from (46).

The authors admit that the sample size was too small to find an association with rare diseases such as systemic sclerosis. The calculated that a study following 62,000 women with implants for 10-years would be needed to detect a doubling in occurrence of a diseases with an annual incidence of 1.6 per 100,000. In addition, subjective symptoms such as arthralgia, myalgia or fatigue were not looked for, and other data were limited to what had been put into the patient's chart. Nevertheless, this was the first major study to demonstrate that silicone breast implants were not associated with large risks for autoimmune diseases.

The reaction to this study was interesting. An accompanying editorial in the journal praised it for allaying the fears of thousands of women. The study was funded in part by the NIH and the Plastic Surgery Educational Foundation, which in turn received support from Dow Corning. Plaintiff's attorneys immediately subpoenaed the editorial files of *The New England Journal of Medicine*, including peer-review documents and 'evidence of payments' to the editors from Dow Corning in exchange for publication (6). Attorneys requested all primary data from Dr. Gabriel, as well as data from every other epidemiological study performed at the Mayo Clinic. These requests were eventually denied.

The Nurses Health Study is a cohort of registered nurses in eleven states who have been sent biennial questionnaires since 1976 (72). In 1992, they were queried about breast implants. These data were correlated with information routinely obtained about rheumatic conditions or complaints. 87,501 women were followed for a total of 1.2 million person-years. 1,183 women reported breast implants, but no connective tissue disease prior to surgery. Participants were asked about the type and indication for implants, diagnoses of specific collagen vascular disorders, as well as forty-one signs and symptoms of disease. Data from questionnaires were validated by inspection of the medical records of a subset of patients. The age-adjusted relative risks failed to show an association of breast implants with either disease or symptoms.

Case	Relative Risk (95% CI) for implants
Self-reported CTD	0.7 (0.5 - 1.0)
Self-reported symptoms	1.5 (0.9 - 2.4)
Documented signs or symptoms	0.7 (0.3 - 1.6)
Definite connective tissue disease	0.6 (0.2 - 2.0)

Data adapted from (72). CTD: connective tissue disease.

Overall rates of definite connective tissue disease in this population were not different from previously reported values. The statistical power of this study is strong, due to its size. Even so, the upper bound of the confidence interval (2.0) for connective tissue disease would be of considerable public health importance. The only valid methodologic criticism of the study is that atypical symptoms were only sought from women who initially reported a rheumatic condition. Plaintiffs attorneys have criticized the study since all 87,000 patients were not personally examined by the researchers.

Finally, a retrospective cohort study of 395,543 female health professionals was published last year (78). 10,830 reported breast implants and 11,805 reported any connective tissue disease between 1962 and 1991. All data were from questionnaires and no validation from medical records was done. The data are summarized as follows:

Event	Implant (10,830)	No Implant (384,713)	RR (95% CI)	p
Any CTD	231	11,574	1.24 (1.08-1.41)	0.0015
RA	107	6,322	1.18 (0.97-1.43)	0.096
SLE	32	1,561	1.15 (0.81-1.63)	0.44
Sjögren's	22	752	1.49 (0.97-2.28)	0.067
PM/DM	20	727	1.52 (0.97-2.37)	0.068
SSc	10	314	1.84 (0.98-3.46)	0.060
Other CTD	83	3,271	1.30 (1.05-1.62)	0.017

Data from (78).

This is the largest study of women with breast implants to date. It detected a 24% increase in the occurrence of all combined self-reported connective tissue diseases that was statistically significant. This finding was largely due to the inclusion of women who reported "mixed connective tissue disease, or other" disorders that did not fit into classical diagnoses. The size of the study makes these findings unlikely to be explained by chance. The most significant problem is that all data were un-validated. The self-reported rates of connective tissue disease in this cohort (with and without implants) were higher than in previous population studies. Although the authors limited the study to diagnoses prior to 1991 in a effort to avoid bias from media publicity linking breast implants to connective tissue disease, the questionnaires were completed from 1992 to 1995. If women with breast implants were more or less likely to participate in the study based on whether they had symptoms, were involved in litigation, or other reasons, the relative risks could be markedly changed. This is known as Berkson's fallacy which describes the spurious association of two events due to differing enrollment of cases and controls. A mathematical example of this is given in the Appendix.

