EXHIBIT 1

Silicone Gel Breast Implant Failure and Frequency of Additional Surgeries: Analysis of 35 Studies Reporting Examination of More Than 8000 Explants

James S. Marotta,[1] Christopher W. Widenhouse,[1] Mutaz B. Habal,[1,2] Eugene P. Goldberg[1]

[1] Biomaterials Center, Department of Materials Science and Engineering, University of Florida, Gainesville, Florida

[2] Tampa Bay Craniofacial and Plastic Surgery Center, Tampa, Florida

Received 2 November 1998; accepted 23 February 1999

Abstract: Although it is well known that silicone gel breast implants (SGBIs) produce many "local" complications (i.e., pain, hard fibrous capsules, disfigurement, chronic inflammation, implant shell failure) and necessitate frequent surgical revisions, no large cohort retrospective quantitative analysis of clinical data has been reported to date, especially for the prevalence of failures and additional surgeries. Data from 35 different studies that encompass more than 8000 explanted SGBIs have now been analyzed and are reported here. Because examination of explanted silicone implants is the definitive method for determining shell integrity, the only studies that were used were ones that reported implant duration, the total number of SGBIs explanted, and the number of SGBIs for which shell rupture or failure ("not intact") was confirmed upon surgical removal. An exponential regression plot of data indicated a direct correlation of implant duration with percent shell failure ($r^2 = 0.63$ and $r = 0.79$). SGBI failure was found to be 30% at 5 years, 50% at 10 years, and 70% at 17 years. The failure rate was 6% per year during the first 5 years following primary implant surgery. ANOVA comparison of three implant age groups (mean implant durations of 3.9, 10.2, and 18.9 years) indicated a highly significant statistical correlation of percent failure with implant duration ($p < 0.001$). Complications necessitating at least one additional surgery occurred for 33% of implants within 6 years following primary implant surgery. Shell failure was found to be an order of magnitude greater than the 4 to 6% rupture prevalence suggested by the AMA Council on Scientific Affairs in 1993, the 0.2 to 1.1% cited by manufacturers at that time, and the 5% rupture that was stated to be "not a safety standard that the FDA can accept." © 1999 John Wiley & Sons, Inc. J Biomed Mater Res (Appl Biomater) 48: 354–364, 1999

Keywords: silicone gel breast implants; explant analysis; silicone implant complications; failure; rupture

INTRODUCTION

Silicone gel breast implant (SGBI) failure, which is the loss of silicone elastomer shell integrity (most often termed implant rupture), is a complication that has been reported with increasing frequency. SGBI failure is often associated with other so-called *local* complications such as pain, disfigurement, chronic inflammation, and frequent additional surgeries.[12,36–38] Local inflammatory processes surrounding SGBIs and the migration of silicone fluid from the "gel" to the parenchyma of the breast, lymphatics, and muscle tissues from even intact SGBIs are well established.[16,22,37,38] The migration of silicone fluid may also be problematic in view of uncertainties about silicone oil biocompatibility. In this regard, silicone fluid injections in humans were reported in 1975 to exhibit "adverse systemic effects" including migration with liver dysfunction and foreign body granuloma.[39] In primate studies, injection of silicone oil into the vitreous of the eye was found to produce retinopathy with marked degeneration of ganglion cells.[40] The most common low molecular weight silicone fluid constituents [i.e., the cyclic tetramer (D4)] are not biostable and their metabolic products have been shown to exhibit adverse toxicological properties. *In vivo* studies in rats and primates have demonstrated that they undergo metabolic oxidative and/or hydrolytic demethylation to silanol compounds,[41–43] and these silanol com-

None of the authors has a financial interest in or financial relationship with any company whose product was studied in this research. One author (E.P.G.) served as a consultant in breast implant litigation both on behalf of women as plaintiffs and plastic surgeons as defendants.

References 1–35 are those used for the failure analysis (see Fig. 1); 36–71 are additional case citations.

Correspondence to: Prof. E. Goldberg, Biomaterials Center, Dept. Materials Science, 317 MAE, University of Florida, Gainesville, FL 32611

Grant sponsors: University of Florida Foundation; and Biomaterials Center, Department of Materials Science and Engineering, University of Florida

© 1999 John Wiley & Sons, Inc. CCC 0021-9304/99/030354-11

J0011517

pounds have been reported to be "profoundly toxic" in rat studies.[44] Inflammatory and toxicological complications are therefore likely to be exacerbated by gross leakage or rupture of SGBIs. As a result, breast implant failures may pose an insidious safety problem with the potential for systemic effects, some of which may not become evident for many years after initial implant surgery.

The composition of most silicone gels is actually 85 to 95% silicone fluid.[45,46] Only a very small amount is a true chemically crosslinked silicone gel. The facile diffusion or "bleed" of this silicone fluid from the so-called gel into and through the shell of polydimethylsiloxane (PDMS) elastomer is a well-established phenomenon. Degradation of the shell mechanical properties occurs due to swelling of the silicone elastomer shell by silicone fluid; for example, for an unimplanted control SGBI, a decrease of 45% in shell tensile strength (from 1350 to 754 psi) and 46% in tear strength (from 80 to 43 lb/in.) was measured 3.5 years after manufacture.[47] For Silastic-I a decrease in tensile strength of 32% (from 808 to 553 psi) and 79% in tear strength (from 98 to 21 lb/in.) was reported after 1 year of shelf life (unimplanted). Similar results were obtained for Silastic-II, but an improvement was observed for fluorosiloxane bleed barrier coated Silastic-II: a 23% decrease in tensile strength but little change in tear strength at 1 year on the shelf.[48] Substantial progressive *in vivo* degradation of SGBI shell properties has also been reported by many investigators.[3,4,9,49–53] This weakening of the shell coupled with prolonged cyclic mechanical stress over time induces failure (i.e., rupture or loss of shell integrity) and can thereby make very large amounts of free silicone gel available for interaction with the physiological environment. For many ruptures, the gel may be substantially retained within intact capsules for some time and so limit the immediate transport of the major gel mass into extracapsular tissues. However, diffusion of the silicone fluid through even intact capsules leads to extracapsular silicone oil migration[16] with consequent more distant tissue interactions.

Few large retrospective clinical studies concerning breast implant failure have been reported, although the number of small studies published by individual plastic surgeons, radiologists, and pathologists has been growing since 1992 coincident with the moratorium on the implantation of SGBIs imposed by the FDA due to a lack of adequate safety data. However, the prevalence of silicone shell failure has remained uncertain. Although manufacturers suggested a range of 0.2 to 1.1% in 1992, the AMA Council on Scientific Affairs report in 1993 suggested a "prevalence" of 4 to 6% rupture.[54] At that time, Kessler et al.[55] noted reports of much higher values (15% to 20%) and indicated that even 5% rupture was not an acceptable standard of safety for the FDA. The time dependence of rupture, hence the *rate* of failure, was also generally ignored at that time. Soon after, various authors began to report much higher rupture values (e.g., 36–95%[3] and 58–81%[1]) and noted that failure prevalence increased at longer implant times. Many more studies, as reported here, especially the important recent large cohort studies by Middleton[34] (for 798 explants) and by Feng[35] (for 1619 explants), also clearly indicate that the prevalence of implant shell failure or rupture for SGBIs is quite high and is indeed directly related to implant duration, which is consistent with the view now expressed by many authors that time *in vivo* is a major factor contributing to weakening and eventual failure of SGBI shells.

Women submit to the risks of additional surgery for SGBI removal due to a variety of serious health concerns and symptoms, most commonly pain, hard breasts due to capsular contracture, disfigurement, evidence of rupture, and various other complaints. The formation of fibrous scar tissue, a "capsule," around breast implants followed by contraction of the capsular tissue is a particularly frequent and well-known complication following breast implant surgery. Gabriel et al.[12] indicated capsular contracture to be the most common reason for reoperation in their 749 woman cohort. It was an indication for 131 of the 178 women (74%) who had additional surgery within 5 years of primary implant surgery. In a prospective study, Hakelius and Ohlsen[56] replaced 17 of 25 smooth SGBIs (68%) due to breast hardness within 5 years. Capsular contracture is therefore an important complication that causes pain, hardness, breast disfigurement, possible tissue necrosis and implant extrusion *and is an indication for frequent revision surgery to remove even intact prostheses.*

Given this background, it is instructive to consider the retrospective 749 woman cohort Mayo Clinic epidemiological study published by Gabriel et al. in 1994[57] that has been so widely cited in support of the safety of SGBIs because it concluded that there was little evidence in this small patient cohort for silicone induced autoimmune disease. Data were not reported in this article for the incidence of revision surgery or rupture of implants. However, such data had been collected and were subsequently published by Gabriel et al. in 1997.[12] This later article indicated that there were frequent so-called "local complications" (i.e., pain, capsular contracture, and rupture) necessitating surgery for 24% of patients (178 of 749) within the first 5 years following initial implant surgery. Some women required as many as three, four, or even five surgeries during that time. The prevalence of ruptures was also given for this group. Explanted patients exhibited 24% rupture (43 of 178) at an average implant duration of 2.5 years.[12] It is interesting that Gabriel et al. reported rupture as only 5.7%.[12] However, this percentage was based on the use of the total patient cohort in the denominator (assuming, *with no evidence*, that all 571 women who did not have surgery had intact implants). In our view, only the explanted patient population should have been used in the calculation to give a scientifically valid result. Surgery to remove and examine an implant is the "gold standard," the only reliable method available, for judging the structural integrity of SGBI prostheses.[58]

Several articles used in this study were primarily concerned with the evaluation of different imaging techniques for detection of implant failure. Surgical removal of the SGBI was used in these studies to confirm implant rupture.[2,8,15,24,25,27,28,33,34] For example, Berg et al. examined 122 single-lumen and 22 double-lumen SGBIs using mag

netic resonance (MR) and ultrasound (US) imaging followed by surgical removal and explant examination.[2] Those explants that exhibited gross rupture or gel leakage were considered to have failed: 80 of 144 (56%) failed at a mean implant age of 12 years. Forsberg et al.[9] evaluated US imaging for 45 SGBIs with 19 explants exhibiting rupture (42%) when examined at surgery. The mean implant age was 9.8 years. Reynolds et al. compared MR, US, and mammography for 24 implants prior to surgical removal with 13 of 24 (54%) failing at 12 years.[25] Caskey et al. evaluated 221 implants by US but only 41 were explanted. Nineteen of 41 (46%) were found to be ruptured at a mean implant age of 10.5 years.[27] Petro et al.[28] presented a preliminary study of 154 implants evaluated by US. However, only 22 were explanted with seven of 22 (32%) ruptured at a mean implant time of 3.1 years. Palmon et al. examined 64 implants using gray-scale sonography. At surgery, 26 implants (41%) were found to be ruptured.[33] In a recent report for 798 explants by Middleton,[34] MR was investigated for rupture diagnosis.

Many other articles on the evaluation of noninvasive imaging techniques to determine breast implant failure have not clearly reported implant age for prostheses removed surgically to confirm their imaging results. Such studies are therefore of little value for implant duration versus failure analyses. Furthermore, the literature on noninvasive imaging of SGBIs clearly indicates that, although expensive and sophisticated MRI methods may prove more helpful and more accurate than US or mammography, *explant surgery is the only reliable method available for determining the status of SGBIs.*[28] Unfortunately, because so many articles concerning SGBI revision surgery present incomplete data, especially for implant duration, results for thousands of reported explants have been "lost" for analysis.

In view of the foregoing and the call for more scientific information on rupture by the July 1998 UK House of Commons sponsored review of breast implant safety,[59] it was considered important to expand our preliminary failure analysis for 1652 explants that was published in July 1997.[60] Because our data base now encompasses more than 8026 explanted SGBIs from 34 articles and the authors' research, the study reported here is far more extensive and statistically reliable than any published to date for evaluating the frequency of failure and additional surgeries for SGBIs.

METHODS

Data Base Criteria

Medline data bases were searched, including PubMed and Silver Platter servers, from 1969 through the early part of 1998 to find articles containing SGBI data for this study. This was augmented by manual review of the surgery literature. Articles were reviewed to determine the number of breast implant failures, the total number of SGBIs explanted, and the associated mean implant times (sometimes average or median). To insure unequivocal failure data, only reports involving surgical removal with direct inspection of SGBIs were used in our analysis.[58] Although literature data were reported in many different formats, we were careful in our analysis of each data set to reconcile these differences to create a uniform and self-consistent data base. More detailed explanations of how this was done for many articles is presented in the following section. Also included in our data base were results from the authors' research to date that involved the examination of 74 explanted SGBIs with a mean implant duration of 10 years. For this series, 31 (42%) were found to be ruptured.[19]

A wide variety of terms have been used in the literature to describe implant "failures," by which the various authors mean implants that are "not intact," that is "ruptured" or have "lost shell integrity." This not intact criterion that defines the term *failure* for this study encompasses such terms as "ruptured," "leaking," "damaged," "torn," "punctured," "disrupted," "destroyed," "disintegrated," "implant dissolution," "pin hole" (1–2 mm holes or tears), "fragmented," "gross leakage," "loss of shell integrity," "disintegration of the shell," "not intact," etc. All of these terms have been used by different authors to indicate failure of the silicone elastomer shell. However, reports of "oily" explant shell surfaces characteristic of normal SGBI bleed were not regarded as failures for this study.

Data Used for Analysis of Percent Failure Versus Implant Time

This analysis encompassed data from 33 peer reviewed articles plus a lecture presented by Feng[35] at the July 1998 Institute of Medicine Workshop on the Safety of SGBIs. Also included was our series of 74 SGBI explants with a mean implant age of 10 years (range 4–25 years) indicating 31 ruptures (42%).[19] All studies provided data for the total number of explants, the number of failed explants or percent failure, and the mean or average explant age. Note that the terms "implant age," "implant time," "explant time," "explant age," "implant duration," etc., all refer to the time that implants have been *in vivo* prior to explantation. Percent failure was plotted at mean (or sometimes average) explant time intervals, estimated to the nearest half-year. The mean percent failure was determined for each time point. Where detailed raw data were available (six articles[3,6,21,28,34,35]), explants were grouped into three major implant duration time periods of about 0 to 8 years (*early*), 9 to 16 years (*middle*), and 17 to 25 years (*late*). A maximum mean or average implant time point of 20 years was used for calculations (which, of course, included data beyond 20 years) because of the relatively small number of very long-term explants reported. For example, for the article by Peters et al.,[7] which presented four explant age groups, the two later groups (data to 26 years) were combined and plotted at an average age of 18.5 years for 28 explants, 18 of which (64%) had failed. Similarly, for the two most extensive recent studies, additional data for 798 explants[34] and 1619 explants[35] were kindly provided by the authors and older explants in each

study were combined into single mean age groups of less than 20 years. Such combinations of smaller groups of implants older than 20 years were made for five articles.[1,7,9,14,15] In the case of the five group data set of Robinson et al.,[1] numerical explant failure data were estimated from an enlarged copy of Robinson et al.'s Figure 1. The last two explant groups, covering a time period of 16 to 25 years, were combined into one group with an average age of 20 years. In another article by Peters et al., data were presented for different periods of manufacture and implant designs, designated generations 1 and 2.[15] Median implant times for these two groups were therefore used. The earliest time given by Reynolds et al.[25] was 8 years. Therefore, only middle and later time groups were plotted. However, for Cohen et al., it was possible to use three groups as presented in their article.[20]

Three relevant studies were included that unfortunately provided only information on the number of *patients* that had surgical revisions and ruptures rather than the number of individual SGBI implants that were removed.[12,14,23] These data points are designated with an asterisk on our failure versus time plot (Fig. 1). Because the number of explants in these reports was actually greater than two per patient due to multiple revisions (e.g., 2.3 explants/patient within 5 years for Gabriel et al.[12]), the total number of explants involved in our data base exceeds 8026. In the 1997 Gabriel report 24% (178 of 749 women) required at least one surgical revision due to complications within the first 5 years following initial SGBI surgery and ruptured breast implants were found for 43 of the 178 patients.[12] This is 24% failure for the 178 *patients* explanted. For Shoaib et al.[14] only data for *explanted patients* were reported (three with silicone injections and one accidentally ruptured were excluded), resulting in 57 of 96 patients with ruptures (59%). A third data point based on the number of patients rather than the number of explants was from Thomas et al.[23] in which 11 of 25 patients (44%) were found to have at least one ruptured implant at a mean implant time of 10.4 years.

