



AMERICAN SOCIETY OF
PLASTIC SURGEONS



THE AMERICAN SOCIETY FOR
AESTHETIC PLASTIC SURGERY, INC.

April 9, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**In re: Comments on Draft Guidance for Industry and FDA Staff on Saline, Silicone Gel,
and Alternative Breast Implants**

Dear Sir or Madam:

The American Society of Plastic Surgeons (ASPS) and its affiliated Plastic Surgery Educational Foundation (PSEF), and the American Society for Aesthetic Plastic Surgery (ASAPS) and its affiliated Aesthetic Society Education and Research Foundation (ASERF) are pleased to provide the following comments on the agency's Draft Guidance for Industry and FDA Staff on Saline, Silicone Gel, and Alternative Breast Implants (the "Draft Guidance" or the "Guidance"). Our organizations have formed a joint Breast Implant Work Group to address issues that arose at the FDA's Advisory Panel meeting on silicone breast implants in October 2003.

We understand that the purpose of the agency's Draft Guidance is to identify device description, preclinical, clinical, and labeling information that the FDA proposes to recommend that manufacturers or others include in a premarket approval (PMA) application for breast implants filled with saline, silicone gel, or alternative filler intended for breast augmentation, breast reconstruction, and/or revision. While many of the topics addressed in this Draft Guidance are specific to manufacturers, ASPS and ASAPS would like to offer comments on what we believe are reasonable and attainable from a medical perspective. Additionally, we will identify issues raised in the Draft Guidance document that are at the discretion and independent medical judgment of the operating surgeon.

OVERVIEW

Our comments focus on reasonableness related to several key themes.

- **Choices for Patients** - As physicians and patient advocates, our primary concerns are the safety, health and satisfaction of our patients. This is in everyone's best interest. For the many women who undergo cosmetic breast augmentation and a variety of breast reconstruction procedures, we want to be able to offer women choices in types of implants and composition of implants to meet their personal goals and expectations for surgery. Plastic surgeons, certified by the American Board of Plastic Surgery, have a long-standing clinical experience with women who, for various personal reasons, have sought breast implant surgery. We counsel our patients on realistic expectations for surgery, provide them with patient education materials, work with them as they make decisions on whether

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implant surgery is the right choice for them, and communicate with them on the informed consent process. ASPS and ASAPS believe greater choice will benefit patients in terms of safety outcomes and satisfaction.

- **Data** – ASPS and ASAPS believe, as did the FDA advisory panel at the hearings in October, 2003, that there is now sufficient data for approval of postmarket conditions. To our knowledge, the review given to breast implants has been unlike that of any other medical device. In 1999, the Institute of Medicine produced an exhaustive review of the safety of breast implants and concluded that there was no evidence that silicone gel breast implants caused serious illnesses. Similar learned scientific evaluations have allowed both silicone gel-filled and saline-filled breast implants on the market in virtually every other country in the world. To the best of our knowledge, negative scientific information of significance has not emerged from the ongoing wide spread use of this device outside of the United States.

ASPS and ASAPS urge the FDA to take a balanced view of the regulatory history of silicone breast implants and apply reasonable standards in its requests for data – the same standards applied to other medical devices. We are concerned that the additional research and lead-time required to bring this and similar devices to market will make such products outdated when they are finally approved.

- **In-Vitro Testing** – In general ASPS and ASAPS support the agency's request for improved mechanical testing of breast implants, but are concerned that test methodologies intended to mimic in-vivo conditions may be unrealistic and not predictive of in-vivo performance. We would recommend that manufacturers continue to investigate the possibility of new and improved test modalities, but that FDA acknowledge the potential limited clinical significance of these types of tests.
- **Safety and Efficacy** – Today we all recognize that no device lasts a lifetime and no device is perfectly safe. Shunts, pacemakers, artificial knees and joints, and breast implants all have risks and complications. Product labeling and patient education are important tools to help patients understand the benefits and limitations of medical devices and aid them in making informed decisions about surgery with medical devices. The FDA's approval should be an assurance to the public that medical devices on the market have a reasonable level of safety and efficacy. We believe this has been demonstrated with silicone gel-filled breast implants.
- **Collaborative Partnerships and Postmarket Conditions** – ASPS and PSEF are interested and willing to establish collaborative partnerships with the FDA and industry on a breast implant registry. Our organizations have resources and skills to help ensure that this postmarket condition will be fulfilled. The National Breast Implant Registry (NaBIR), developed and started by ASPS/PSEF several years ago, could be the beginning of a joint effort between the FDA, manufacturers and plastic surgeons. We are prepared to consider modifying it as necessary and to include our sister society, ASAPS, in future developments. Preliminary meetings with the FDA and industry have been generally supportive of this kind of approach.