Several meta-analyses of the different epidemiological data have been performed (80-82). A review by the FDA cautioned against such analyses saying that the underlying studies were flawed, particularly with regard to the lack of information on 'atypical connective tissue diseases'. The Dow Corning Corporation published a meta-analysis that attempted to combine only studies of similar design and method, adjusting individual relative risks to achieve homogeneity.

Condition	# of Studies	RR (95% CI)	Homogeneity p
All CTD	12	0.76 (0.55 - 1.04)	0.073
Systemic sclerosis	7	0.98 (0.57 - 1.64)	0.006
Rheumatoid arthritis	6	0.79 (0.48 - 1.26)	0.602

Data from (80).

These data are in agreement with the Nurses Health Study (above) and reinforce the conclusion that exposure to silicone in the form of breast implants does not substantially increase the risk of developing a definite connective tissue disease. How the data are used in both public health, regulatory, and individual decision-making circumstances depends on the point of view. Assuming the worst case of the upper bound of most confidence intervals is ~2, then one could argue that ~250 women will get a connective tissue disease because of their implants. Association is equated with causation in this argument, which has not been demonstrated. Alternatively, one could state that the risk of getting scleroderma is raised from 0.003% to 0.006% of the population, which could be an acceptable risk in an individual patient considering silicone implants.

A large, high-quality, study of implant recipients and atypical symptoms such as disabling fatigue, myalgias, and arthralgias has not been done, although a small study of undifferentiated connective tissue disease found no association with breast implants (77). Case-series of such patients often fail to find objective evidence of disease. There are many reasons why a definitive study could probably never be done given the history of silicone breast implants. The overwhelming reason is that an acceptable case definition of "silicone-related disorder" has never been established. Groups of rheumatologists involved with breast implant litigation have attempted to do so. In essence, they have generated a scheme where the symptoms of a disease define the disorder. While this superficially seems similar to the classification of rheumatic diseases such as SLE or rheumatoid arthritis, it is not. In those cases, patients with connective tissue diseases were first classified by expert panels, based on decades of clinical experience. For example, clear-cut cases of SLE and scleroderma are easily distinguishable, even though both may have an anti-nuclear antibody. The clinical and laboratory features with the highest sensitivity and specificity for accurate classification were determined. If the only discriminating feature between idiopathic fibromyalgia and "silicone-related disorder" is the presence of breast implants, then it will be impossible to do case-control studies.

Local Complications

With the weight of the evidence suggesting that exposure to silicone gel-filled implants is not associated with the development of connective tissue diseases, one of the most important questions from both a product liability standpoint, and for the future of both cosmetic and reconstructive breast implants is their fate as a bioprosthesis. The main local complications of silicone gel implants include capsular contracture (the formation of a hard, uncomfortable, or disfiguring fibrous capsule around the implant), and rupture of the implant with migration of gel into the surrounding tissues (as well as throughout the body). Incidence rates for implant rupture vary widely. It is suspected when there is a change in implant size or shape, the onset of breast pain , or the appearance of subcutaneous nodules. It has been documented in up to 5% of asymptomatic patients (83). Physical examination, mammography, ultrasound, and magnetic resonance imaging can all be used to detect rupture, although only examination at surgery is definitive (84). Reasons for rupture of breast implants include trauma, compression mammography, and closed capsulotomy to relieve contracture. It appears that many cases of rupture are related to implant age. Like other prostheses, they wear out over time. Three studies looked at a total of 745 implants in 388 women who were seen by plastic surgeons for implant related problems (85-87). They documented the number of prevalence of non-traumatic ruptures in various age groups.

Study	# of implants	Implant age (yr) and % not intact	
		Group I	Group II
de Camara	51	1-9 (35.7)	10-17 (95.7)
Peters	102	2-10 (31.1)	11-26 (40.2)
Robinson	592	1-10 (58.1)	11-25 (80.7)

Adapted from (88).

In a cohort-based study from the Mayo clinic, Gabriel, et al. found that 5.7% of all women who had received implants had been re-operated on for rupture after a mean follow up of 7.8 years (89). Some authors have advocated the prophylactic replacement of all implants after 8 years to lessen the risk of rupture or exposure to

silicone gel. Numerous case reports and case-series have found granulomatous reactions to leaking silicone gel as well as axillary lymphadenopathy in patients who have leaking implants explanted (62,90-99).