The remaining studies provided results from which only one mean or average time point for percent failure was available, as stated in each article. For example, Duffy and Woods[30] presented results for 200 patients who received a total of 681 implants (3.4/patient) with surgical findings of 577 (85%) intact and 104 (15%) failed at a mean time of 49 months. Guidoin et al.[5] listed several age groups from which one implant time of 5.7 years was calculated (and plotted) at 5.5 years. Medot et al.[29] also provided several age groups from which a mean implant age of 10.7 years was calculated (plotted at 10.5 years). For the paper by Forsberg et al.[8] indicating 19 of 45 explants failed (42%) at a mean age of 9.8 years (plotted at 10 years), the abstract data were used because there appeared to be a conflicting numerical error in the text of the article. Malata et al.[13] reported 19 of 83 explants ruptured at a mean implant time of 7 years. Examination of 74 explants by Goldberg et al.[19] encompassed Dow Corning, Baxter/H-S, and Surgitek single-lumen SGBIs, and McGhan single- and double-lumen SGBIs. In this research 31 of 74 explants were found to be ruptured (42%) with a mean implant duration of 10 years.

The period of explant surgery covered by data from different articles that appeared to have been published by the same research group were compared to insure that no significant error could be attributed to redundant reporting of the same data (three cases, six articles). For example, Berg et al.[3] published results for prostheses removed from January 199[3] to October 1994, whereas the data presented by Caskey et al.[27] (apparently from the the same research group) presented results for implants removed during the period January 199[2] to November 1992 and was therefore not redundant.

Two articles used in this study were primarily concerned with the measurement of silicon concentrations in near and distant tissues surrounding explants,[11,16] and two examined the migration of silicone fluid through the capsule histologically.[21,22] Although they provided useful implant rupture results for explanted SGBIs, they also shed considerable light upon the extent to which silicone fluid is transported away from the local site of implant leakage or rupture.

Most authors (all except six) presented various reasons for revision surgery. From these articles, which often afforded rather qualitative information, it was estimated that about 60% of explants were from patients who were asymptomatic (but had serious health concerns) and/or had severe capsular contracture, 30% were from patients with various symptomatic complaints, and 10% had suspected ruptures.

Data Analysis and Curve Fit for Percent Failure Versus Implant Time

Several mathematical relationships were evaluated using SigmaStat 2.0 and SAS 6.12 to determine the best correlation between implant duration and percent failure. These included multiple order polynomial (first, second, and third order) and exponential nonlinear regression, and logit analysis.[31] Selection of the most meaningful analysis and curve fit was based upon the dual criteria of high statistical significance and most logical data curve fit. Primary considerations for the most logical curve fit were that the curve exhibit a 0% failure at the zero time point and not exceed 100% failure at any time. Equations and constraints for these analyses are presented in Table I. Data for three age groups spanning the entire data base (mean implant durations of 3.9, 10.2, and 18.9 years) were also subjected to statistical analysis (ANOVA) to compare the differences in percent failure as a function of implant duration.

RESULTS

Results obtained from regression analyses are summarized in Table II. On the basis of statistical and logical criteria, exponential regression, which satisfies both the zero time zero failure and 100% maximum limits and exhibits the highest r^2 (0.63) and correlation coefficient ($r = 0.79$) afforded the most satisfactory correlation of percent fail-

TABLE I. Mathematical Relationships Evaluated for Correlation of Implant Duration with Mean Percent Failure

Analysis	Equation	Constants	Constraints
First-order polynomial	$f = a + bt$	a = intercept b = slope (failure rate)	None
Second-order polynomial	$f = a + bt + ct^2$	a = intercept b & c = constants	None
Third-order polynomial	$f = a + bt + ct^2 + dt^3$	a = intercept b, c, & d = constants	None
Exponential	$f = a(1 - e^{-ct})$	a = asymptote c = constant	$a = 100\%$, $c > 0$
Logit analysis	$\log(f/1 - f) = a + bt$	a = intercept b = constant	None

For all equations, f is the percent failure and t is the mean implant duration.

with mean implant duration. A highly significant statistical difference ($p < 0.001$) in mean percent failure for three age groups (25.4% failure at 3.9 years, 45.2% at 10.2 years, and 71.6% at 18.9 years) was found by ANOVA. Pairwise multiple comparisons of individual groups also showed significant differences between all pairs (Bonferroni t test; $p < 0.05$).

Figure 1 is a master curve for the exponential regression based on the mean percent failure data points at different implant times. Open diamonds represent data for the 35 individual data sets and are presented with numerical reference labels. The mean value for percent failure at each time point is shown as a dark circle. Table III summarizes data for the number of explants, number failed, and percent failure at each time-point.

From this analysis, at any implant time, the percent failure of an SGBI may be calculated from the equation

$$f = 100(1 - e^{-0.07t}),$$

where f is the percent failure and t is the implant duration. The effect of weighting the percent failure values as a function of the number of explants at each time point in the data base was also evaluated but no significant deviation from the master curve presented in Figure 1 was observed. This may be attributed to the nature of the exponential equation with zero time/0% failure constraints. It is also noteworthy that the data base exhibits a fairly uniform numerical distribution of explanted SGBIs for the initial three 5-year time periods (n = 2035 for 0–5 years, n = 2560 for 5–10 years, n = 2332 for 10–15 years).

DISCUSSION

A growing number of SGBI studies now indicate that the prevalence of failure and other local complications is many times higher than suggested only a few years ago. Unfortunately, the consequences of these complications to women's health seem to have been almost entirely ignored in the wake of the overwhelming attention that has been focused on the "autoimmune disease" controversy. However, autoimmune disease is not the only important safety issue for these devices. Epidemiology and immunology studies and editorial articles that have been cited in support of SGBI safety (i.e., Gabriel et al.[57], Hennekens et al.[62], Angell[63], Connell[64]) have devoted almost no attention to the health consequences of the local complications of pain, capsular contracture, disfigurement, chronic inflammation, rupture, silicone migration, and frequent surgical revisions. Gabriel et al. acknowledged the gravity of these complications in their most recent article.[12] In this context, what is striking is the apparently cavalier attitude of those who have endorsed the "safety" of SGBIs while paying so little attention to the scientific basis for the inherent materials and design flaws in this prosthesis and the mental anguish and surgical risks that confront so many women who now realize that local complications can prove to be very serious. The large data base analysis of SGBI failure presented here was undertaken to provide a more comprehensive and reliable scientific basis for evaluating the likelihood of SGBI shell failure and additional surgery.

TABLE II. Regression and Curve Fit Analysis

Equation	Curve Fit	Correlation Coefficient	Intercept	Maximum	Statistical & Logical Correlation
First-order regression	r^2=0.59	0.77	14.6%	∞	No
Second-order regression	r^2=0.60	0.78	5.1%	77%	No
Third-order regression	r^2=0.60	0.78	1.0%	∞	No
Exponential regression	r^2=0.63	0.79	0%	100%	Yes
Logit analysis	p<0.0001	N/A	19.4%	100%	No

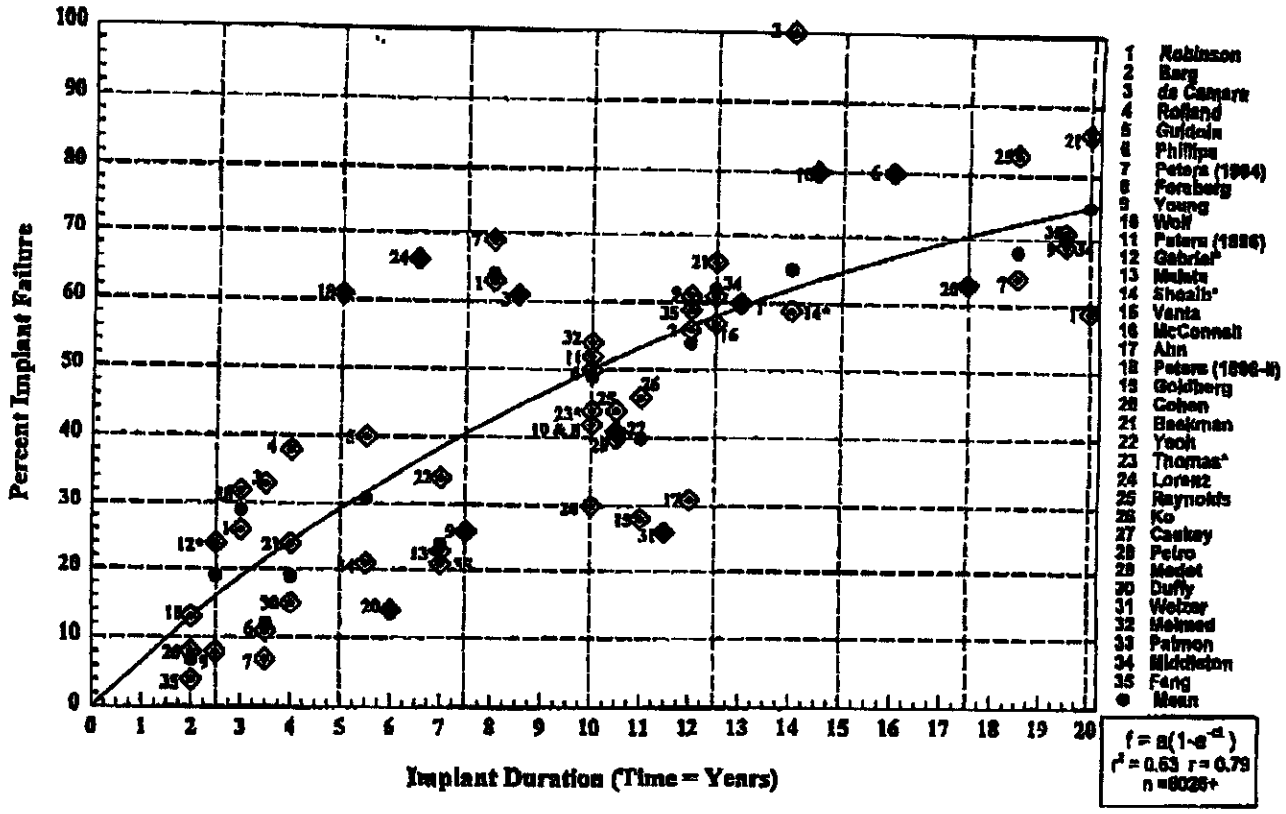

Figure 1 Percent failure vs. implant duration for silicone gel breast implants.

Prevalence and Rate of Failure for SGBI

To the best of our knowledge, the analysis of SGBI failure versus implant duration presented here is the most comprehensive available to date. It is unequivocal in assessing mechanical failure of SGBI shells because it is based entirely upon the examination of explanted breast implants. Explant results from 33 peer reviewed articles from a diversity of research groups plus an NAS-Institute of Medicine lecture by Feng[35] and studies from the authors' laboratory[19] are represented. These data encompass more than 8026 explanted SGBIs. They range in implant duration from 1 to 30 years and 3409 of 8026 (42%) exhibited silicone shell failure. Because failure versus time has been plotted, the true failure *rate* may be determined from the data or the slope of the tangent to the curve at various time intervals rather than just the *incidence or prevalence of failure* that have so often and so incorrectly been referred to as a *rate* in much of the literature and manufacturers' reports.

It may seem simplistic to emphasize the need for the correct use of the term rate here, but the problem is so widespread in the breast implant literature that it is evidently necessary to make it clear that a failure or rupture *rate* requires "time" as an associated parameter. Therefore, to properly use the term rate the time must be indicated [e.g., miles per hour (not miles) for a rate of speed and percent rupture per year (not percent rupture) for a rate of breast implant rupture].

The loss of structural integrity for a breast implant is a safety problem that can be just as important to a patient's health as the potential for autoimmune disease complications. Percent failure versus implant duration is presented in Figure 1 as an exponential regression plot of data for the more than 8026 explanted SGBIs in this study. This curve is similar to that published in a preliminary report from this laboratory for 1652 explants.[60] Figure 1 indicates 30% failure at 5 years of implant time, 50% at 10 years, and 70% at 17 years. From the data one may also estimate an SGBI *failure rate* at any time point or *average failure rates* for some interval of time (i.e., 6% per year during the first 5 years of implant life, 4% per year during the next 5 years, and 2.9% per year for years 10–17).

The prevalence and the rate of failure now indicated by the many explant studies cited here is so much higher than suggested only 5 to 6 years ago that one wonders if there was in fact any valid scientific basis for estimates presented to the FDA by manufacturers and some plastic surgeons during 1991 to 1993. Even now, some medical professionals (neither plastic surgeons nor biomedical device or biomaterials scientists) have published articles, books, and editorials on silicone breast implants (without peer review), making assertions about safety with almost total disregard for women's health problems caused by local complications. For example, Angell[65] stated in a reply to a 1996 letter on "Evaluating the Health Risks of Breast Implants" in the New England Journal

TABLE III. Data Base for Regression Analysis of Silicone Gel Breast Implants: Mean Percent Failure vs. Implant Duration (years)

Implant Duration	No. Failed	No. Explanted	Mean Percent Failure
2.0	35	475	7
2.5	50	261	19
3.0	14	49	29
3.5	8	66	12
4.0	187	967	19
5.0	133	217	61
5.5	180	579	31
6.0	8	58	14
6.5	80	121	66
7.0	171	705	24
7.5	21	82	26
8.0	146	228	64
8.5	14	23	61
10.0	377	764	49
10.5	103	253	41
11.0	95	237	40
11.5	42	160	26
12.0	429	799	54
12.5	285	459	62
13.0	183	307	60
14.0	73	112	65
14.5	4	5	80
16.0	8	10	80
17.5	45	72	63
18.5	23	34	68
19.5	588	840	70
20.0	107	143	75
Total	3409	8026	42

of Medicine by one author of this article (E.P.G.)[66] that "the rate [of rupture] is probably closer to 5 percent." Statements of this quality (*probably 5%?*; a rate?, an incidence?) with no apparent scientific basis are not uncommon. Ironically, such "junk science" has often been used by those who have themselves referred to literature they do not like as "inferior" or junk science. A further example is a 1998 article on SGBIs by Connell in the Journal of Women's Health.[64] Fully 10 pages were devoted to the "dire implications for women's health" caused by *litigation* and *junk science*. The "well known complications such as capsular contracture, rupture, and bleed," also termed by Connell as "well-known local side effects of breast implants," were virtually ignored with no consideration of the rate of failure, the frequency of related local complications, their consequences, or the need for frequent additional surgeries. These are examples of the limited or biased scientific perspective that still exists in some literature on SGBI safety and emphasizes the need for additional research and more quantitative analytical data.

Concerning the implications of local complications such as SGBI failure for increasing the potential for adverse local and systemic immune disease, an important question remains regarding the role, if any, that silicone fluid induced inflammatory processes may play. On this question, comments by Rose in a 1996 editorial in the journal Arthritis and Rheumatism[67] are helpful in clarifying *what we do not know*. He stated "Silicone breast implants give rise to inflammatory responses . . . cells involved in the inflammatory response are the same as those involved in immune reactions . . . Inflammation, however, does involve the production of cytokines, agents that may have profound local and systemic effects. . .the effects of chronic inflammation, and its relationship to immunity and autoimmunity, raise fundamental immunological issues that can profitably be explored." These are especially provocative observations because they come from an academic scientist who has published extensively on immunology and immune diseases and who appears to have considerable skepticism regarding the causal evidence available to date for silicone gel implant induced autoimmune disease.

Potential for Bias in SGBI Explant Data Meta-Analyses

Exponential regression analysis of explant results best satisfied the dual criteria of good statistical correlation and most logical curve fit for plotting an SGBI master curve for percent failure versus implant duration. The strong statistical correlation between the *percent failure* and *time* parameters substantially mitigates any significant influence of random events upon the outcome of this analysis. Nevertheless, it may be appropriate to question whether random events such as implant damage during insertion and/or explantation, noninvasive capsulotomies, various accidental events involving chest trauma, etc., could play a significant role in influencing the results of this study. If so, one would expect a much greater random scatter of data than was found and a much poorer statistical correlation of failure versus implant time. Considering the diversity of the clinical data coming from so many different research groups and including many different SGBI styles and manufacturers, the correlation found here was quite good.

One might also question the data base used here as biased or "selected" because it is derived from the evaluation of only explanted breast implants from women who exhibited local or systemic complications or anxiety severe enough to warrant undergoing additional surgery. However, the data cannot be regarded as selected by the authors of this article because they come from so many different peer reviewed articles that reported results for more than 8026 SGBI explants; these data, in fact, represent the only scientifically reliable data available (i.e., from examination of SGBIs at explant surgery).