Additionally, ASPS and ASAPS bring significant experience and expertise in developing and implementing physician education programs and patient education materials. These

activities are core to the mission of our organizations. We are interested in working collaboratively with FDA and industry on these initiatives.

COMMENTS

Our comments on the specific sections of the Draft Guidance of concern to our organizations are as follows.

6. Mechanical Testing

6.1 General Information - While the agency recommends testing that “mimics in-vivo conditions,” the human variables regarding breast health and activity make the simulated environment for testing unrealistic. We are concerned about how the physical differences in patients are included as well as the variable medical history that alters the environment in which the implant resides. The metabolic and chemical environment of each patient cannot be replicated in the laboratory. In contrast to the rigid environment of the orthopaedic device where stress can be more accurately measured in the laboratory, the nature of the human breast does not allow for such stress analysis. We would recommend that manufacturers continue to investigate the possibility of new and improved test modalities, if possible, but that FDA acknowledge the potential limited clinical significance of these types of tests. In light of the substantial amount of clinical data now available or accessible, we believe the development of such tests be a postmarket condition.

6.2 Fatigue Rupture Testing of Total Device – In general ASPS and ASAPS support the agency’s request for improved mechanical testing of breast implants. Current testing methods do not produce helpful data regarding shell failure over time. As noted above, we are concerned that test methodologies intended to mimic in-vivo conditions may be unrealistic and not predictive of in-vivo performance. The artificial testing laboratory should to some degree mimic the real life experience of the device. It should measure tolerances of the shell to implantation techniques, which are surgeon specific, and changes in the implant shell that may occur after a period of time in vivo. If mechanical testing in a laboratory can be correlated to real time in vivo stress, or in some way exceed those stresses, then the realistic durability of the shell can be measured. Variables, such as a woman’s lifestyle and the type and level of her physical activities are important factors that influence wear and tear of the implant, however, these cannot be fully taken into account in mechanical testing.

6.5 Bleed Testing

Silicone Gel-Filled Breast Implants – The FDA recommends that a complete report be provided of gel bleed bench testing based on a protocol that mimics in-vivo conditions. We do not believe that achieving an accurate replication of in-vivo conditions is possible and recommend that review of published studies on this subject, including the study by Evans on tissue analyses for silicone from patients with implants and female cadavers¹, is preferable.

7. Modes and Causes of Rupture

Retrieval Study – We believe that examination and analysis of explanted breast implants can provide important information and are very encouraged by the FDA’s recognition of the work in

¹ Evans, G.R.D., and Baldwin, B.J. From cadavers to implants: silicon tissue assays of medical devices. *Plast Reconstr Surg*, 100:1459, 1997.

this area by Brandon, et. al.² Funded in 2002-03 by our affiliated National Endowment for Plastic Surgery and ASERF, this study was conducted to determine the modes, causes and rates of implant failure. It demonstrated the types of scientific analyses needed for each type of implantable device used by plastic surgeons and resulted in development of a standardized protocol, which gives surgeons a clear approach for handling explanted breast implants. We suggest that if any future studies are conducted, they should be developed in collaboration with our societies, academics and the industry. Our organizations offer research opportunities through a competitive granting process.