The most common local reaction to breast implants is the development of capsular contractures. Estimates of this problem vary. A small, randomized clinical trial comparing silicone-filled to saline-filled implants suggested that it can occur in up to 54% of patients. In Gabriel's study of re-operation rates in women from Olmsted County, capsular contracture required surgery in 17.5% of women in the cohort (89). While these complications are well-recognized by plastic surgeons today, they were not publicized by implant manufacturers. One of the central issues in the resolution of the breast implant controversy, both from a medical and legal standpoint is whether women were ever given proper informed consent as to how long their implants would last. Until 1983, Dow Corning told patients that they expected implants to last a women's "natural lifetime", and that complaints relating to capsular contracture were "occasional" (100). Prior to that time, they also mention closed capsulotomy, a procedure with a high risk of causing implant rupture, as an alternative to re-operation. By 1985, the package insert for Dow Silastic implants pointed out the potential complications of implants including contracture, leakage, and (at that time) risk of immunological sensitization. They stressed the plastic surgeon's responsibility to inform the patient of all these risks.

Medical-Legal Issues

Dow-Corning stopped selling silicone breast implants in March, 1992, one month prior to the FDA ban. Over 16,000 individual product liability lawsuits ensued in the next two years, with 10,000 directed against Dow Corning. Attorneys openly advertised for women to come forward and sue. Ultimately, Dow Corning was the target of over 30,000 actions. In 1994, a federal class action settlement was announced. $4.25 billion was set aside for women with implants prior to 1993. Women were to be compensated if they developed a connective tissue disease or merely symptoms of such within the thirty years after their surgery. The amount of compensation was determined by the "grid", a table listing the patient's age and diagnosis. The younger a patient was and the more severe or definite the diagnosis, the more they would be entitled to. Individual awards ranged from $140,000 to $1.4 million plus medical costs. Husbands and children were also entitled to awards under the terms of the settlement. Patients came their doctors (including the Parkland Arthritis Clinic) asking to be "put on the grid". All that was required was documentation in the medical record that appropriate signs or symptoms were present. A woman who had felt fine until she received the class action mailing could answer affirmatively to questions about fatigue, joint and muscle aches, and atypical chest pain, and be certified to receive hundreds of thousands of dollars. No work-up or verification was needed.

440,000 women, approximately one-fifth of all implant recipients, registered for compensation under the class action. The amount of money set aside was clearly insufficient to cover the costs. The Dow Corning Corporation declared bankruptcy in May, 1995. As the major contributor to the class action-settlement pool, Dow's bankruptcy effectively negated the agreement. A less-generous, more restrictive settlement was tentatively worked out with the remaining manufacturers. All claims against Dow Corning will have to go through bankruptcy court proceedings in Midland, Michigan. In the meantime, some jurisdictions have allowed Dow Chemical, the parent company, to be sued for Dow Corning's liability In October

1995, a Reno, NV jury awarded a woman $14.2 million in damages in a suit against Dow Chemical (100). Other jurisdictions have disallowed the suits against the parent company (101).

Many women opted out of the class-action lawsuit in order to seek higher awards on their own. A large number of these suits were from Texas. Certain law firms became well known as they got multi-million dollar judgments for their clients, and were retained by thousands of women. One notable example is John O'Quinn of Houston. O'Quinn is reported to be one of the highest paid trial lawyers in the country, with an annual income in the tens of millions of dollars. In 1995, he had 2,000 breast implant cases and predicted an average trial award of $10 million each, including a 1992 award for $25 million. Since most cases get settled out of court, the final plaintiffs awards (and 40% contingency fees) may only be $1 million or less.

Several physicians have had a profound influence on breast implant litigation, with Texans again playing a prominent role. Their practices consisted of patients referred by plaintiffs attorneys. They insisted on performing serology and chemistry batteries, MRI, bone scans, and nerve biopsies on all their patients. Nearly all of the patients they saw were diagnosed as ill, regardless of signs, symptoms, or test results. In some cases, immunosuppressive therapy has been suggested to treat asymptomatic "disease". Needless to say, these physicians have been paid well for their opinions with expert witness fees of $300 to $600 per hour and annual incomes in excess of $1 million from the examination, testing, a reporting of breast implant patients. Silicone researchers have also formed companies to test blood samples from patients to document "siliconosis" or "silicone-related disease". Since none of these tests are licensed by the FDA, their advertisement in trial lawyer's publications has resulted in some sanctions.