A question that may be more reasonable to raise and more difficult to answer with complete certainty is how well these data for explanted breast implants reflect the condition of all SGBIs that remain implanted (which may be as many as 1.5 million). In this regard, there are good reasons to consider this

meta-analysis to be of considerable significance for evaluating the safety risks that confront the many women who still have SGBIs. A compelling argument is based on the fact that more than 25,000 surgeries have been performed each year during the past 5 to 6 years to remove SGBIs. During 1994 alone, 37,853 breast implant revisions[68] were reported but the condition of these explants went largely unreported. At least 150,000 implants have been removed during the past 6 years. It may therefore be reasonable to conclude that the results of this explant meta-analysis for more than 8026 explants (5.3% of 150,000) are, at the very least, representative of the failure prevalence for all explanted SGBIs. Furthermore, because the total number of explanted SGBIs has become so large, estimated to be 10% or more of all remaining implants, it may also be reasonable to conclude that the very large data base presented here points to a serious time-dependent failure problem for most remaining implants, especially for those SGBIs manufactured with weaker silicone elastomers and thinner shells. In this regard, it is instructive to note that Peters et al., who published several excellent explant studies, stated in a 1996 article that "about 80% of all second generation [1973–1987 manufacture] silicone-gel implants are currently ruptured or leaking."[18]

Mechanistic Aspects of SGBI Failure

The results from this study are strongly supported by reports indicating the substantial weakening of silicone elastomer shells by swelling with silicone fluid[45,46] and the time-dependent *in vivo* degradation of mechanical strength properties (i.e., reduced tensile and tear strength and reduced elasticity or strain to break) that have been published by many investigators. The measured decrease in the silicone shell strength properties has often been 40 to 50% or more within 1 to 5 years following SGBI implantation. For example, Phillips et al.[6] reported a decrease in shell tensile strength from about 10 to 5 MPa (from 1450 to 725 psi) within 3 to 4 years following primary implant surgery and then to 3–4 MPa (as low as about. 450 psi, a loss of almost 70% of tensile strength) after 7 years of implant time. Similarly, van Rappard et al.[50] indicated a 50% reduction in strength within 6 years of initial implantation. More recently, Brandon at al.[51] reported a large decrease in strength for SGBIs made with even the newer high performance (Silastic II) silicone shells, indicating that after 8 years of implant time there was a decrease of about 50% in tensile strength, a 30% decrease in elongation, and a 40% decrease in tear strength.

Our own exhaustive extraction studies with silicone gel from explants and unimplanted controls[46] are consistent with a 1979 Battelle Research Institute report[45] that revealed that silicone gels used in SGBIs are not true polymer gels at all but are in fact almost entirely composed of silicone fluid (85–95%) with only a minor amount (5–15%) of chemically crosslinked silicone gel. The composition of the so-called gel, the swelling of the shells with silicone fluid, and the degradation of the shell elastomer tensile and tear strengths are of fundamental importance to an understanding of SGBI failure. Our research[46] also confirmed that silicone shells for both controls and explants are normally swollen with as much as 15 to 20% silicone fluid. Tensile strengths and strain (elongation) to break for explants were reduced by 35 to 50%, and inner lumen shells for double-lumen explants were often too fragile to handle to even obtain tear strength test specimens.[53]

Such studies are persuasive in supporting the view that a primary mechanism for rupture must be the progressive (time dependent) cyclic mechanical stress induced creation and enlargement of tears in weakened silicone fluid swollen silicone elastomer shells at sites of folds and/or defects where stress is concentrated. A breast implant is after all a mechanical structural device that is subjected to continuous cycles of varying small and large stresses and strain deformations. To be properly engineered, breast implants should therefore have been designed using finite element analysis and cyclic stress fatigue testing (measuring stress vs. number of cycles to fail; i.e., *S/N* tests) as is normally done for critical automotive and aircraft parts and some medical devices, such as heart valves and one piece intraocular lens haptics. The materials selection and engineering design should have insured that the shell would remain stronger throughout the life of the breast implant than the most severe *S/N* failure stress limit that might be encountered in use. At the very least, the shells of each lot of the *final products* (the gel-filled, packaged, and sterilized breast implants) should have been routinely sampled and tested for mechanical properties to assure reproducible product manufacture. There is little evidence that even this final product testing was done for routine quality assurance by breast implant manufacturers.

Frequency of Additional Surgeries

In view of the foregoing discussion and the extensive literature concerning fibrous capsule contraction, pain, disfigurement, and patient anxiety, which are major indications for additional surgery, there is little need for further discussion here on these complications. A perceptive 1996 editorial by Melmed, a plastic surgeon, is noteworthy in that it affords a brief, thoughtful, and authoritative review of the subject.[69] However, the high frequency of multiple surgeries following primary SGBI implant surgery is of growing concern and deserves much more attention.

This study confirmed not only a remarkably high prevalence of SGBI failure and statistically significant direct correlation of failures with breast implant duration, but also the fact that additional surgeries are so frequently required within only a few years of primary implant surgery. Table III indicates 2672 revisions within a mean implant time of 6 years. This represents 33% of the total implant population in the study. It is a disturbing finding and is consistent with the report by Gabriel et al.[13] wherein 178 of 749 women (24%) required at least one additional surgery within 5 years of initial implant surgery with some requiring as many as four or five reoperations during this 5-year time period.

CONCLUSIONS

1. A statistically significant direct correlation of percent SGBI failure with increasing implant duration was evident from the data and a plot of percent failure versus implant duration afforded a *master curve* (Figure 1) from which the *prevalence* of failure, as well as the *rate* of failure, may be determined.
2. The *prevalence* and the *rate* of SGBI failure, based on data for more than 8026 explants, are far higher than suggested only a few years ago.[54,55]
3. Representative results for *SGBI* failure were found to be 30% at 5 years of implant time and 70% at 17 years.
4. The *rate* of failure was found to average 6% *per year* during the first 5 years following primary SGBI surgery, declining to an average *rate* of 4% *per year* during the next 5 years according to the exponential percent failure versus implant duration relationship.
5. The prevalence of multiple surgeries necessitated by capsular contracture, pain, disfigurement, various disease symptoms, implant failure, and patient anxiety is disturbingly high. At least 24% of patients required one or more additional surgeries within 5 years from one report[12] and 33% of implants required at least one additional surgery within a mean implant duration of 6 years based on the data from this study.
6. Because the silicone *gel* is actually constituted of 85 to 95% silicone fluid, which has been shown to migrate and to exhibit adverse toxicological and immune modulating (i.e., inflammation inducing) properties, more research is needed to better evaluate the likely relationship between the loss of SGBI shell integrity and various long-term local and systemic complications.
7. With so many revision surgeries required each year, more than 37,000 reported for 1994 alone,[68] it is disheartening that data on the condition of most explanted SGBIs have not been reported. Therefore, an important goal of this report is to encourage more widespread collection and publication of explant data for shell integrity and implant duration in the future.

During the 1991 and 1992 FDA Breast Implant Advisory Panel deliberations, the lack of data on the failure of SGBIs was noted.[70] The difficulty in providing adequate guidance to doctors and patients on complications such as implant failure without having meaningful clinical data was well recognized as was the fact that SGBIs would certainly not "last a lifetime." In the absence of such information, the intent of this study was to assemble the first large data base for SGBI failure analysis. The importance of improving the scope and reliability of such information for patient guidance and *informed consent* is qualitatively evident. A recent article by Collis and Sharpe[71] highlights this problem in a survey of cosmetic clinics in the United Kingdom. They concluded that "information available to the general public needs to be redressed by improving the quality of information available to them." A July 1998 Independent Review Group Report on SGBIs sponsored by the House of Commons in the United Kingdom also recommended that more research and more data are needed on the subject of SGBI rupture.[59] In addition to providing a basis for developing improved breast implants, it is therefore hoped that the results of this study will prove helpful to better assess the clinical status of patients who currently have silicone gel implants and afford more realistic risk and benefit guidance for those women contemplating cosmetic SGBI surgery.

Statistics consultations with J. S. Hartzel, Dept. of Statistics, University of Florida, are gratefully acknowledged.

Duplicates

REFERENCES

1. Robinson OG, Bradley EL, Wilson DS. Analysis of explanted silicone implants: a report of 300 patients. Ann Plast Surg 1995;34:1–7.
2. Berg WA, Caskey CI, Hamper UM, et al. Single- and double-lumen silicone breast implant integrity: prospective evaluation of MR and US criteria. Radiology 1995;197:45–52.
3. da Camara DL, Sheridan JM, Kammer BA. Rupture and aging of silicone gel breast implants. Plast Reconstr Surg 1995;91:828–834.
4. Rolland C, Guidoin R, Marceau D, Ledoux R. Nondestructive investigation of ninety-seven surgically excised mammary prostheses. J Biomed Mater Res 1989;23(Suppl. A3):285–298.
5. Guidoin R, Rolland C, King M. A non-destructive investigation to identify the failure mechanisms of 313 retrieved mammary prostheses. Proc Soc Biomater 1992;48.
6. Phillips JW, de Camara DL, Lockwood MD, Grebner CC. Strength of silicone breast implants. Plast Reconstr Surg 1996;97:1215–1225.
7. Peters W, Keystone E, Smith D. Factors affecting the rupture of silicone-gel breast implants. Ann Plast Surg 1994;32:449–451.
8. Forsberg F, Conant EF, Russell KM, Moore JH. Quantitative ultrasonic diagnosis of silicone breast implant rupture: an *in vitro* feasibility study. Ultrasound Med Biol 1996;22:53–60.
9. Young VL, Brandon HJ, Jarina KL, Wolf C, Schorr MW. Failure characteristics of explanted breast implants. Proc Soc Biomater 1996;306.
10. Wolf CJ, Brandon HJ, Young VL, Jarina KL, Srivastava AP. Chemical, physical and mechanical analysis of explanted breast implants. Curr Topics Microbiol Immunol 1996;210:25–37.
11. Peters W, Smith D, Lagowski S, McHugh A, MacDonald P, Baines C. Silicone and silicone levels in patients with silicone implants. Curr Topics Microbiol Immunol 1996;210:39–48.
12. Gabriel SE, Woods JE, O'Fallon WM, Beard CM, Kurland LT, Melton LH. Complications leading to surgery after breast implantation. N Engl J Med 1997;336:677–682.
13. Malta CM, Varma S, Scott M, Liston JC, Sharpe DT. Silicone breast implant rupture: common/serious complication. Med Progress Technol 1994;20:251–260.
14. Shoaib BO, Patten BM, Calkins DS. Adjuvant breast disease: an evaluation of 100 symptomatic women with breast implants or silicone fluid injections. Kelo J Med 1994;43:79–87.
15. Venta LA, Salomon CG, Flisak ME, Venta ER, Izquierdo R, Angelats J. Sonographic signs of breast implant rupture. Am J Roentgenol 1996;166:1413–1419.
16. McConnell JP, Moyer TP, Nixon DE, et al. Determination of silicon in breast and capsular tissue from patients with breast implants performed by inductively coupled plasma emission spectroscopy—comparison with tissue histology. Am J Clin Pathol 1997;107:236–246.

17. Ahn CY, Ko CY, Wagar EA, Wong RS, Shaw WW. Microbial evaluation: 139 implants removed from symptomatic patients. Plast Reconstr Surg 1996;98:1225–1229.
18. Peters W, Smith D, Lugowski S. Failure properties of 352 explanted silicone-gel breast implants. Can J Plast Surg 1996; 4:55–59.
19. Goldberg EP, Maroma JS, Widenhouse CW, Amery DP, Martin PJ. Data from ongoing University of Florida Biomaterials Center research.
20. Cohen BE, Biggs TM, Cronin ED, Collins DR. Assessment and longevity of the silicone gel breast implant. Plast Reconstr Surg 1997;99:1597–1601.
21. Beekman WH, Feitz R, Hage JJ, Mulder JW. Life span of silicone gel-filled mammary prostheses. Plast Reconstr Surg 1997;100:1723–1726.
22. Yeoh G, Russell P, Jenkins E. Spectrum of histological changes reactive to prosthetic breast implants: a clinopathological study of 84 patients. Pathology 1996;28:232– 235.
23. Thomas WO, Harper LL, Wong SW, et al. Explantation of silicone breast implants. Am Surg 1997;63:421–429.
24. Lorenz R, Stark GB, Hedde JP. Significance of US for detection of complications after silicone implant for breast augmentation or reconstruction. Fortschr Roentgenstr 1997;166:233–237.
25. Reynolds HR, Buckwalter KA, Jackson VP, Siwy BK, Alexander SG. Comparison of mammography, sonography and magnetic resonance imaging in the detection of silicone-gel breast implant rupture. Ann Plast Surg 1994;33:247–257.
26. Ko CY, Ahn CY, Ko J, Chopra W, Shaw WW. Capsular synovial metaplasia as a common response to both textured and smooth implants. Plast Reconstr Surg 1996;97:1427–1433.
27. Caskey CI, Berg WA, Anderson ND, Shath S, Chang BW, Hamper UM. Breast implant rupture: diagnosis with US. Radiology 1994;190:819–823.
28. Petro JA, Klein SA, Nizzi Z, Salzberg CA, Byrne D. Evaluation of ultrasound as a tool in the follow-up of patients with breast implants: a preliminary prospective study. Ann Plast Surg 1994; 32:580–587.
29. Medot M, Landis GH, McGregor CE, et al. Effects of capsular contracture on ultrasonic screening for silicone gel breast implant rupture. Ann Plast Surg 1997;39:337–341.
30. Duffy MJ, Woods JE. Health risks of failed silicone gel breast implants: a 30-year clinical experience. Plast Reconstr Surg 1994;94:295–299.
31. Weizer G, Malone RS, Netscher DT, Walker LE, Thornby J. Utility of magnetic resonance imaging and ultrasound in diagnosing breast implant rupture. Ann Plast Surg 1995;34:352–361.
32. Malmed EP. A review of explantation in 240 symptomatic women: a description of explantation and capsulectomy with reconstruction using a periareolar technique. Plast Reconstr Surg 1998;101:1364–1373.
33. Palmon LU, Foshager M, Parantainen H, Everson LI, Cunningham B. Rupture or intact: what can linear echoes within silicone breast implants tell us? Am J Roentgenol 1997;168:1595–1598.
34. Middleton MS. Magnetic resonance evaluation of breast implants and soft-tissue silicone. Topics Magn Reson Imaging 1998;9:92–137.
35. Reng LI. Significant findings on breast implant rupture from a seven year study of 1619 explants. Presented at the NAS-Institute of Medicine Workshop, July 22, 1998, Washington, DC, with additional data from personal communications.
36. Goldberg EP. Silicone breast implant safety: physical, chemical, and biological problems. Plast Reconstr Surg 1997;99:258–260.
37. Carpaneda CA. Inflammatory reaction and capsular contracture around smooth silicone implants. Aesth Plast Surg 1997;21: 110–114.
38. Ricci J, Alexander H, Steiner G, et al. Status of retrieved breast implants and their surrounding tissues. Proc Soc Biomater 1995 327.
39. Ellenbogen R, Rubin L. Injectable fluid silicone therapy: human morbidity and mortality. J Am Med Assoc 1975;234:308–309
40. Mukai N, Lee PF, Oguri M, Schepens CL. A long term evaluation of silicone retinopathy in monkeys. Can J Ophthal 1975 10:391– 402.
41. Spielvogel DE, Robinson RJ. Metabolism of octamethylcyclotetrasiloxane in the monkey. Dow Corning report 5265 Midland, MI: Dow Corning. 1980.
42. Malczewski RM, Varaprath S, Bolger C. An assessment of the $MeSiO_{3/2}$ content of feces and urine obtained 24 hours after the oral administration of D_4 to rats. Dow Corning report 1362-19. Midland, MI: Dow Corning. 1988.
43. Varaprath S, Salyers KL, Plotzke KP. Non-regulated study: identification of major metabolites of octamethylcyclotetrasiloxane (D_4) in rat urine. Dow Corning report 1997-10000-43454. Midland, MI: Dow Corning. 1997.
44. McCarty RN, Speier JL. Chemical research progress report 2964: on pharmacologically active substance believed to be present in DC 555 fluid. Midland, MI: Dow Corning. 1966.
45. Thompson RM, Howard CC, Brewer EJ, DeRoos FL, Hattery GR, Leininger R. Compositional analysis of silicone prostheses. Battelle report 233-77-5038 Task 6 to FDA. Battelle Institute, Columbus, OH. 1979.
46. Maroma JS, Goldberg EP. Extraction studies with breast implant silicone elastomer shells and "gels" indicate very high concentrations of soluble uncross-linked silicones. Proc Soc Biomater 1997;332.
47. Menikian M. Long term physical property evaluation of Silastic mammary prosthesis. Dow Corning report. Midland, MI: Dow Corning. 1971.
48. Peters S. Physical properties versus time for Silastic II and Standard prosthesis. Dow Corning report. Hemlock, MI: Dow Corning. 1981.
49. Greenwald DP, Randolph M, May JW. Mechanical analysis of explanted silicone breast implants. Plast Reconstr Surg 1996; 98:269–272.
50. van Rappard JH, Sonneveld GJ, van Twisk R, Borghouts JMHM. Pressure resistance of breast implants as a function of implantation time. Plast Reconstr Surg 1993;21:566–569.
51. Brandon H, Young VL, Wolf C, Jerina KL. Mechanical analysis of explanted breast implants. Proc Soc Biomater 1996;302.
52. Brandon HJ, Young VL, Jerina KL, Wolf CJ. Assessment of long term aging of silicone gel breast implants. Proc Soc Biomater 1998:369.
53. Maroma JS, Amery DP, Widenhouse CW, Martin PJ, Goldberg EP. Degradation of physical properties of silicone gel breast implants and high rates of implant failures. Proc Soc Biomater 1998;374.
54. Council on Scientific Affairs, American Medical Association. Silicone gel breast implants. J Am Med Assoc 1993;270:2602–2606.
55. Kessler DA, Merkatz RB, Schapiro R. A call for higher standards for breast implants. J Am Med Assoc 1993;270:2607–2608.
56. Hakelius L, Ohlsen L. Tendency to capsular contracture around smooth and textured gel-filled silicone mammary implants: a 5 year follow-up. Plast Reconstr Surg 1997;100:1566–1569.
57. Gabriel SE, O'Fallon WM, Kurland LT, Beard CM, Woods JE. Melton JL. Risk of connective-tissue diseases and other disorders after breast implantation. N Engl J Med 1994;330:1697–1702.
58. Brown SL, Silverman BG, Berg WA. Rupture of silicone-gel breast implants: causes, sequelae, and diagnosis. Lancet 1997: 350:1531–1537.
59. Sturrock RD, et al. Silicone gel breast implants: the report of the Independent Review Group. July 1998 report to the Chief Medical Officer requested by the UK Minister of Health.