The FDA's recommendations for the design of a retrieval study suggest some variables that are clearly within the purview of the operating surgeon. These include:

- device handling prior to insertion
- device position
- implantation technique
- the type of glove worn by the surgeon, i.e., powdered or non-powdered
- the use of drains
- the technique employed in closure of the wound
- the type of post-operative dressing utilized
- the post-operative instructions given the patient
- the nature of the explantation of the device.

Additionally, the method and technique of explantation would need to be reviewed for variables, which would also have to be factored into the analysis of the reasons for the device rupture. The increasing number of variables make it more difficult to determine the timing and cause of the device rupture to a reasonable certainty. The manufacturer depends on surgeon compliance to provide this detailed history covering a time period of the life of the implant. And the surgeon, in turn, relies on patient compliance for the simple post-operative periodic evaluation. Unfortunately, not all patients are as willing to cooperate in these studies.

We believe that retrieval study data, which accurately defines the mode(s) and cause(s) of rupture provides useful information. We believe this can be done postapproval, and do not believe approval should be delayed until a new methodology can be implemented.

9. Clinical Studies

9.2 Lost-to-Follow-Up Analyses - With regard to lost-to-follow-up analyses, ASPS and ASAPS can play a role in encouraging physicians who are serving as investigators in manufacturers' clinical studies to increase their patient follow-up efforts. There is precedent for this cooperation, as the ASPS/PSEF worked collaboratively with the FDA, Mentor and McGhan (now Inamed) in the mid-90s to encourage saline implant clinical investigators to expand their patient follow-up efforts.

Patients lost to follow-up represent a problem, but first-hand experience has taught us that patient compliance in clinical practice among this often mobile population can be a significant challenge. Many of the women who have benefited from breast implant surgery quickly adapt to their implants, move on with their lives, and do not follow-up as requested. In our experience, manufacturers' incentives have been helpful and often necessary in encouraging some patients to return for periodic follow up per the implant protocol.

² Brandon, H.J., Young, V.L., Watson, M.E., Wolf, C.J., and Jerina, K.I. Protocol for retrieval and analysis of breast implants. *J. Long Term Eff Med Implants*. 13:49, 2003.

9.3 Safety Assessment: Rupture of Silicone Gel-Filled Breast Implants – Device rupture is one of the primary safety concerns that has been raised regarding breast implants, particularly silicone gel-filled breast implants. The Guidance identifies MRI as the current method of choice for detecting silent rupture, and the FDA recommends that “patients in the silent rupture cohort undergo MRI evaluations at 1, 2, 4, 6, 8 and 10 years, if not more frequently.” We understand that the manufacturers have agreed to a “silent rupture cohort” that will utilize MRI’s to identify the statistical risk of silent rupture. We believe that this should continue postapproval. A ten-year follow-up period would be excessive for pre-market approval.

While we understand this recommendation applies to the clinical study, we would have concerns if this recommendation were to be applied to the general population post-approval. ASPS and ASAPS are concerned about its potential impact on patient follow-up. At current costs for MRI (estimated at \$800 per exam), this would add \$4,800 in expense per patient (six MRI exams over 10 years) without certainty of gaining the desired information. Post-approval this cost would be borne by patients or insurers and could have an inappropriate influence on patients in their choice of implant. The decision to proceed to MRI in the case of any individual patient outside the “silent rupture cohort” should be a choice between physician and patient.

While the expected lifespan of breast implants is not clear, the risk of implant rupture increases with increasing implant age. The rupture study by Holmich, et al based on the Danish Registry estimates a rupture-free survival of 98% at five years and 83-85% at 10 years.³

An alternative approach for monitoring and detecting silent rupture would be a breast examination by a plastic surgeon every two to three years. Algorithms for clinical care of women with implants have recently been developed through a consensus conference organized by members of the ASPS/ASAPS Breast Implant Work Group. Their summary report and algorithms have been submitted for publication in the peer-reviewed journal *Plastic and Reconstructive Surgery*.