Media scrutiny of the breast implant controversy has been immense. This ranges from criticisms by consumer groups of the epidemiological evidence to editorials decrying the use of "junk science" in the courtroom. Breast implant manufacturers have used the media to promote favorable scientific studies - a practice that resulted in the mistrial of several implant lawsuits (100).

Medical Testimony and the Federal Rules of Evidence

Despite the lack of rigorous evidence, the physicians and researchers hired by plaintiff's attorneys have convincingly testified to the absolute certainty that silicone causes autoimmunity in general and is the likely cause of the woman's specific complaints. These experts often based their opinions on anecdotal evidence or hypotheses they had generated without doing any type of relevant research. There is concern over the role of such expert testimony. Who constitutes an expert and what can they tell a jury? Several federal and Supreme Court cases this century have dealt with the issue of expert testimony and relate to current breast implant litigation. In 1923, the Federal trials and appeals courts ruled in *Frye v. United States* on the inadmissibility of a type of sphygmomanometer designed as a lie detector (102). Reversing previous nineteenth century Supreme Court decisions allowing all testimony, the courts in *Frye* said that expert testimony must be generally accepted in the relevant discipline. Such general acceptance might include peer review, ability to be replicated by other investigators, and ability to generate new, testable hypotheses. Detractors of the *Frye* decision claimed that it allowed only narrowly-defined, "safe" testimony by the establishment, and that novel thinkers such as Galileo would be prevented from having their say.

The standard for expert testimony was relaxed in 1975, with the adoption of the Federal Rules of Evidence (103). Basically, Rule 702 allows testimony if a witness is qualified on the basis of "knowledge, skill, experience, education, or training," and may testify in the "form of an opinion, or otherwise." Essentially, any relevant testimony may be offered, whether it has passed the test of general acceptance or not. In Rule 703, the facts and data that the expert can use to form his opinion are specified, although they need not be admissible as evidence if they are "of a type reasonably relied upon by experts in the given field." In essence, these rules say that the witness must have knowledge that is valid, and that the knowledge be helpful, i.e., reliable, and relevant, and that they be qualified. Rule 702 does not require that the testimony of the expert be based on methods or data that are generally acceptable. This "let-it-all-in" approach gave opposing attorneys considerable latitude in providing testimony that fit their case.

The U.S. Supreme Court tried to reconcile the "general acceptance" approach of *Frye* with the more lenient Federal Rules in their decision in *Daubert v. Merrell Dow Pharmaceuticals, Inc.* In this case, the plaintiff argued that Bendectin had led to birth defects. The trial court and the Ninth Circuit Court of Appeals ruled for the defendant (manufacturer) claiming that the plaintiff's expert evidence was inadmissible. In a parallel to the breast implant situation, the defense noted the extensive epidemiological studies that failed to show a link between the drug and birth defects. The plaintiff's experts offered their opinions to the contrary without being able to cite any scientific evidence. The Supreme Court did not undertake the question of whether Bendectin caused birth defects, or whether Merrell Dow was liable. It sent the case back to the Ninth Circuit with the decision that the Federal Rules did supersede *Frye*, but that federal trial judges must evaluate expert testimony and determine whether the knowledge will be helpful or not (103,104). The opinion written by Justice Blackmun requires judges to make an assessment of the validity of the reasoning and methodology underlying the testimony, and whether it can be applied to the particular case at hand. *Daubert* attracted the attention of numerous groups, including medical and scientific organizations, who filed *amicus curae* briefs supporting a stricter standard for expert testimony. Unfortunately, the *Daubert* opinion gave no practical guidance to the judiciary in order to make their decisions. Some concepts are familiar to the scientific but not the legal community: the ability to explain observations, the falsifiability of the hypothesis, logical consistency, the degree to which the hypothesis has been tested, its consistency with accepted theories, its application and use in the scientific community, its precision, and peer review and publication. The *Daubert* decision has been applied inconsistently by federal judges in different courts (Bert Black, personal communication), suggesting that another Supreme Court case will be needed in order to settle the issue.