60. Goldberg EP, Widenhouse C, Marotta J, Martin P. Failure of silicone gel breast implants: analysis of literature data for 1652 explanted prostheses. Plast Reconstr Surg 1997;100: 281–283.
61. Hartzel, JS. Personal communication.
62. Hennekens CH, Lee IM, Cook NR, et al. Self-reported breast implants and connective tissue diseases in female health professionals: a retrospective cohort study. J Am Med Assoc 1996; 275:616–621.
63. Angell M. Evaluating the health risks of breast implants: the interplay of medical science, the law and public opinion. N Engl J Med 1996;334:1513–1518.
64. Connell EB. The exploitation of autoimmune disease: breast implant litigation and its dire implications for women's health. J Women's Health 1998;7:329–338.
65. Angell M. Evaluating the health risks of breast implants: reply. N Engl J Med 1996;335:1156.
66. Goldberg EP. Evaluating the health risks of breast implants. N Engl J Med 1996;335:1154.
67. Rose NR. The silicone breast implant controversy: the other courtroom. J Arthritis Rheum 1996;39(10):1615–1618.
68. Top 12 plastic/reconstructive surgery procedures in the U.S. Med Pro Month Med Data Int 1996;July/August:166 (37 853 breast implant removals in 1994; from Am Soc Plast Reconstr Surg data).
69. Melmed EP. Silicone Implants: aesthetic triumph or surgical disaster? Plast Reconstr Surg 1996;98:1071– 1073.
70. Deliberations of the 1991 to 1992 FDA Advisory Panel on Breast Implants. p 79–82.
71. Collis N, Sharpe DT. Breast implants: a survey of cosmetic clinics. Br J Plast Surg 1998;51:311–312.

EXHIBIT 2

NOTICE:
THIS MATERIAL MAY BE
PROTECTED BY COPYRIGHT
LAW (TITLE 17 U.S. CODE)

Silicone Gel Breast Implant Failure: Evaluation of Properties of Shells and Gels for Explanted Prostheses and Meta-analysis of Literature Rupture Data

James S. Marotta, PhD
Eugene P. Goldberg, PhD
Mutaz B. Habal, MD, FRCSC, FACS
Drew P. Amery, PhD
Paul J. Martin, MS
Daniel J. Urbaniak, MS
Christopher W. Widenhouse, PhD

After 30 years of clinical use, the 1992 Food and Drug Administration moratorium on silicone gel breast implants (SGBIs) resulted from a paucity of scientific data concerning their safety. The frequency of rupture and reoperative procedures was not known, nor were reliable data available for changes in the physical properties of shells and the composition of gels that might lead to SGBI failure. For this reason the authors conducted large-cohort meta-analyses of failure data for SGBIs based on numerous literature reports and also investigated systematically shell and gel properties from explanted SGBIs. They report their failure analysis data for more than 9,770 SGBIs (an update of an earlier study of more than 8,000 implants) as well an examination of the properties of shells and gels for 74 explanted SGBIs that ranged in age from 2 to 19 years (mean implanted age, 9.9 years). The explants tested were from several different manufacturers. For the modest-size explant cohort that was tested, 31 of 74 implants (42%) were found to be ruptured (some extensively). Even many ruptured shells were so weakened that only 51 shells had sufficient strength to enable preparation of samples for testing of mechanical properties and for analysis of composition by solvent extraction. Shells were found to contain 15 to 25% of extractable silicone. Exhaustive extraction of gels showed that they actually contained very little crosslinked silicone—85 to 95% being extractable soluble silicone fluid. Tensile and tear strengths of explanted silicone elastomer shells were lower than unimplanted prostheses and were generally well below reported manufacturers' values. This updated large-cohort failure analysis continues to show that shell rupture is related directly to implant duration (e.g., from analysis of variance statistics, 26% failure at 3.9 years, 47% at 10.3 years, 69% at 17.8 years; $p \leq 0.001$). However, for the relatively small series of explants for which physical property data are reported, no significant correlation was observed between implant duration and the degradation of implant strength. It therefore appears most reasonable to conclude that after early weakening of shells as a result of swelling of the shell elastomer by diffusion of silicone oil from the gel, SGBI failure can occur in a time-dependent manner as a result of continuing implant motion and cyclic stresses that are exacerbated by stress concentration at thin areas, defects, and folds in the shells.

Marotta JS, Goldberg EP, Habal MB, Amery DP, Martin PJ, Urbaniak DJ, Widenhouse CW. Silicone gel breast implant failure: evaluation of properties of shells and gels for explanted prostheses and meta-analysis of literature rupture data. Ann Plast Surg 2002;49:227–247

From the Biomaterials Center, Department of Materials Science and Engineering, University of Florida, Gainesville; and the Tampa Bay Plastic and Craniofacial Surgery Center, Tampa, FL.

Received Aug 1, 2001, and in revised form Dec 18, 2001. Accepted for publication Dec 18, 2001.

Address correspondence and reprint requests to Dr Goldberg, Biomaterials Center, 317MAE, MSE Department, PO Box 116400, University of Florida, Gainesville, FL 32611.

There were numerous reports of perceived and suspected clinical problems associated with the use of silicone gel breast implants (SGBIs) during the 30 years of use before the 1992 Food and Drug Administration (FDA) moratorium. Adequate, scientifically sound physical and chemical property data and large-cohort prospective or retrospective clinical studies were lacking, thereby precipitating the withdrawal of these valuable cosmetic implants from general use in the United States.[1,2] As a result, there has been a large increase in research concerning the behavior of SGBIs since 1992 to provide a basis for more realistic risk–benefit assessments by plastic surgeons and patients. It is worthwhile to emphasize that such research has benefited most from the close collaboration of biomaterials scientists and surgeons. In this context, it was the objective of our joint physical science/clinical research study to contribute helpful new information.

Copyright © 2002 by Lippincott Williams & Wilkins, Inc.

J0068684

Annals of Plastic Surgery Volume 49 / Number 3 / September 2002

An SGBI is a unique prosthesis in that the silicone elastomer shell was intended to contain a so-called silicone "gel," which was in fact not really a gel but was predominantly (85–95%) uncrosslinked silicone. From basic polymer science principles, it should therefore have been obvious that the fluid in such "gel" would: 1) diffuse readily into and through the elastomer shell (continuously releasing silicone into the surrounding tissues; the so-called "bleed"); and 2) that the swelling of the shell by silicone fluid from the "gel" would affect adversely the mechanical properties of the shell.

We previously published the first large-cohort retrospective failure analysis for explanted SGBIs (for more than 8,000 explants from 35 studies) that showed a highly significant statistical correlation between implant duration and elastomer shell failure (25%% within 3.9 years and 71.6% at 18.9 years).[3] A high frequency of reoperative procedures (33% within 6 years) was also found.[3] That report is updated here, showing little change in the statistical results. This analysis now encompasses more than 9,770 implants from 42 different studies. However, one should note that this analysis does not take into account the changes in implant design that have occurred over the years and the likely greater predisposition for failure for certain designs such as the so-called second-generation implants made with thinner shells and more fluid gels. To understand better the high rate of failure observed from this explant failure analysis, as well as complications that may necessitate additional surgery, it is therefore important to obtain more data concerning the mechanical properties and composition of explanted breast implant components from different periods of manufacture. This was one objective of the current study.

Early reports of mechanical testing of SGBIs, by plastic surgeons rather than manufacturers, involved experimental compression of the entire prosthesis to determine the breaking strength or "breaking pressure."[4,5] These tests were intended primarily to model the compressive forces associated with "closed capsulotomy"—a technique that had been used commonly to break up the fibrous scar tissue responsible for capsular contracture. This stressful mechanical procedure was designed to rupture the fibrous capsule noninvasively. However, there was concern that the prostheses might also be ruptured by the applied stresses. These early studies noted that there was considerable variation among the prostheses tested, and even marked lot-to-lot variations from the same manufacturer. Most important, low breaking strengths for explanted prostheses were measured compared with new unimplanted controls.[4,5] The technique of manual manipulation for closed capsulotomy was generally abandoned during the late 1980s, in large part because of concerns that implant rupture might occur during this procedure.

Only in recent years have several studies compared manufacturer data[6] and the mechanical properties of shells determined from explanted and unimplanted control prostheses.[7–11] It now also appears that shells from newly manufactured unimplanted silicone gel-filled prostheses were not tested routinely for mechanical properties by manufacturers for engineering design assurance and quality control—a normal quality assurance procedure for most medical devices. Various investigators have found consistently that the mechanical properties of explanted prostheses were considerably poorer than unimplanted controls and data reported by manufacturers.[6] Phillips and colleagues[10] concluded that there was a correlation between the strength of explanted shells and the implantation time, suggesting a degradation of silicone shell mechanical properties with time. Brandon and associates[7] tested the mechanical properties of shell samples after extraction of silicone fluid from the shell. Their data indicated that once the silicone oil that swells the shells was extracted, the mechanical properties returned to the original strength values. They therefore suggested that no chemical degradation of the elastomer shell occurred for their samples. Their results confirmed the decrease in strength resulting from swelling of the shells with silicone oil. Unfortunately, patients are always exposed to implants with oil-swollen shells that therefore have impaired mechanical properties. This degradation in mechanical properties, resulting from swelling of the implant shell with oil, has been suggested as a notable cause of the high incidence of rupture for SGBI implants.[3,8,12]

There were two primary objectives of the current study. One was to update to 9,774 explants

J0068685

Table 1. Fifty-one Breast Implants Examined

N	Implant Manufacturer	Lumen	Mean Age, yr	Implant Age Range, yr	Types of Explants
10	Dow Corning	Single	9	5–15	6 Silastic II and 4 standard gel
20	McGhan	Double	12	8–16	20 Style 76
14	Surgitek	Single	7	4–15.25	6 Meme, 4 Replicon, 2 SCL low bleed, 2 standard gel
4	Surgitek	Double	5	4.75–5.5	4 SCL low bleed
3	Other	Single	18	16.5–19	1 Heyer-Shulte and 2 Cronin Seamless

SCL = strong shell, cohesive gel, low bleed.

our previously reported SGBI meta-analysis of failure for 8,000 explants. A second objective was to measure the physical properties of SGBIs retrieved from patients after various times of implantation and compare these results with reported properties of unimplanted prostheses. These property changes are important to our understanding the ability of SGBIs to withstand the forces to which they are subjected during implant life (i.e., the cyclic stresses that occur in vivo). Of particular interest were the mechanical properties of the silicone elastomer shells, the variations in shell thickness, and the amount of uncrosslinked soluble silicone in both the gels and shells.

Materials and Methods

Physical Properties and Extraction of Uncrosslinked Silicone

SGBI Explant Samples

The 74 gel implants were received in containers after explantation by several different surgeons. They were handled gently with powder-free gloves, removed to a stainless steel pan in a germ-free class II laminar-flow hood, and were examined carefully by at least two investigators. Visual and tactile characteristics, and the integrity of the prostheses were observed and photographed. From these explants, 51 that were found to be suitable for testing (i.e., not too weak to be handled) were sterilized using ethylene oxide gas sterilization to ensure safety during further handling. Sterilization was similar to the original manufacturers' specification using an ethylene oxide gas sterilization cycle of 2 hours at 130°F followed by aeration for 12 days at 120°F. The explants excluded (N = 23) were generally so fragile or so grossly ruptured that inadequate samples for testing could be prepared. Of the 51 implants tested, 31 were ruptured.

Sample Preparation

The 51 explants were sectioned as indicated later and were evaluated by extraction and by tensile and tear testing (Table 1). Implants were from four different manufacturers and included both single- and double-lumen explants. In addition, one unimplanted Silastic-II single-lumen breast implant, which was probably manufactured during the late 1980s and was therefore probably more than 10 years old, was tested as an unimplanted control. In the case of double-lumen implants, samples were cut from both inner and outer shells for testing. Surgical scissors were used to cut rectangular samples from the implant shells. First, three large rectangular samples (9 × 2.5 cm) were cut from the posterior side of the implant for tear test specimens. Implant patches were removed. Then, five smaller samples (5 × 1 cm) were cut for the tensile specimens. Gels were transferred to labeled containers. Two square samples (2 × 2 cm) of shells were cut for extraction analysis. The remaining pieces of shells were retained.

Mechanical Property Measurements

Tensile strength (psi), tear strength (pounds per inch), and percent elongation at break were determined. Adherent gel was removed from the shell samples by gentle wiping with lint-free tissue, and thickness measurements were made for each sample (at five different areas), measured to 0.0001 in using a pressure-sensitive micrometer (Starrett). To ensure that test specimens did not slip out of the Instron tensile machine test grips, any residual gel was cleaned from the

J0068686

Annals of Plastic Surgery Volume 49 / Number 3 / September 2002

sample ends using chloroform-soaked tissue paper. In addition, masking tape strips were attached to these ends of the tensile specimens.

The tensile strength of five samples from each shell was measured on a model 1122 Instron machine using the procedures described in ASTM D412-92.[13] Samples were cut using an ASTM D638M-certified type M-III dog-bone die. Testing was conducted at room temperature using roller grips with a 200-lb load cell (full scale load, 5 lb). A strain rate of 20 in per minute was used, and results for five specimens were averaged for each shell. Data are reported for the tensile strength (psi) and strain to break (percent elongation) for each shell tested.

The tear strength for each shell was measured using the "type B with nick for silicone" method as defined in ASTM D624-91.[14] ASTM B-type tear specimens were cut using a certified die. When feasible, three tear test samples were cut from each shell. However, many of the inner lumen shells of McGhan double-lumen implants were too fragile to handle and tore into pieces too small to test. All tear testing was conducted using the Instron machine at room temperature with pneumatic grips (1 cm^2 grip area and a grip pressure of 50 psi), conducted at 20 inches per minute with data reported as pounds per inch.

Solvent Extraction Tests

Complete solvent extraction of shell and gel samples was performed in a glass Soxhlet apparatus. Shell elastomer samples were wiped clean gently with a lint-free tissue to remove any superficial gel. Exhaustive (complete) extraction of "gel" samples involved adding 3 to 4 g of gel (weighed to 0.0001 g) to a cellulose extraction thimble and then placing an additional thimble on top of the first to create a sealed extraction thimble. This ensured that no gel would float out of the thimble during the extraction process. Extraction was performed using chloroform and was concluded when no further weight loss was detected for each sample (usually 3 days for implant shells and 14 days for gels). The resulting final weight loss values represent the amount of soluble (uncrosslinked) silicone that was present in elastomer shells and the gels.