An algorithm would be used to help diagnose rupture clinically. If lumps or changes in the consistency of the breast tissue are found on examination, a mammogram or sonogram would be done. Depending on the results, a MRI may also be indicated. We recommend that patients with implants and no symptomatology discuss with a plastic surgeon the status of their implant and the advisability of undergoing replacement or an MRI at 10 years following implantation. Patients should be urged and advised, by both the implanting surgeon and implant manufacturer, that in the absence of any clinical symptoms or problems, a follow-up with the implanting surgeon every 2-3 years is highly recommended. Information on the patient’s follow-up exam could be added to the patient’s entry in a breast implant registry.

The FDA also recommends that if a rupture, because of the mechanical or chemical properties of the device, cannot be visualized using MRI, an alternative method with comparable sensitivity and specificity be developed. This recommendation presupposes a better (or equally effective alternative) technology than MRI exists or will exist in the future. Since this technology has been developed within a different field of medicine and device manufacturers, ASPS and ASAPS believe this is an impractical expectation. Such new imaging modalities are not necessary to demonstrate the safety and effectiveness of this device.

³ Holmich, L.R., Friis, S., Fryzek, J.P., Vejbo, I.M., Conrad, C., Sletting, S., Kjoller, K., McLaughlin, J.K., Olsen, J.H. Incidence of silicone breast implant rupture. *Arch Surg.* 138:801, 2003.

9.3 Connective Tissue Diseases (CTDs) – The FDA recommends that a sponsor collect information on diagnoses of CTD, and specifically that information on rheumatic disease and rheumatic syndromes be provided to patients enrolled in the Core Study. ASPS and ASAPS believe that patients in the Core Study, all breast implant patients and potential breast implant patients, should be provided with clear information regarding risks, possible complications, and benefits of breast implant surgery. The information provided should be accurate and factually based, and not unduly alarming. Thus, any information on CTDs should accurately reflect the results of the many studies on this issue. The National Institutes of Health⁴ in May 2003 reported to Congress that a large meta-analysis published in the *New England Journal of Medicine*⁵ concluded there was NOT sufficient evidence to support any relationships with connective tissue disorders. This followed the landmark 1999 Institute of Medicine⁶ review of the literature that reached similar conclusions, as well as other studies, such as the CTD report published in the *Archives of Internal Medicine*.⁷

As part of the algorithm project mentioned in section 9.3 undertaken by members of the ASPS/ASAPS Breast Implant Work Group, an algorithm has been developed for clinical management of CTD and rare diseases that some have thought could be related to breast implants. This treatment guideline for physician management of care has been submitted for publication in the journal *Plastic and Reconstructive Surgery*.

In light of the many studies that have not found a causal link between CTD and breast implants, we believe that manufacturers should provide information on CTDs, rheumatic disease, and rheumatic syndromes to women in the Core Study, with qualifications. Information should include what a reasonable patient needs or wants to know before deciding whether to undergo a surgical procedure, i.e., there have been anecdotal reports by women with implants, however, no causal link has been established by scientific studies, and the relative incidence of connective tissue diseases within various female age populations without implants is within the same range.

9.4 Effectiveness Assessment

Health Related Quality of Life (HRQL) – The FDA recommends that manufacturers conduct HRQL assessments to measure the beneficial impact of the device. ASPS and ASAPS support the use of well-designed assessments of effectiveness and patient satisfaction, such as the study by Cash et al, which examined women's psychosocial outcomes of breast augmentation with silicone gel-filled implants in a two-year prospective study.⁸

⁴ Breast Implants: Status of Research at the National Institutes of Health, May 2003.

⁵ Janowsky, E.C., Kupper, L.L., Hulka, B.S. Meta-analysis of the relation between silicone breast implants and the risk of connective tissue diseases. *N Engl J Med.* 342:781, 2000.

⁶ Bondurant, S., Ernster, V., Herdman, R. *Safety of Silicone Breast Implants*, Report of the Committee on the Safety of Silicone breast Implants (IOM), Washington, D.C.: National Academy Press, 1999.

⁷ Kjoller, K., Friis, S., Mellekjær, L., McLaughlin, J.K., Winther, J.F., Lipworth, L., Blot, W.J., Fryzek, J., and Olsen, J.H. Connective tissue disease and other rheumatic conditions following cosmetic breast implantation in Denmark. *Arch Intern Med* 161:973, 2001.