The *Daubert* decision has already been used in breast implant litigation. A federal court in Oregon recently disallowed plaintiff's expert testimony on the grounds that it lacked relevence. One of the proposals for settling the remaining cases in the class-action is to convene exeperts picked by the judge, a move in keeping with the spirit of *Daubert*. The influence of *Daubert* on expert testimony may be one factor in the drop off of jury awards against implant manufacturers in the last year:

Year	Plaintiff	Defense	Total Verdicts ($million)
1984	1	0	1.7
1987	0	1	0
1990	1	0	0.14
1991	3	2	17
1992	1	1	25
1993	1	1	0
1994	3	4	30
1995	8	10	29.2
1996	2	10	3

Data from (105).

Regulation

The litigation surrounding silicone breast implants has threatened the biomaterials industry in this country. Dow Corning is limiting or discontinuing the manufacture of silicone for other medical devices such as pacemakers, prosthetic heart valves, and intraocular lenses. The availability of arteriovenous and ventriculostomy shunts has been questioned. Both Dow Chemical and DuPont have announced that they will no longer supply raw materials such as Dacron polyester and Teflon used in vascular grafts or prosthetics. The medical uses of these materials are a very small portion of total sales compared to their commercial and industrial uses. The expense of defending the company against the threat of litigation is not felt to be profitable. Bills are now pending in both the U.S. House and Senate that will protect suppliers of biomaterials from product liability lawsuits directed against manufacturers.

Conclusions

Although much is clear with regard to silicone exposure and autoimmunity, much is left to resolve.

- No definite link has been found between silicone gel-filled breast implants and classical connective tissue diseases in over 15,000 women studied.
- However, implant material that was once felt to be biologically inert and would last a lifetime is now known to be inflammatory under proper circumstances and prone to significant failure. A number of interesting preliminary studies have been performed in symptomatic implant recipients. These need to be the basis for clearly quantitative population-based studies to look for an association of silicone exposure with atypical syndromes or fibromyalgia.
- Its ability to stimulate the immune system in either specific or non-specific ways is of unclear significance scientifically, but has been the center of debate in a number of arenas including professional medical societies, the courts, and Congress.
- Public health issues exist in the proper study and treatment of women who feel their symptoms are due to their breast implants.

- There are ethical questions about informed consent and the public's right to all medical intervention, regardless of risk that are not answered.

The experience with silicone breast implants over the last thirty years is likely to re-shape physicians relationships with medical deveice manufacturers and and their patients.

Appendix

Berkson's Fallacy

Criticisms of current epidemiological studies of the safety of silicone breast implants have largely focused on the size of the study populations or the failure of the researchers to verify appropriate medical records or document atypical symptom complexes. One problem that has not been dealt with explicitly is differential rates of entry into the study by patients and controls. In a prospective study where the investigator has control over the clinical parameters of study subjects and the intervention being studied, this is not a problem. In studies of disease association, particularly in an area filled with psychosocial and medico-legal aspects, this can take on significant proportions.

As an example, consider a hypothetical retrospective, case-control study to link a disorder such as fibromyalgia to silicone breast implants. For this example, assume the true prevalence of breast implants in fibromyalgia patients is 2.5 times that of patients without symptoms. The data from 1,000 individuals that represent this population perfectly would be:

Implants	No Fibromyalgia	Fibromyalgia
Present	10	25
Absent	990	975
Total	1,000	1,000
Percent with implants	1%	2.5%

The chi-square value is 5.70 and is highly significant ($0.01<p<0.05$)

In real life, individuals may come from these populations at different rates. Desire for medical attention, willingness to participate in research, and pending litigation may influence retention of eligible participants. Misclassification of implant status or subjective symptoms may occur. Careful study design can overcome some of these problems, but only to the extent that the researcher is aware of them.

Assume that the probability of asymptomatic women (regardless of implant status) entering the study from the true population is 20%; that of symptomatic women is 80%; and of women with implants regardless of symptoms is 50%. If these probabilities act independently, then the rate of entry of asymptomatic women with implants is 60%; symptomatic women with implant is 90%; asymptomatic alone is 20%; and symptomatic alone is 80%. Now the data table is as follows:

Implants	No Fibromyalgia	Fibromyalgia
Present	(10)(.6) = 6	(25)(.9) = 22.5
Absent	(990)(.2) = 198	(975)(.8) = 780
Total	204	802.5
Percent with implants	2.9%	2.8%

There is no apparent association between implants and fibromyalgia with this data. Increasing the size of the study will not change the outcome since the rates of entry will still be different. This example shows how differential retention/reporting can obscure a true association. Equally, a spurious association can be seen even when it does not occur in the true population.

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