Meta-analysis of SGBI Rupture Literature for 9,774 SGBI Explants

Also presented is an update of the earlier meta-analysis by Marotta and colleagues[3] for SGBI failure. That analysis encompassed 8,026 gel implants and was based on 35 studies reporting results from examinations of explanted prostheses. Now, from 42 different studies reporting data for 9,774 explanted SGBIs, we have applied the same statistical analyses that were described in detail in our 1999 study[3] (exponential regression and analysis of variance [ANOVA]). One result of this analysis is a small improvement in the statistical correlation of failure vs. time for the exponential regression curve, with $r = 0.68$ and $r^2 = 0.83$ (compared with 0.63 and 0.79 for the previous smaller database).

The regression analysis results are consistent with ANOVA comparison of three different implant age groups: 26% failure at 3.9 years, 47% at 10.3 years, and 69% at 17.8 years ($p \leq 0.001$).

Discussion

As early as 1971, implant manufacturers had data showing that filling silicone implant shells with gel would allow oil from the gel to swell the implant shell and reduce drastically shell mechanical strength properties.[15] This deterioration in mechanical strength properties clearly had the potential to influence greatly the ultimate performance of these devices. Despite earlier adverse experiences, during the 1980s some manufacturers produced gel implants with thinner shells and gels with very high uncrosslinked silicone oil content. Such changes were intended to provide a more natural aesthetic quality. However, the thin shells (0.003–0.010 in thick) were weak—a design problem that was exacerbated by two- to threefold variations in individual shell thickness. In this regard, there appears to have been little engineering design and development for shells to define the minimum strength required to ensure prolonged, safe performance of SGBIs.

Attempts to slow the "bleed" and the swelling of shells with internal phenyl or fluorocarbon-modified silicone barrier layer coatings resulted in the introduction of so-called low bleed shells

J0068687

during the 1980s. However, there was little information in the literature on the adhesion of these coatings to the shells, their uniformity, and their long-term effectiveness. Because the viscoelastic properties of the barrier coatings differed from the normal polydimethylsiloxane elastomer shell substrates, crazing, cracking, and delamination of the barrier coatings under the cyclic stress conditions of use may be possible with possible changes in barrier properties. The potential for a decrease in barrier properties is consistent with our extraction data, which showed high concentrations of silicone oil even in explanted barrier shell Silastic-II implants that were removed surgically after 5 years or longer.

Evaluation of Silicone Gel Implant Properties

The structural integrity of the 74 SGBI explants examined in this study ranged from *intact* with no visible shell defects, to those with *ruptures or tears* of various dimensions, to shells that were almost completely *obliterated*, in which few if any discrete pieces could be found. Implant duration ranged from 2 to 19 years (mean implant age, 9.9 years). The appearance, feel, and composition of the gels was also quite variable. Of the 10 smooth-wall single-lumen Dow Corning explants, 6 were Silastic-II and 4 were older standard gel filled. All 20 smooth-wall McGhan explants were style 76 double-lumen gel/saline prostheses that had been implanted during the early 1980s. For the Surgitek explants, 4 were smooth-wall, double-lumen gel/saline prostheses and 14 were single-lumen gel filled. Of these, 6 were Meme-MP urethane coated, 4 were Replicon urethane coated, and 4 were smooth-wall SGBI prostheses. No evidence of the urethane coatings could be found on the outer surfaces of the urethane explants. They had a rough textured surface appearance. On close examination, the Meme-MP shells were found to be opaque with a microscopic hexagonal foam imprint. The Replicon shells were clear with the appearance of a second clear layer of silicone on the outer surface of the shells (Figs 1 and 2).

The shell mechanical properties measured were tensile strength (psi), tear strength (pounds per inch), and percent elongation at break, and are presented in separate figures (Figs 3–7) according to manufacturer and type of explant. The

Fig 1. (A, B) Electron micrographs of Surgitek Meme-MP shell outer surface. No urethane coating is present, but the microscopic imprint is visible (original magnification ×20 [A] and ×100 [B] before reduction).

mean and standard deviations of mechanical property data for each explant are plotted. Also plotted are the reported values for these unimplanted silicone breast implants. Tensile and tear strength were generally found to be degraded from published values for unimplanted prostheses, and were well below the manufacturers' values for silicone gel-filled shells (Table 2). The pattern of tear was characterized by formation of a lip at the site of initiation followed by propagation across the sample. In the series of explants reported, no correlation was found between implant duration and deterioration of implant mechanical properties. Shell thickness varied considerably between implants, as well as within each implant shell. Values ranged from 0.0055 to 0.0236 in.

J0068688

Annals of Plastic Surgery Volume 49 / Number 3 / September 2002

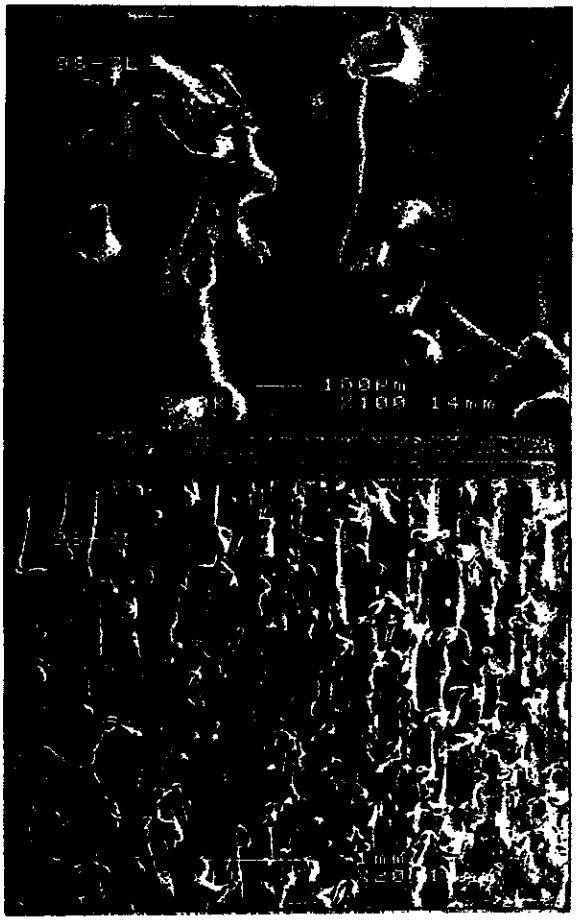

Fig 2. (A, B) Electron micrographs of Surgitek Replicon shell outer surface. No urethane coating is present, but a clear adhesive is visible on the surface of the explant shell (original magnification ×20 [B] and ×100 [A] before reduction).

Silicone Shell Mechanical Properties

The mechanical properties of Dow Corning single-lumen prostheses are presented in Figure 3. Results for individual implants are plotted vs. implant age, with Silastic-II implants on the left of the solid black bar and the four older, standard gel-filled implants on the right. Data for a new unimplanted Silastic-II single-lumen gel-filled implant are shown as the year 0 control. Values for the control implant are in close agreement with results reported in 1986 by Morey and North.[6]

Tensile strength values for explanted Silastic-II prostheses averaged 42% lower than unimplanted values. Tear strength and percent elongation for the Silastic-II explants were also both lower by an average of 26%. Tensile and elongation values for the standard gel-filled explants were similar to values reported in 1986, but the tear strengths were significantly lower (−48%) than the previously reported values. It should be noted that it is unclear how long the standard unimplanted Dow Corning implants had been sitting on the shelf before the results reported in 1986 by Morey and North[6] were measured.

Figure 4 documents results for the smooth-wall McGhan double-lumen gel/saline protheses, plotted as a function of implant age. Also plotted are dotted lines that represent the reported data for unimplanted McGhan Intrashiel prostheses in 1986. No significant difference was found in the mechanical properties comparing the inner and outer lumens. Tensile strength and elongation values were lower by an average of 35% and 27% respectively when compared with reported data. Tear strength could not be determined for some inner shells because they were so fragile. During removal of gel, these shells often broke into pieces too small for tear specimens. Tear strength was found to be greatly degraded for these shells when measurements were possible—an average of 82% lower than the reported values (22 lb per inch vs. 125 lb per inch).

The mechanical properties of smooth-wall Surgitek SCL (strong shell, cohesive gel, low bleed) double-lumen gel/saline prostheses are plotted in Figure 5. Mechanical properties for unimplanted SCL prostheses have been published[8] and are presented as a dotted line, but tear strength was not reported. Tensile strength values decreased an average of 40%, and percent elongation was 44% lower. No difference was found between the mechanical properties of inner and outer shells from the same implants.

Data from polyurethane foam-coated Surgitek single-lumen explants are presented in Figure 6. Surgitek Meme-MP-coated prostheses are plotted on the left side of the solid black bar and Replicon explants are shown on the right side of the bar. Also presented for comparison are the reported values for uncoated Surgitek shells. Tear strength values for the Meme-MP explants were extremely low—an average of 18 lb per inch—indicating a dramatic weakening of the shell. Replicon shells also showed signs of delamination during tear testing, which may have been the

J0068689

Table 2. Reported Mechanical Properties of Unimplanted Silicone Breast Implants

Implant Type	Tensile Strength, psi	Elongation, %	Tear Strength, lb/in	Reference
Dow Corning, standard gel	1,050	610	195	Morey and North 1986[6]
Dow Corning, Silastic II	1,675	1,110	225	Morey and North 1986[6]
Mentor Corp./Heyer–Schulte	1,350	600	135	Morey and North 1986[6]
McGhan, Intrashiel	1,050	600	125	Morey and North 1986[6]
Surgitek, standard gel	950	600	180	Morey and North 1986[6]
Surgitek, SCL low bleed	1,400	1,060	N/A	Lockwood, 1995[8]

SCL = strong shell, cohesive gel, low bleed; N/A = not applicable.

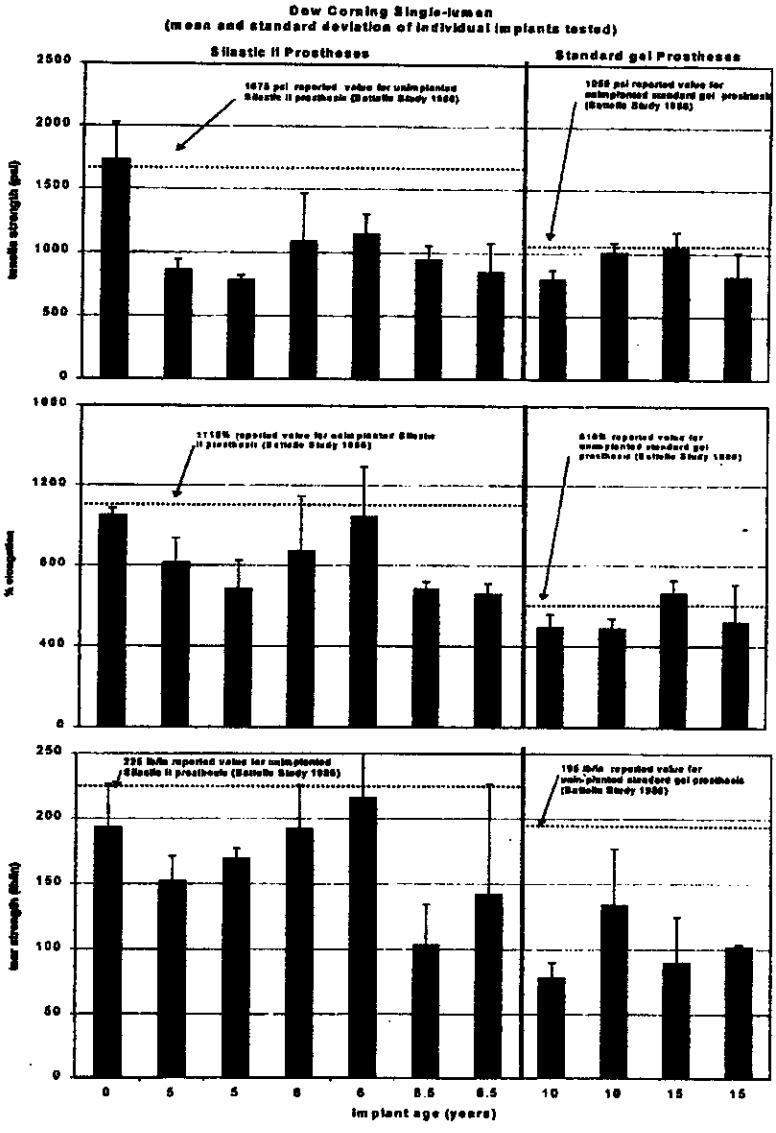

Fig 3. Dow Corning single-lumen implants (mean and standard deviation of individual implants tested).

result of the clear adhesive layer being weaker than the shell.

Smooth-wall Surgitek single-lumen explant data are plotted in Figure 7 and represent two generations of explants from this company. Two Surgitek SCL explants are plotted on the left side of the black bar and two standard Surgitek explants are plotted on the right. Tensile strength

Annals of Plastic Surgery Volume 49 / Number 3 / September 2002

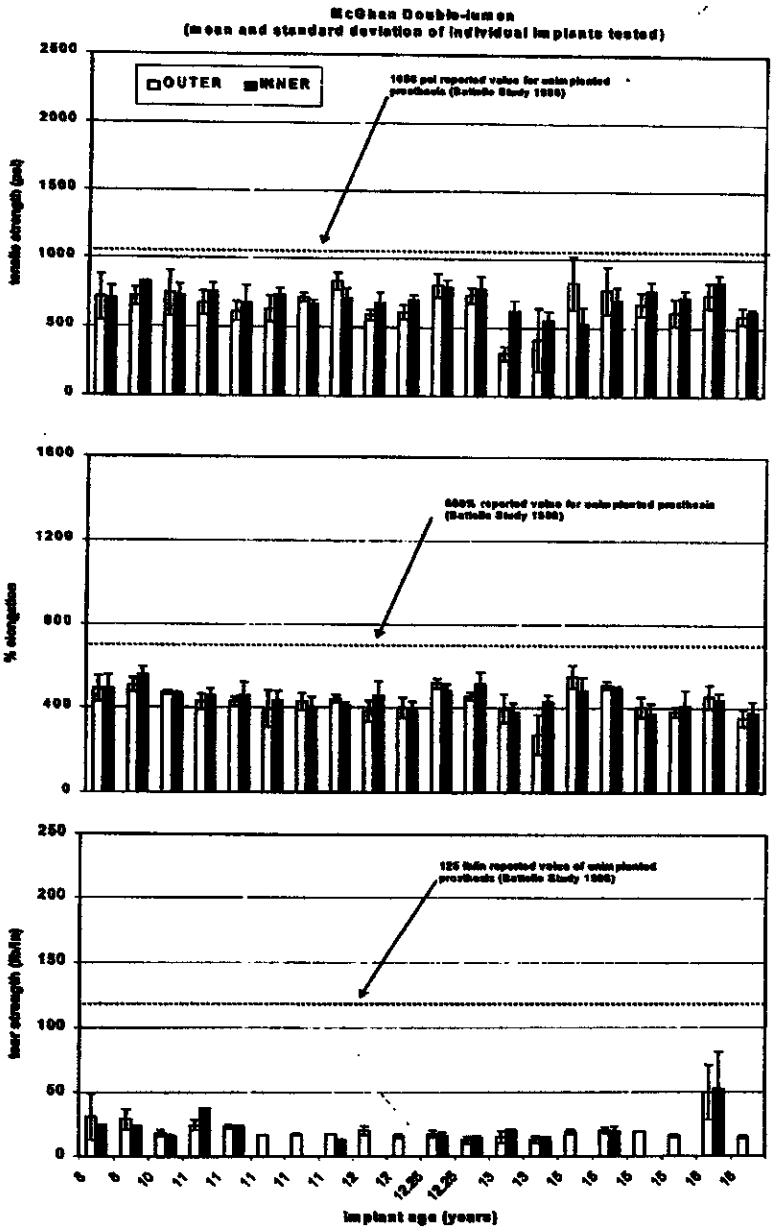

Fig 4. McGhan double-lumen implants (mean and standard deviation of individual implants tested).

and percent elongation were 45% and 44% lower respectively than reported values for an unimplanted SCL prosthesis. Tensile strength and percent elongation were reduced 30% and 24% respectively. The average tear strength of the standard Surgitek prostheses was 36% lower than the reported values.