⁸ Cash, T.F., Duel, L.A., and Perkins, L.L. Women's psychosocial outcomes of breast augmentation with silicone gel-filled implants: a 2-year prospective study. *Plast Reconstr Surg.* 109:2112, 2002.

At the FDA advisory panel on silicone gel-filled breast implants in October 2003, the ASAPS presented the results of two retrospective outcome studies of more than 5,000 women with or considering breast implants.⁹ The research was funded by the ASERF. Each survey was posted on the independent website www.implantinfo.com over a period of months. Both surveys showed that women's motivation for having their breasts enlarged primarily relates to their sense of self. In the first survey, the top reasons for choosing breast augmentation for 79 percent or more of the respondents were: to look better in clothes, to feel better about themselves, to feel more confident and to feel less self-conscious. Pleasing others was one of their lowest priorities. Results of both surveys showed that women's expectations were met by the procedure. Ninety-two percent said they were happy about their decision to get breast implants, and 89 percent said the augmentation completely or mostly met their expectations and 94 percent said they would recommend breast augmentation to their friends or family. If they could choose, based on what they know today, 84 percent of the women with implants in this survey said they would very likely get them again. Additionally, 82 percent reported an improvement in self-confidence.

9.5 Supplemental Clinical Information – The ASPS and ASAPS strongly support the FDA's recommendation that manufacturers provide supplemental clinical information outside of the PMA protocol (from other U.S. or European retrospective or prospective studies), as well as relevant information from the published literature. We encourage the flexibility of informational sources suggested by the Draft Guidance document, as FDA reviews implant PMA applications.

The manufacturers of breast implants for use within the United States are the same companies that manufacture breast implants used in other parts of the world. The FDA's willingness to allow consideration of additional clinical information presents a unique opportunity for implant manufacturers to provide long-term data on silicone gel-filled breast implants. In most countries in the European Union, silicone gel-filled breast implants have never been taken off the market and this allows for a 30 year track record in some markets. In Europe, silicone gel-filled breast implants are used in roughly a 9:1 ratio over saline breast implants.¹⁰ This history permits the collection and evaluation of data on a cohort of patients over a longer time period to determine the frequency of device rupture and the clinical consequences of such rupture. Numerous studies of silicone gel-filled implants^{11, 12, 13, 14} have come from Europe, particularly the Scandinavian countries, which

⁹ Casas, L. Testimony before the FDA General and Plastic Surgery Devices Panel, Gaithersburg, MD, Oct. 15, 2003. <http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3989T1.htm> (accessed March 31, 2004).

¹⁰ Spear, S. Testimony before the FDA General and Plastic Surgery Devices Panel, Gaithersburg, MD, Oct. 15, 2003. <http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3989T1.htm> (accessed March 31, 2004).

¹¹ Winther, J.F., Friis, S., Baach, F.W., Mellemkjaer, L., Kjølner, K., McLaughlin, J.K., Lipworth, L., Blot, W.J., and Olsen, J.H. Neurological disease among women with silicone breast implants in Denmark. *Acta Neurol Scand*, 103:93, 2001.

¹² Signorello, L.B., Fryzek, J.P., Blot, W.J., McLaughlin, J.K., and Nyren, O. Offspring health risk after cosmetic breast implantation in Sweden. *Ann Plast Surg* 46:279, 2001.

¹³ Jensen, B., Kjølner, K., McLaughlin, J.K., Danneskiold-Samsoe, B.D., Bliddal, H., Blot, W.J., and Olsen, J.H. Muscular rheumatism following breast surgery in Denmark. *Clin Exp Rheum* 19:229, 2001.