The results of the testing reported here are strongly supported by other reports, published by many investigators, and confirm the substantial weakening of SGBI silicone shells. The decrease in the shell strength has often been reported as 40 to 50% or more within 1 to 5 years after SGBI implantation. For example, Phillips and associates[10] reported a decrease in shell tensile strength from an original value of approximately 10 MPa to 5 MPa (from 1,450 psi to 725 psi) within 3 to 4 years after primary implant surgery. A further decrease to 3 to 4 MPa (approximately 450 psi)—a loss of almost 70% of tensile strength—was indicated after 7 years of implant time. Similarly, van Rappard and coworkers[5] indicated a 50% reduction in strength within 6 years of implantation. Brandon and colleagues[7] reported

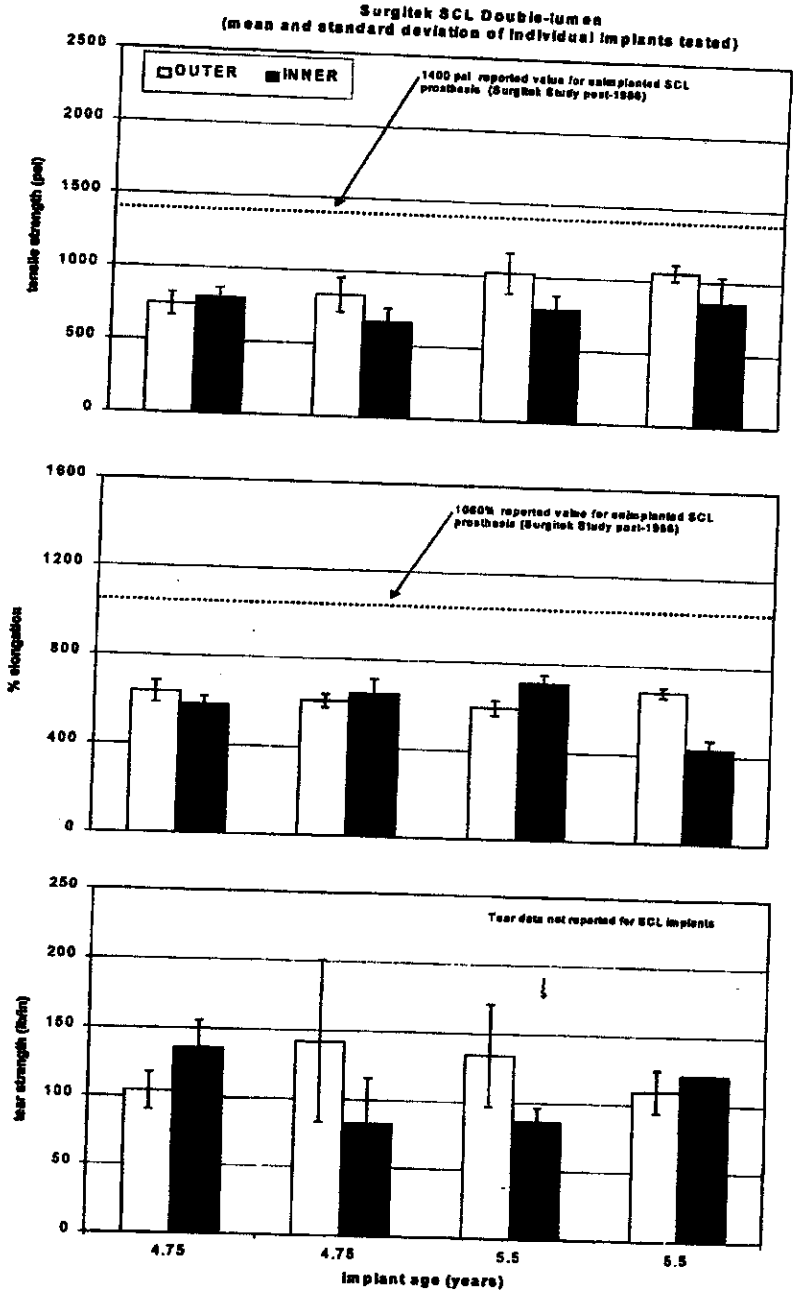

Fig 5. Surgitek SCL double-lumen implants (mean and standard deviation of individual implants tested).

a large decrease in strength for SGBIs made with Silastic-II silicone shells. After 8 years of implantation they noted a decrease of approximately 50% in tensile strength, a 30% decrease in elongation, and a 40% decrease in the tear strength.

Degradation of shell mechanical properties occurs to a marked extent as a result of swelling of the silicone elastomer shell by silicone fluid from the gel. This degradation begins once the implant is filled with gel, and it continues whether the implants are sitting on the shelf or are implanted in the patient. For example, in tests of archived unimplanted standard gel SGBIs from Dow Corning, Manikian[15] reported a 43% decrease in shell tensile strength (from 1,350 psi to 754 psi) and a 46% decrease in tear strength (from 80 lb per inch to 43 lb per inch) when measured 3.5 years after manufacture. For an unimplanted Silastic-I prosthesis, a decrease in tensile strength of 32% and 79% lower tear strength was reported after a

Annals of Plastic Surgery Volume 49 / Number 3 / September 2002

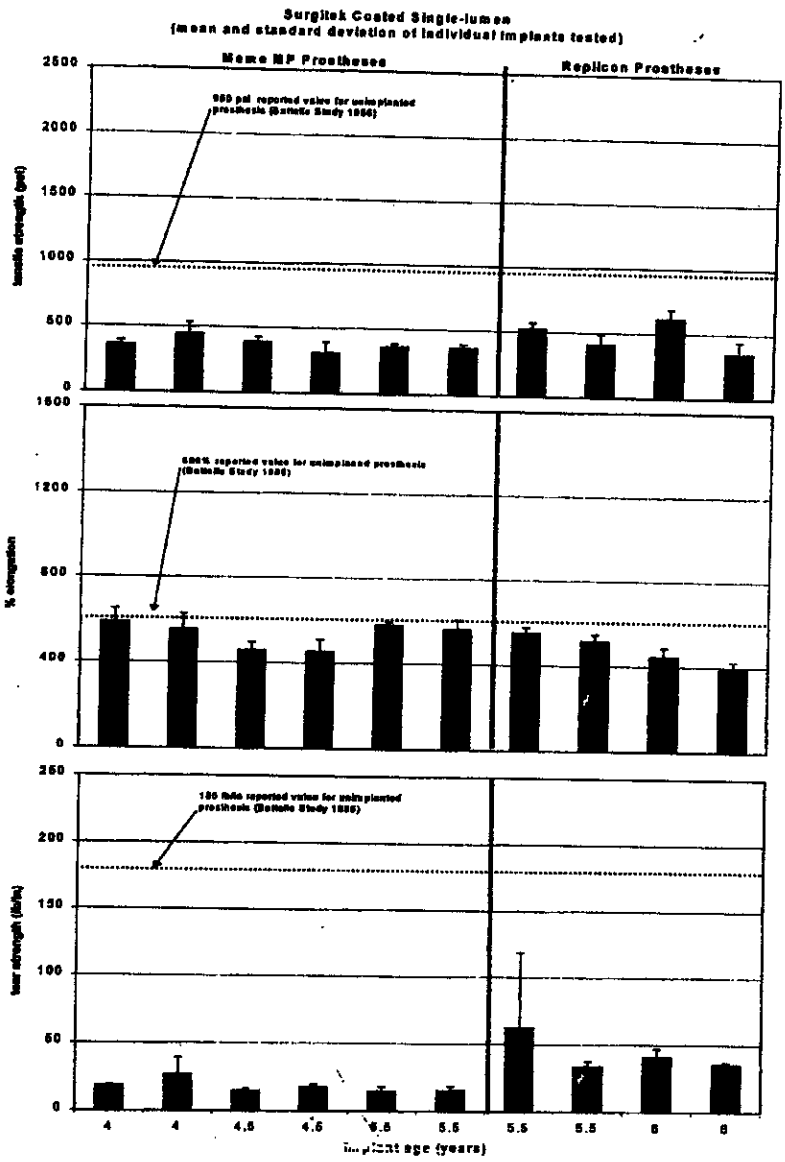

Fig 6. Surgitek coated single-lumen implants (mean and standard deviation of individual implants tested).

1-year shelf life. Slightly better results were reported for low-bleed Silastic-II prostheses: a 23% decrease in tensile strength with little change in tear strength after 1 year of shelf life.[16,17] Possible causes of the substantial variability in mechanical strength of different gel-filled implants, even within a single manufacturing lot, are the inherent wide variations in shell thickness (resulting from the multiple dip coating process used in manufacture), variations in crosslink density, and consequent differences in the effect of silicone fluid diffusion into elastomer shells from implant to implant.

Complete Solvent Extraction of Shells and Gels

Virtually all of the previously reported results for shell or gel extraction have been deficient in either using arbitrarily short extraction times or relatively poor silicone oil solvents. The single exception is an excellent 1970 Battelle study commissioned by the FDA that afforded results that are in complete agreement with our own; in other words, that most gels have been composed of 85 to 95% soluble silicone and therefore actually contained relatively little crosslinked silicone.[18] The experiments reported here used an exhaustive extraction procedure in Soxhlet ex-

J0068693

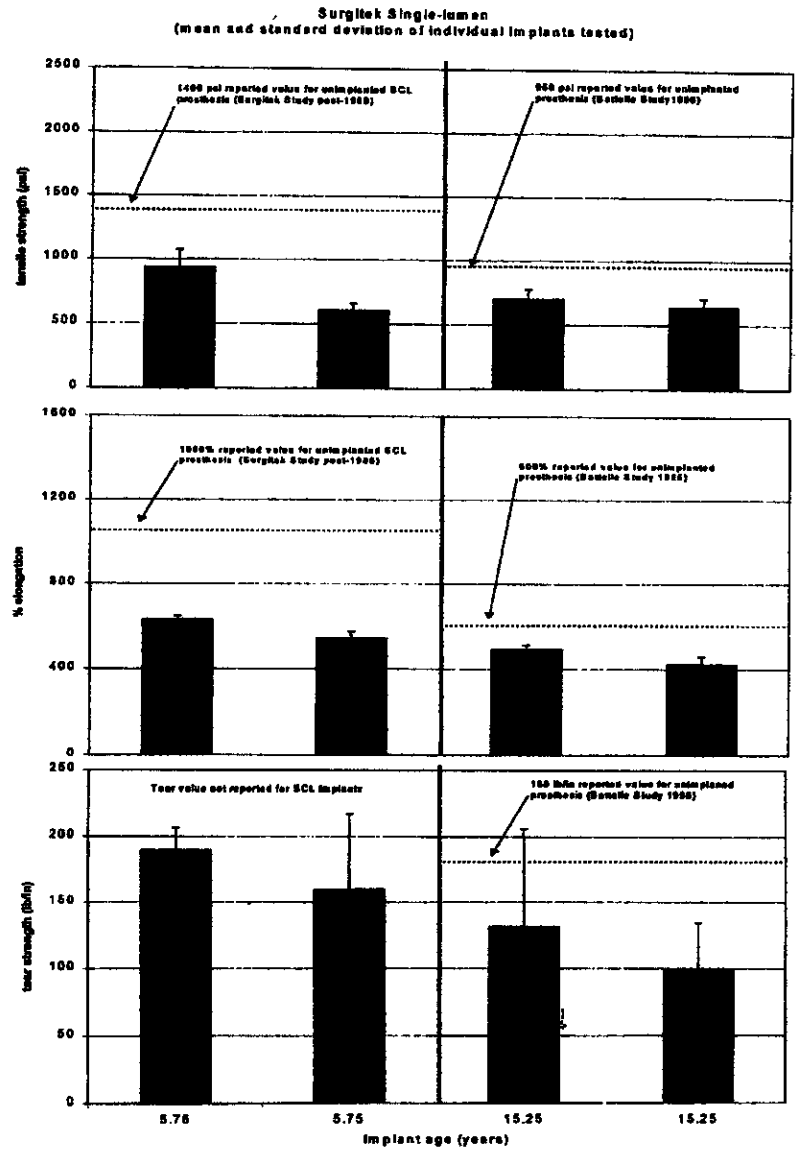

Fig 7. Surgitek single-lumen implants (mean and standard deviation of individual implants tested).

tractors with a good silicone solvent (chloroform) to measure quantitatively the uncrosslinked silicone content of shells and gels.

Extraction results for the shells of explants are presented in Figures 8 through 11. Our data for Dow Corning explants and the one more than 10-year-old unimplanted Silastic-II control are shown in Figure 8. Gel extraction results indicated that as much as 96% of the silicone gel was not crosslinked. Therefore, the gels were predominantly uncrosslinked, and silicone was freely available to swell the silicone shells and diffuse through them. This is the cause of the so-called "bleed." Dow Corning shells were found to be swollen with an average of 20% of soluble silicone oil. Control Silastic-II shell samples, from a new implant, contained only 8% extractable oil. Furthermore, there was no difference observed between the low-bleed Silastic-II explants and the standard shells. This clearly indicates that the barrier coatings on these explanted barrier polymer-coated low-bleed prostheses did not, in fact, permanently reduce the swelling of shells with silicone oil over the long term (more than 5 years). This is likely the result of disruption of the barrier coatings over time. Maximum swell-

J0068694

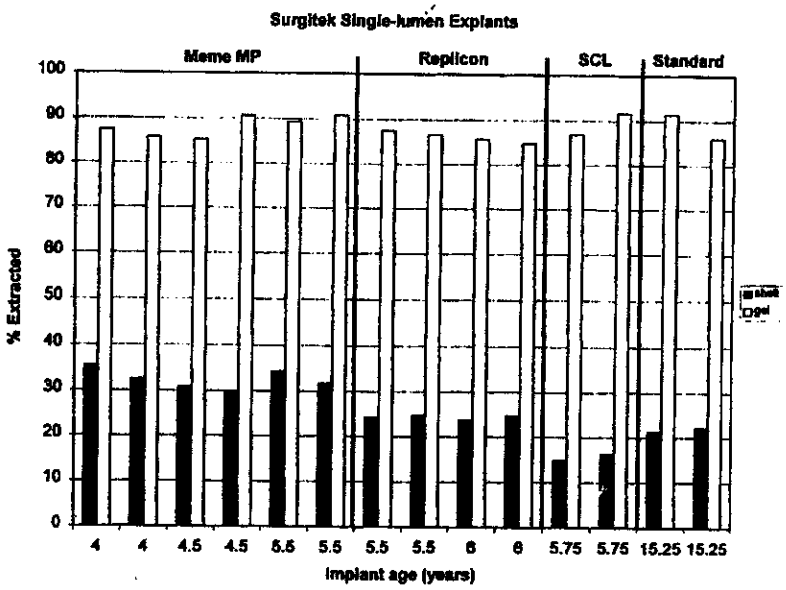

Fig 10. Surgitek single-lumen explants.

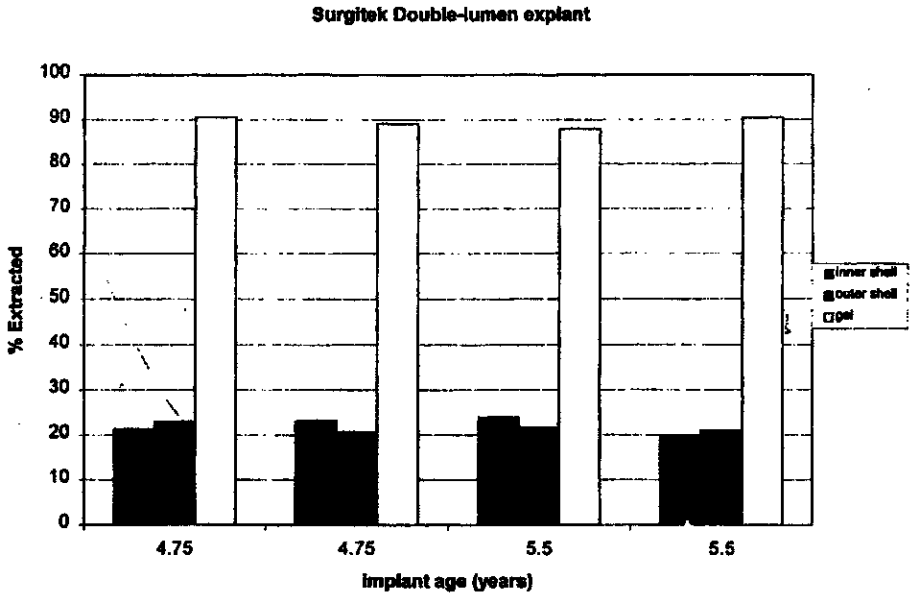

Fig 11. Surgitek double-lumen explant.