¹⁴ Holmich, L., Kjølner, K., Vejborg, I., Conrad, C., Sletting, S., McLaughlin, J.K., Fryzek, J., Lipworth, L., Jacobsen, P.H., Breiting, V., Brandt, B., Jorgensen, A., and Olsen, J.H. Prevalence of silicone breast implant rupture among Danish women. *Plast Reconstr Surg*, 108:848, 2001.

have unique nationwide databases and data-linking possibilities. We believe that the significant body of well-controlled epidemiological studies on breast implants in the scientific literature will directly address rupture and other long-term safety issues raised by the Panel in October 2003. The existing studies and literature support the FDA panel approval, and the long history of use in Europe will allow data evaluation to continue during the postapproval phase.

9.6 Supplemental Literature Information – We agree with the FDA’s recommendation that companies provide a current review of the literature for specified topics. Additionally, our Breast Implant Work Group monitors the scientific literature on breast implants and provides information that is used to guide directed-research projects in areas of identified concern and to support ongoing education of our organizations’ members. An annotated bibliography summarizing the scientific literature over the past several years was submitted to the FDA General and Plastic Surgery Devices Panel in October 2003. An updated document is attached. (Attachment A).

9.7 Postapproval Requirements – The Draft Guidance lists certain conditions for PMA approval that the FDA may require of manufacturers postapproval or to comply with restrictions relating to the sale, distribution or use of a company’s device. Our organizations are ready to establish collaborative partnerships with the FDA and industry with respect to these postapproval activities. Preliminary ASPS/PSEF meetings with the FDA and industry have been generally supportive of collaboration on a breast implant registry, physician education and patient education.

Continued follow-up – ASPS and ASAPS believe continued follow-up of Core Study patients can be done postmarket and that our organizations could play an important role in urging physicians who are clinical investigators to be diligent in their clinical follow-up responsibilities. We have seen that clinical investigators, in cooperation with the manufacturers, are working to ensure adequate follow-up of this highly mobile population. Manufacturer-provided incentives for patient follow-up have proven helpful in some cases. Other mechanisms and inducements may need to be considered to improve compliance for women who are not exhibiting problems and have no implant-related concerns.

ASPS and ASAPS are willing to work with manufacturers to identify individual plastic surgeons who will commit to the serious responsibilities of being a clinical investigator.

Additional Studies to address modes and causes of rupture – The ASPS/PSEF believes that collecting basic data on breast implant procedures and complications could be addressed by requiring manufacturers to initiate a voluntary patient registry. The National Breast Implant Registry (NaBIR), developed by the PSEF in 2000 as a research tool and launched by the ASPS/PSEF in July 2001, can be expanded and developed in cooperation with manufacturers and the FDA. NaBIR’s advantages are that it is a secure, internet-based, HIPPA-compliant program designed to collect breast implant data across manufacturers and implant types. Patient and surgeon confidentiality is assured and data collection and analysis is performed in real time. As of April 2, 2004, NaBIR has collected data on 11,839 surgeries, 18,451 implants and 2,814 explants. We believe that this is a reasonable approach. A summary report of the registry is attached (Attachment D). (See discussion below for additional comments on the registry)

An education and certification program – ASPS and ASAPS strongly support the concept of physician education on breast implants. Our organizations have many years of experience in developing and implementing all aspects of physician education programs, and have the necessary infrastructure to do it well. Our organizational expertise includes collaborative program planning, logistics implementation, program evaluation, and accreditation by the Accreditation Council on Continuing Medical Education (ACCME). ACCME accreditation enables ASPS and ASAPS to

grant physicians Continuing Medical Education (CME) credits verifying attendance at an educational program. We plan to work collaboratively with manufacturers in implementing breast implant educational programs. Faculty selected for our educational programs are experienced clinicians and skilled educators.

ASPS and ASAPS believe that physician education on breast implants can be safely implemented postmarket and that education should be voluntary. We suggest that manufacturers' websites recognize surgeons who have participated in specific breast implant surgery education to give women interested in implant surgery additional information on which to select their surgeon.

Our ASPS/ASAPS Breast Implant Work Group has developed a new four-hour continuing medical education program on breast implants to be presented this month in Vancouver, BC at the annual meeting of the American Society for Aesthetic Plastic Surgery. The program outline is attached. (Attachment B). The program is designed to train surgeons on surgical technique, patient selection, patient monitoring, and management of complications. It will also cover how to improve patient communication to better manage patient expectations and reduce the number of elective reoperations. The content, program length, format and delivery will be critically evaluated following this program and will change as improvements are made for future instructional courses and symposia. We will be working to complete an internet-based CME educational program for those physicians who may be unable to travel to these programs. Additional treatment algorithms for infection, capsular contracture, stretch deformity, implant size exchange and rupture, developed by members of the ASPS/ASAPS Breast Implant Work Group, will be incorporated into the educational curriculum content. An interactive patient-physician consent algorithm is also currently under development.

We also should note that ASPS and ASAPS are experienced in collaborative development of educational programs and partnerships with industry. For example, the societies developed and implemented the ultrasound-assisted lipoplasty workshop series several years ago to educate plastic surgeons on patient safety issues of using this new technology.

ASPS and ASAPS recognize that some physicians who may not be members of our societies will seek training options. Our educational programs are open and available to all interested physicians.

A patient registry: National Breast Implant Registry – ASPS and ASAPS believe that all women who receive breast implants – silicone gel, saline, or alternate fill -- should be offered the option of enrolling in a scientifically-directed patient registry. This could be addressed by requiring manufacturers to support a voluntary patient registry post approval. A registry would gather outcomes data and could be used to as a guide to locate patients for follow-up or notification or to target them for additional study data collection. Due to the heightened publicity related to the review of this device, we believe that the breast implant registry should be administered by a third party. Funding could be handled using a patient pass-through fee to the third-party.

ASPS and ASAPS believe that the NaBIR Registry, developed by the PSEF in 2000 as a research tool and launched by the ASPS/PSEF in July 2001, can be used to meet the panel-recommended condition for a breast implant registry. NaBIR's advantages are (a) it is already established and functioning, (b) it is a secure, internet-based, HIPPA-compliant program designed to collect breast implant data across manufacturers and implant types, and (c) it is run by a neutral third party. Patient and surgeon confidentiality is assured and data collection and analysis is done in real time. In the future, we believe that there will be added value in linking patient satisfaction data collection

and the ASPS/ASAPS Silicone Breast Implant Surgery online patient information booklet¹⁵ (Attachment C) to the web-based registry and adding the follow-up patient satisfaction survey as another component. As of April 2, 2004, more than 100 sites are participating in NaBIR, and data has been contributed on 11,839 implant surgeries and 18,451 implants.

The ASPS/PSEF National Breast Implant Registry is linked to an innovative web-based outcomes data collection program called TOPS – Tracking Operations and Outcomes for Plastic Surgeons, which has been developed as a shared initiative of the American Society of Plastic Surgeons and the American Board of Plastic Surgery. This internet data collection mechanism provides valid clinical /practice information to plastic surgeons and allows the individual surgeon to compare his/her own outcomes against national benchmarks. ASPS and ASAPS believe NaBIR and TOPS could provide a mechanism for additional data collection on implants.

NaBIR has allowed ASPS/PSEF to lead the way in international collaboration on breast implant data collection. The European Union has mandated that its member countries have breast implant registries, and plastic surgery societies in several countries have endorsed NaBIR as the model of choice. As a result, the International Breast Implant Registry was formed to allow collaborative data collection and analysis among the U.S., European, South American and Australian organized plastic surgery societies.

ASPS/PSEF and ASAPS/ASERF are interested in further dialogue with the FDA and manufacturers regarding the establishment of a breast implant registry. The use of a single uniform internet-based data entry portal for all implantations can provide the information sought by the FDA, manufacturers, and surgeons. We would like to participate in a meeting to discuss the pertinent data elements, structure and governance necessary for administration of a registry. We would encourage the FDA to convene such a meeting.

10. Clinical Data Presentation

10.4 Safety Data Presentation – Complications

Reasons for Device Removal and Reoperation – ASPS and ASAPS are in agreement with the FDA that data on device removal and reoperation should be collected. As clinicians we know that some patients elect reoperation for size change and we are taking steps to improve surgeons' communications with patient pre-operatively in order to better manage patient expectations and reduce the number of elective reoperations.