88%, 86%, 89%, and 89% uncrosslinked silicone respectively. Some differences were found for the shell extraction results. Meme-MP explanted shells were swollen with an average of 32% oil—a higher silicone oil content than any other implant type tested. Replicon shells contained 24% extractable oil, the Surgitek SCL explant shells averaged 16%, and standard shells had 22% soluble oil. Extraction data for Surgitek double-lumen explants are presented in Figure 11. Gel extraction values were similar to the single-lumen data and averaged 90% soluble silicone in these explant gel. There was no significant difference between the extraction values for the inner and outer shells of these explants; both averaged 22% silicone soluble oil.

Dow Corning Silastic-II control shell extraction data indicated almost twice the soluble silicone

J0068696

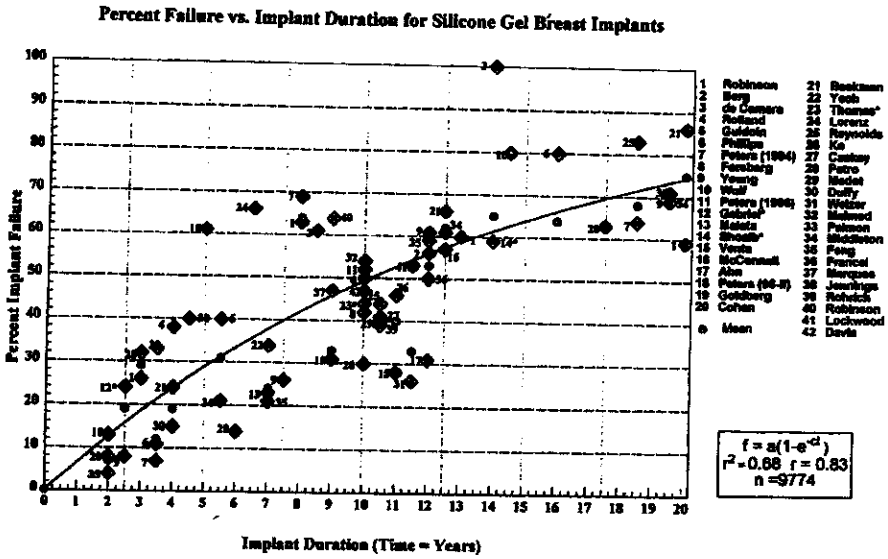

Fig 12. Percent failure vs. implant duration for silicone gel breast implants.

oil content reported previously for unfilled silicone shells (5% by Picha and Goldstein[19]). This much higher value was likely the result of the fact that storage of gel-filled shells allows continuous diffusion of soluble silicone into the shells. Our shell extraction values varied from 8% for the one stored, unimplanted Silastic-II control to as high as 35% for explanted prostheses.

Meta-analysis of SGBI Failure for 9,774 Explants

Before earlier research,[3] no large-cohort meta-analysis of implant rupture had been reported. Such retrospective analyses are crucial to determining the safest and most effective drug therapies, surgical protocols, and implant or device performance characteristics. For just the years 1996 to 2001, more than 2000 meta-analysis papers have appeared in the literature covering all aspects of medicine. Reported here is an update of our earlier retrospective failure analysis for approximately 8,000 explants, which brings our database up to 9,774 explants based on 42 different studies. The same statistical methodology described in detail in our earlier work[3] (exponential regression and ANOVA) was used for the enlarged database. The results of this analysis and plot of percent failure vs. implant duration (Fig 12) were virtually unchanged except for a slight improvement in the statistical correlation for the new regression plot (r^2 value increased from 0.79–0.83). This plot clearly shows the direct correlation of rupture with implant time. ANOVA statistics, applied to three different age group cohorts from the database, also afforded a highly significant correlation of rupture vs. time: 26% failure at 3.9 years mean implant duration, 47% failure at 10.3 years, and 69% failure at 17.8 years ($p \leq 0.001$). In addition to the high failure rate observed, data from the 42 studies used in this meta-analysis reinforce concerns about the risks associated with the high frequency of additional surgeries that are required (i.e., approximately one third of all women will require at least one additional surgery within 6 years after primary SGBI implant surgery).

In connection with our failure analysis, the recent paper by Brown and colleagues[20] is important to reference. Their FDA–National Institutes of Health–United States Department of Health and Human Services-supported magnetic resonance imaging (MRI) study of SGBI rupture and related health effects for a cohort of 344 women found 236 of 344 women (68.8%) had at least one ruptured implant with a mean implant age of 16.5 years. This result falls precisely on our Figure 12 failure vs. time plot.

The importance of the noninvasive MRI study by Brown and colleagues[20] with respect to our explant analysis is to support strongly the view that our use of explant rupture data are indeed representative of the implant aging properties

and rupture characteristics of the general population of SGBIs that remain implanted.

Conclusions

Our studies confirm the general reduction in tensile strength, tear strength, and elongation for all types of explanted elastomer shells, representing a remarkable loss in the strength and toughness of the shells. This adverse change in properties has made these prostheses vulnerable to the forces exerted on them during implantation and the cyclic stresses incurred during use. We regard this deterioration in strength as a major factor in the high rupture/failure rate observed in the current study and previously.[3] These data support the view that a primary mechanism for rupture must be the progressive cyclic mechanical stress-induced creation and enlargement of tears in weakened silicone fluid-swollen silicone elastomer shells. These tears are most likely to be initiated at sites of folds and/or defects, where stresses are concentrated. Our meta-analysis data for SGBI failure and the frequency of additional surgeries, as well as the results reported by many of the investigators we have cited, are consistent with the view that there may be a greater risk of SGBI failure and a greater frequency of surgical revisions than has generally been appreciated.

We would be remiss if we did not also comment here, in the context of this report, on the realities of patient needs for breast augmentation plastic surgery. In the absence of SGBIs in the United States, saline implants have been used increasingly during the past 8 years for new augmentation and to replace an estimated 500,000 gel implants that have been removed since 1992. Almost 200,000 saline implants are now implanted each year, reflecting the continuing need and great patient demand for a satisfactory prosthesis. Growing concerns regarding the relatively high rate of saline implant complications (data reported in FDA-approved McGhan and Mentor 2000 PMA applications) and poorer aesthetic outcomes compared with gel implants are now stimulating renewed interest by some plastic surgeons to a return to more general clinical use of gel implants (with some qualification that they should be removed before they are likely to rupture, perhaps within 6–8 years of implantation). Such an option, even with modified shell and gel materials, requires further research and clinical investigation and may have merit if the following conditions are met:

First, there must be continuing emphasis on informed consent with some consideration to regular MRI checkups[20] and possible prosthesis replacement. Note that such constraints are not unusual for other medical implants, such as 6 to 10-year replacement for hip joints resulting from wear, and 1 to 2-year replacement of small-diameter vascular grafts resulting from thrombogenic events and intimal hyperplasia.

Second, there must be design, manufacturing, and materials improvements, perhaps including thicker shells (nominally 0.020 in) and more highly crosslinked gels (i.e., the newer McGhan 410 gel implant for which United States clinical trials were initiated in April 2001, and which claims to have a much more coherent gel than ever used before).

Third, there must be no notable further evidence of SGBI-induced disease.[20]

References

1 FDA Advisory Panel on Breast Implants. Deliberations of the 1992 FDA Advisory Panel on Breast Implants. 1991

2 Kessler DA, Merkatz RB, Shapiro R. A call for higher standards for breast implants. JAMA 1993;270:2607–2608

3 Marotta JS, Widenhouse CW, Habal MB, et al. Silicone gel implant failure and frequency of additional surgeries: analysis of 35 studies reporting examination of more than 8000 explants. J Biomed Mater Res (Appl Biomater) 1999; 48:354–364

4 Peters W. The mechanical properties of breast prostheses. Ann Plast Surg 1981;6:179–181

5 van Rappard J, Sonneveld G, van Twisk R, et al. Pressure resistance of silicone breast implants as a function of implantation time. Ann Plast Surg 1988;21:566–569

6 Morey S, North J. Final report on low bleed mammary implants: technical report to Dow Corning Wright from Battelle Research Inst, Columbus, Ohio 1986.

7 Brandon H, Young V, Wolf C, et al. Mechanical analysis of explanted breast implants. Presented at the 1996 Fifth World Biomaterials Congress. Toronto, Canada.

8 Lockwood M. Strength, strain, energy and toughness of silicone breast implant shells. Master's thesis. Champaign–Urbana, IL: University of Illinois, 1995

9 Marotta J, Amery D, Widenhouse C, et al. Degradation of physical properties of silicone gel breast implants and high rates of implant failures. In: 1998 Trans 24th Annual Meeting Soc Biomaterials, 374

10 Phillips J, deCamera D, Lockwood M, et al. Strength of

J0068698

silicone breast implants. Plast Reconstr Surg 1996;97: 1215–1225
11 Wolf C, Brandon H, Young V, et al. Physical and chemical analysis of explanted breast implants. Curr Top Microbiol Immunol 1996;210:25–38
12 Goldberg EP, Widenhouse C, Marotta J, et al. Failure of silicone gel breast implants: analysis of literature data for 1652 explanted prostheses. Plast Reconstr Surg 1997;100:281–284
13 ASTM D-412-92 standard test methods for vulcanized rubber and thermoplastic elastomers. 1992 Annual ASTM Standards 09.01:99–111
14 ASTM D-624-91 standard test methods for tear strength of conventional vulcanized rubber and thermoplastic elastomers. 1991 Annual ASTM Standards 09.01:115–125
15 Manikian M. Long term physical property evaluation of Silastic mammary prosthesis. Midland, MI: Dow Corning, 1971
16 Peters S. Physical properties versus time for Silastic-II and standard prosthesis. Hemlock, MI: Dow Corning, 1981
17 Peters S, Gant R. Fluorosilicone coated mammary prosthesis: gel bleed, physical properties and laminate integrity. Hemlock, MI: Dow Corning, 1983
18 Thompson RM, Howard CC, Brewer EJ, et al. Compositional analysis of silicone prostheses. 1979 Battelle report no. 233-77-5038 Task 8 to FDA. Columbus, OH: Battelle Memorial Institute, 1979
19 Picha GJ, Goldstein JA. Analysis of soft-tissue response to components used in the manufacture of breast implants: rat animal model. Plast Reconstr Surg 1991;87:490–500
20 Brown SL, Pennelo G, Berg WA, et al. Silicone gel breast implant rupture, extracapsular silicone, and health status in a population of women. J Rheumatol 2001:28: 996–1003

Invited Discussion

Harold J. Brandon, DSc *†
V. Leroy Young, MD *
Clarence J. Wolf, PhD †
Kenneth L. Jerina, DSc †
Marla E. Watson, MA *
Joseph K. McLaughlin, PhD ‡

The preceding article by Marotta and colleagues from the University of Florida updates the group's meta-analysis of failure data reported in the literature for nearly 9,800 explanted silicone gel breast implants. They also present results from their testing of 51 single- and double-lumen explanted silicone gel breast implants (with various implantation times, made primarily by three manufacturers) plus one Dow Corning Silastic II control implant (never implanted). Because the authors do not say how or why these explants were selected for testing, we cannot know whether the 51 explants are representative in any way of all breast implants. Were they chosen at random from a larger pool of explants or were they simply what were available? Aside from duration of implantation, we are not given important details on the tested devices, such as implant style and lot, status at the time of explantation, and differences between those not strong enough for testing and those tested.

Marotta and colleagues maintain that reductions in mechanical properties—tensile strength, breaking energy, and tear resistance—of breast implants lead to a "significant loss" in shell strength and toughness over time. They link the higher failure frequencies over time (shown in their Fig 12) to the effects of elastomer swelling and hypothesize that mechanical properties of elastomer degrade as noncrosslinked, low-molecular-weight silicone molecules diffuse from the gel into the shell. Without any scientific proof, the authors assert that early weakening of shells resulting from swelling is responsible for silicone gel breast implant failure. Our research indicates that implant rupture has numerous potential causes (not just one), including implant handling before surgery, in vivo processes, trauma to the breast, and unintentional surgical damage during implantation or explantation.

In their implant testing, Marotta and colleagues found no significant correlation between implantation time and shell strength properties. Our work at Washington University has produced similar findings. We are therefore puzzled as to why the authors neglected to reference almost all our published data.[1–8] Although not scientifically offensive, this "oversight" is perplexing because we have conducted a substantial amount of implant properties testing during the last decade. Although our work supports their *data*, it also refutes many of their *conclusions*. For example, our research has described various types of silicone gel breast implants that have remained intact with a large degree of shell swelling (20–40%) for implantation times ranging from 13 to 32 years.[1,3,5]

The authors are consistently selective when citing published studies on the variability of mechanical properties of control implant shells. They ignore our data for Dow Corning control and explanted implant shells[1–6] and choose instead to reference studies of explants that did not characterize the devices according to manufacturer, specific type, or manufacturing lot, and did

EXHIBIT 3

Biographical Summary of P. Blais (Curriculum Vitae)

I. BACKGROUND AND EDUCATION

I was born in Montreal, Canada. I am a research specialist in materials and medical devices, in particular for materials and devices with long term contact with human tissue with applications in medicine and dentistry. Such items are generally termed "medical implants". I have B.Sc. (Hons. Chem.) and Ph.D. degrees in Chemistry from McGill University, Montreal, Canada where I completed graduate and postgraduate studies in polymer chemistry, polymer synthesis, catalysis, physical chemistry of polymers, radiation physics of polymers, crystallography, plant pathology and physics of natural and synthetic materials. I received a Post-Doctoral Fellowship in materials engineering from Case-Western Reserve University, Cleveland, Ohio.

1.1 Professional Experience

Prior to receiving my B.Sc. and Ph.D. degrees from McGill University, I held positions in clinical pharmacy and as laboratory technician. Concurrent with university studies, I continued as part-time laboratory technician and held university lecturing and administrative positions. I also had lecturing responsibilities in materials engineering during my post-doctoral fellowship at Case Western Reserve University. After completing my studies, I served as Research Officer with the National Research Council of Canada from 1969 to 1976 on chemical, material science and chemical engineering projects. In June 1976, I was seconded to the Department of National Health and Welfare Canada becoming a full-time research scientist with the Bureau of Medical Devices of the Health Protection Branch of Health and Welfare Canada, an organization similar to the U.S. FDA. I became Senior Scientific Adviser to the Medical Devices Program in 1983, leaving my post in late 1989. I concurrently served in official and elected capacities with the Association of Chemical Professionals of Ontario, including Vice-President and President.

During employment at the Bureau of Medical Devices of the Canadian Department of National Health and Welfare, I dealt with scientific, engineering and clinical performance of medical devices. The Bureau had a role similar to its U.S. counterpart, now the Center for Devices and Radiological Health of the FDA. I performed research, investigations and class studies on high risk products in support of regulatory activity including acceptability criteria for medical devices. I was responsible for clinical trial and tracking of investigational products. I conducted laboratory research and supervised joint university-government studies on medical devices.

I participated in drafting of regulatory proposals, adverse reaction reports, ministerial briefings, public advisory documents, 'Dear Doctor letters', recall recommendations and briefings on manufacturing practices, failure mechanisms and other topics pertinent to the Canadian Medical Device Regulations and the Food and Drug Act. Such activity provided me with the training and background to assess safety and efficacy of medical devices, product inserts, warnings and other areas which complement my training and education in science and technology of medical products. Because of my long period of employment which overlaps on a crucial phase in the development of breast implants, I would be deemed to be a participant in the evolutionary process and in the events which have surrounded the use of breast implants in North America.

I have had other connected responsibilities with international standards organizations on medical devices as well as official analyst to the Department of National Health and Welfare and delegated consultant to provincial coroners in the context of investigations on adverse events from the use of medical devices. From 1977 to the present I have held visiting lecturer status for several Canadian and foreign universities. I am presently a consultant specializing in design and failure analysis of health care products.

1.2 Professional Memberships

Since 1962, I have participated in a number of projects related to medical devices and biomaterials of relevance to medicine, dentistry and biology. These activities are reflected in publications and in professional memberships as shown below. I have also provided official testimony in the context of U.S. Congressional Hearings on Human Resources and Intergovernmental Relations on medical device safety, FDA Hearings on medical devices and Canadian Parliamentary Hearings on health care issues.

1.3 Listing of Professional Memberships

1) Association of Chemical Professionals of Ontario, Member (1976-present)
2) Association of Chemical Professionals of Ontario, Vice President (1980-81)
3) Association of Chemical Professionals of Ontario, President (1981-82)
4) Chemical Institute of Canada, Member (1959- present)
5) Chemical Institute of Canada, Section Chairman (1983-85)
6) Canadian Biomaterials Society, Member (1978-present)
7) Controlled Release Society, Member (1985-present)
8) Association Canadienne Française pour l'Avancement des Sciences, Member (1969-present)
9) Association Canadienne Française pour l'Avancement des Sciences, Représentant Régional (1975)

1.4 Honours and Awards

1) Clinicien Honoraire, Ordre des Dentistes du Québec (1982)
2) Honorary Clinician , Intraocular Implant Society (1984)
3) Fellowship, Chemical Institute of Canada (FCIC) (1985)
4) Canadian Delegate, Ophthalmic Speakers Program Karolinska Institute, Stockholm, Sweden (1985)
5) Canadian Delegate, ISO TC 150, Medical Implants (1985-90)
6) Canadian Delegate, ISO TC 157, Mechanical Contraceptives (1986)
7) Speaker, Permanent Medical Education Programme, Telemedicine Canada Toronto, Ontario, Canada (1986)
8) Invited Faculty, Saskatchewan Association of Optometrists, Continuing Education Program, Regina, Saskatchewan (1986)
9) Honorary Lecturer, American Association of Pediatrics (1986)
10) Member, Editorial Board, Implantation Transplantation Today (1987)
11) Member, Editorial Board, Biomedical Materials Research Journal (1988)

1.5 Teaching Positions

I have served as a visiting professor of chemistry and medical technology at several universities. These positions were held concurrently with employment as Research Officer and Senior Scientific Advisor. They include:

1) Professeur Invité, Département de Génie Mécanique, Ecole Polytechnique, Montréal, Québec (1979-83)
2) Guest Lecturer, Biological and Chemical Technology Programme, Algonquin College, Ottawa, Ontario (1979)
3) Visiting Professor, Department of Chemical Engineering, Rensalaer Polytechnical University, Rensalaer, N.Y. (1980)
4) Professeur Invité, Département de chimie, Université de Montréal Montréal, Québec (1983)
5) Professeur Invité, Département de médecine communautaire Faculté de Médecine, Université de Montréal (1984)
6) Visiting Professor, Department of Mechanical Engineering, Queen's University Kingston, Ontario (1987)
7) Professeur Invité, Département de chirurgie expérimentale, Université Laval Québec City, Québec (1988)
8) Visiting Lecturer, Faculty of Pharmacy, University of Toronto Toronto, Ontario (1989)
9) Professeur Invité, Département de Pharmacologie, Faculté de Médecine, Université de Montréal, Montréal, Québec (1988-1991)

2. PUBLICATIONS

I have authored over 300 published articles, book chapters, patents and official reports as well as briefing papers. Many were issued during my service with the Department of Health and Welfare Canada, which has a similar role to the FDA's Center for Devices and Radiological Health. In addition, I presented many lectures on design of medical devices, socio-economic aspects of medical technology and safety issues in medical systems. A status summary of these works is provided below.

2.1 Collective Publications

1) 270 articles/book chapters on applications of polymers in medicine, on biomaterials and on medical technology issues

2) 350 reports and documents for restricted distribution in the biomedical sciences and in the regulation of medical products

3) 410 oral presentations, courses and symposia, principally in biomaterials applications, plastics in medicine, family planning and commercial development of biomedical technologies

4) 6 Patents on plastics and membrane separation technologies, Canada and U.S.

2.2 Typical Publications

Publications I have authored deal primarily with polymers, their structure, their method of synthesis and their performance in the context of health care applications. They include studies on the impact of such materials on tissue and the converse phenomena where changes in the materials take place as a result of continued exposure to biological environments. Many publications include studies on implant technology and performance of implants used clinically. Typical publications are shown below. They are selected from a listing of more than 270 titles.

1) P.Blais, Breast Prostheses in the Nineties; in Dangers of Silicone Breast Implants, Proceedings of the Congressional Hearing Before the Human Resources and Intergovernmental Relations, Subcommittee Hearing of December 18, 1990, 100th U.S. Congress; Page 42-55, U.S. Government Printing Office, Washington D.C. (1991).

2) P. Blais, Quality Assurance in Ophthalmic Dispersibles in Viscoelastic Substances in Ophthalmology, O. Hockwin, Editor, Springer Verlag, Berlin (1990).

3) P. Blais, Letter to Editor (The Polyurethane Breast Implant), J. App. Biomaterials, 1, 197 (1990).

4) P. Blais, Vinyls in Medicine, Journal of Vinyl Technology, 11 (2), 71-8 (1989).

5) A.S. Chawla, P. Blais, I. Hinberg and D.L. Johnson, "Degradation of Explanted Polyurethane Cardiac Pacing Leads", Biomaterials, Artificial Cells, Artificial Organs, 16(4), 785-800 (1988).

6) P. Blais, The Polyurethane Breast Implants: A Basis for Caution 5 (Sept), 28-29 (1988).

7) P. Blais, A.R. Alexander and E. Napke, Contact Lenses and Corneal Vascularization; an Emerging Problem, Transplant., Implant. Today 4 (Sept), 6-13 (1987).
8) G. Biro and P. Blais, Perfluorocarbon Blood Substitutes, C.R.C. Critical Reviews in Oncology/Hematology 6 (4), 311-374 (1987).

9) M. Smith and P. Blais, Preliminary Findings on Used Cervical Caps, Contraception 29 (6), 6527-6535 (1984).

10) P. Blais and R. Guidoin, Biocompatibility in Fertility Control Technology , Chapter 4 in Biocompatibility in Clinical Practice, Vol. 1, D.F. Williams, Editor; C.R.C. Press, Boca Raton, Florida, U.S.A. (1983).

11) P. Blais, Silicone Breast Implant: Technological and Physicochemical Aspects, Chapter 35 in Biomaterials in Reconstructive Surgery, L.R. Rubin, Editor; C.V. Mosby, St. Louis, Missouri, U.S.A. (1983)

12) P. Blais, Industrial Polymers as Implants: Their Value and Their Limitations, Chapter 7 in Biomaterials in Reconstructive Surgery, L.R. Rubin, Editor; C.V. Mosby, St. Louis, Missouri, U.S.A. (1983)

13) T. Matsura, P. Blais, A.G. Baxter, S. Sourirajan, Method of Concentrating Natural Fruit Juices by Reverse Osmosis, U.S. Patent No. 4,322,448, U.S. Printing Office (1982)

3. OFFICIAL TESTIMONY, CONGRESSIONAL HEARINGS AND COURT INVOLVEMENT

Since 1977, I have appeared in U.S. Food and Drug Administration hearings and Congressional Hearings as an expert witness and Analyst. I have been deposed as an expert witness in medical devices-related cases in the U.S. and Canada and have been accepted as an expert on medical implant technology and extracorporeal medical devices by courts in Texas, Florida, California, Maryland, Washington, Louisiana, Massachusetts, New Mexico, Colorado, Nevada, Utah, Oregon, New York, New Jersey and Connecticut. I have also testified in Canadian trials, Coroners and parliamentary hearings in Ontario, Saskatchewan, Alberta and British Columbia. Over the last four years, I have appeared as an expert witness on behalf of Plaintiffs in the following trials:

Merlin v. Minnesota Mining and Manufacturing Corp., Reno, Nevada, U.S.A., trial testimony, February, 1996

Merlat v. Minnesota Mining and Manufacturing Corp., Santa Clara, California, U.S.A., trial testimony, July, 1996
Cabrera v. Cordis Corporation, Las Vegas, Nevada, U.S.A., trial testimony, August 1996

Vassalo v. Baxter Healthcare Corp., Boston, Massachusetts, U.S.A., trial testimony, September, 1996

Atterbury and Others v. Minnesota Mining and Manufacturing Corp. (3M), Consolidated Cause No. 136-94, Gilmer, Texas, U.S.A., trial testimony, February, 1997

Spitzfaden and Others v. Dow Chemical, New Orleans, Louisiana, U.S.A., trial testimony, April, 1997

Duke v. Minnesota Mining and Manufacturing Corp. (3M), Albuquerque, New Mexico, U.S.A., trial testimony, April, 1997

DuCoeur v. Minnesota Mining and Manufacturing Corp., San Diego, California, U.S.A., trial testimony, October, 1997

Barrow v. Bristol Myers Squibb & Others, Orlando, Florida, U.S.A., trial testimony, November, 1997

Morales & Others v. American Home Products, McAllen, Texas, U.S.A., trial testimony, January, 1998

Crawford v. Richards, Smith & Nephew, Las Vegas, Nevada, U.S.A., trial testimony, February, 1998

B. Green v. Bristol Myers Squibb and Others, Albuquerque, New Mexico, U.S.A., trial testimony, September, 1998

M. Smith v. 3M and Others, San Diego, California, U.S.A., trial testimony, October, 1999

Recommendations on Saline Breast Implants, Regulation of Saline Breast Implants, FDA Advisory Committee, Gaithersburg, MD, U.S.A., March 1-3, 2000

Havard Fisher v. Baxter Healthcare Corp. et al, Cleveland, Ohio, U.S.A., trial testimony, October 2000

Transue v. Bristol Myers Squibb et al, Seattle, WA, U.S.A., trial testimony, April 2001

4. RESEARCH AREAS AND KNOWLEDGE FROM SUSTAINED STUDIES

I am knowledgeable about design, physical characteristics, construction attributes and chemical properties of breast implants, as well as manufacturing technology, performance, mode of failure and clinical limitations accumulated over more than 25 years of research in the field. I am familiar with the many different products and their history. This knowledge base is supplemented by studies performed since 1989 on more than 6000 explanted breast implants. Background information regarding manufacturing is derived from my examination of about 20,000 business and production records including Lot Histories, government documents and research papers of relevance to breast implants. This information is supported by more than 25 years of continuing professional contact with many medical specialties, through joint studies on tissue and failure investigations as well as through teaching involving medical systems and their applications. Thus, I have collateral knowledge and fluency with principles of anatomy, physiology, pharmacology, toxicology, radiology and medicine through constant usage of information from these disciplines. Such knowledge was essential to the discharge of my duties during my employment at the Department of National Health and Welfare Canada.

4.1 Knowledge Derived from Research Activity

I have examined medical systems under simulated conditions of use (in vitro testing) and have extensively studied constituent materials used in implantable products including but not limited to silicones, polyolefins and polyurethanes. I have investigated mechanical, physico-chemical, chemical reactivity and degradation susceptibility of implantable substances. I am also well versed with manufacturing technologies including sterilization processes. These studies include work on permeability to fluids, ability to absorb biological entities, susceptibility to abrasion and fatigue as well as other problems that such materials encounter under conditions of processing and use.

I am versed in all laboratory techniques for studies on failure of materials including optical and electron microscopy, liquid and gas chromatography, electron probe microanalysis, X-ray and electron diffraction, radiography, ESCA (electron spectroscopy), NMR (nuclear magnetic resonance), fractography, dye penetration and other methods with general applicability in the study of materials. This knowledge base was essential for the discharge of my duties as a Senior Scientific Advisor in matters of medical device safety and efficacy. My opinions have been significantly influenced over the years through study of the following material:

4.2 Knowledge Derived from Review of Business and Corporate Research Documents

Collective document registries provided incidental to Class Action litigation, known as MDL 926 or Birmingham Class Breast Prostheses Litigation, have been reviewed using a commercial database published by DocuQuest. This material catalogs more than 18,000 documents pertinent to breast implants. The DocuQuest database includes relevant supplemental documents from regulatory agencies obtained under Freedom of Information (FOI) and counterpart Access to Information legislation in Canada. Lot Histories from implants produced from the sixties to the present were also reviewed.

4.3 Knowledge Derived from Public Domain Publications

In addition to my education, background, training and experience in the design and study of implants, their effect on users and the changes implants undergo in a living environment, I have also derived background information and knowledge from scientific articles, teaching textbooks, commercial brochures and technical reports on medical implants, substances used in medical implants, design of breast implants and related performance aspects of these devices under laboratory conditions and actual conditions of use. This material includes:

1) commercial data, catalogs and promotional brochures for breast implants
2) product inserts included with breast implants and other long term products
3) teaching textbooks on plastic and reconstructive surgery
4) journal publications on breast implant performance and adverse reactions
5) unpublished reports on breast implants and adverse phenomena
6) regulatory documents on breast implants (Federal Register, Canada Gazette, etc.)
7) collective reviews on adverse reactions from breast implants and constituents
8) epidemiological studies on adverse effects from breast implants
9) studies on devices with similar basic properties to breast implants
10) policy and editorial papers on breast implants
11) patents and patent applications
12) S. Bondurant, V. Ernster, R. Herdman; Safety of Silicone Breast Implants: "Reference Lists", pages 285-479; Committee on the Safety of Silicone Breast Implants, Division of Health Promotion and Disease Prevention, Institute of Medicine (IOM), National Academy Press, Washington (2000)
13) government documents on breast implants (National Institute of Health, U.S. FDA, U.K. MDA, Agence française de sécurité sanitaire des produits de santé, etc.)

4.4 Implant and Regulatory Knowledge Derived from Employment

Since 1976 and while at the Bureau of Medical Devices of the Canadian Department of National Health and Welfare, my responsibilities dealt with scientific, engineering and clinical performance of medical devices. I conducted research, investigations and class studies on high risk products in support of regulatory activity including the development of acceptability criteria for medical devices. I had responsibility for clinical trial and investigational product tracking. I conducted laboratory research and supervised joint university-government studies on medical devices including products for cardiac repair, vascular reconstruction, fertility control, ophthalmic surgery, drug administration, dental repair, neurological applications, cosmetic and reconstructive surgery, blood processing, orthopaedic joint reconstruction and wound care.

I participated in drafting of regulatory proposals, adverse reaction reports, ministerial briefings, public advisory documents, 'Dear Doctor letters', recall recommendations and documents on manufacturing technology, failure mechanisms and other topics pertinent to the Canadian Medical Device Regulations and the Food and Drug Act.

I have published and lectured on implant material durability, safety and efficacy, device risks assessment, product performance appraisal, development of standards, review methodology for Medical Device Submissions, a process sometimes referred to as "Pre-Market Approval". I have examined many breast implants and reviewed breast implant submissions by manufacturers to provide guidance on the appraisal of pre-market documentation. I attended meetings of consultants and departmental officials in the context of plastic surgery implants and was responsible for briefing senior department officials on adverse events surrounding the use of such implants.

I was a medical devices technical liaison specialist to the U.S. Food and Drug Administration (FDA) and repeatedly visited FDA laboratories. I was Canada's representative on medical device standards committees attended by FDA representatives. I was responsible for preparation of Tripartite Committee briefings pertinent to implants.

INNOVAL

Founded in 1969 and located in Ottawa, Canada, Innoval specializes in the development of health sciences and materials technology education programs as well as the training of paramedical and technical personnel for hospitals, government and industry.

Its primary expertise includes :

* product failure analysis and forensic studies
* plastics for medical and pharmaceutical applications
* design and testing of medical products
* biological environment simulation
* pre-clinical investigations for medical implants
* biological science and polymer science education

Its services are oriented principally at the biomedical products industry and the health care services sectors. Innoval's experience is concentrated in high technology, high risk biomedical products development, scientific research and university-government-industry technology transfer projects. It also offers technical consulting services, feasibility analyses, recruiting assistance and on-site staff training programs on related topics.

Expertise of the firm is based on more than twenty years of experience in hospital environments, in universities, in government, in international agencies and in the biomedical industry here and abroad.

Projects have included:

- preparation of professional development programs, seminars and continuing education (nursing care, biomedical sciences, materials engineering and production technology)
- development of products, preparation of product inserts and instruction brochures (ophthalmic, family planning, cardiac care, plastic surgery and otolaryngology devices)
- design of medical disposables and packaging
- drafting of product documentation and clinical testing protocols
- development of production systems for family planning products
- preparation of production standards and quality assurance criteria for medical products
- industry-government and international relations, patent development, patent search
- research and technology proposals, market potential evaluations
- failure analyses for medical implants, diagnostic devices, specialty plastics, biomaterials, biosensors, plastic surgery products and membranes for biotechnology applications.

Studies on behalf of clients have included prototype feasibility reviews, materials research, technology licensing proposals, market potential evaluations as well as product liability analyses for medical and diagnostic devices and investigational biomaterials.

Innoval has capabilities for the development of prototype medical products, to identify needs, to adapt production techniques, to locate raw materials and to undertake training programs suitable for emerging countries. It can also provide consultancy, support and management services in such ventures.