We recommend that the reasons listed for removal and reoperation be categorized as follows:

Reasons for device removal:

- 1) mechanical factors, such as rupture and malposition
- 2) inherent risks of surgery, such as infection and hematoma.

Reasons for reoperation:

- 1) patient choice related to size or style of implant
- 2) mechanical factors, such as rupture and malposition
- 3) complications related to surgery, such as infection and hematoma

¹⁵ Silicone Breast Implant Surgery, American Society of Plastic Surgeons and the American Society for Aesthetic Plastic Surgery, 2003. <http://www.plasticsurgery.org> (accessed March 31, 2004)

10.5 Safety Data Presentation – Rupture – ASPS and ASAPS disagree with the agency’s recommendation that tissue sampling data of the surrounding breast tissue and capsule be gathered from all patients with ruptured devices undergoing explantation. As noted above (see Sec. 6.5), the studies by Evans and others have addressed the potential movement of silicone from breast implants, which is predominately restricted to the surrounding capsule. Patients must consent to a biopsy, and performing a biopsy without an appropriate clinical reason is inconsistent with the appropriate practice of medicine. Biopsies should be performed to confirm clinical diagnostic impressions, not to meet FDA requirements for device approval.

11. Labeling

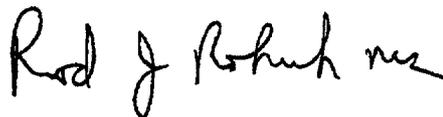
11.4 Patient Labeling – Patient information is very important for informed decision making and for patient satisfaction. We would suggest that the labeling stipulate that, similar to other implantable medical devices, silicone breast implants may eventually need to be removed or replaced. Unknown health concerns can also be addressed through labeling, appropriately advising patients of areas where conclusive data cannot be provided.

11.5 Patient Device Card – ASPS and ASAPS agree with the FDA’s recommendation that patient device cards be provided to the patient by the surgeon immediately following surgery. It is our recommendation that the patient device card link to the voluntary registry. In the future, bar coding should be considered, although we recognize that this should be done as part of a broader FDA initiative applying this technology to all drugs and devices.

Questions or comments regarding this document may be directed to Paul Pomerantz, CAE, ASPS Executive Director, (tel 847-228-3336 or e-mail PP@plasticsurgery.org) or Lousanne Lofgren, CAE, ASPS Assistant Executive Director for Health Policy, Practice and Informatics (tel. 847-228-3328 or e-mail LL@plasticsurgery.org), 444 E. Algonquin Road, Arlington Hts., IL 60005.

Thank you for your consideration.

Sincerely,



Rod J. Rohrich, MD, President
American Society of Plastic Surgeons



Robert W. Bernard, MD, President
American Society for Aesthetic Plastic Surgery

Attachments:

- A. ASPS/PSEF Reviews of Selected Articles on Silicone and Saline Breast Implants, Update, April 2004.
- B. ASPS/ASAPS Silicone Implant Education Initiative, April 16, 2004.
- C. ASPS/ASAPS Silicone Breast Implant Surgery booklet, 2003.
- D. ASPS/PSEF National Breast Implant Registry Report, April 2, 2004.

cc: James H. Wells, MD, Chair, ASPS/ASAPS Breast Implant Work Group
Mark L. Jewell, MD, Co-chair, ASPS/ASAPS Breast Implant Work Group

ABOUT OUR ORGANIZATIONS

This comment document is submitted by the American Society of Plastic Surgeons (ASPS) and its Plastic Surgery Educational Foundation (PSEF), and the American Society for Aesthetic Plastic Surgery (ASAPS) and its Aesthetic Society Education and Research Foundation (ASERF).

American Society of Plastic Surgeons (ASPS) - The ASPS, founded in 1931, represents more than 5,000 physicians certified by the American Board of Plastic Surgery or the Royal College of Physicians and Surgeons of Canada. It is the largest organization of board-certified plastic surgeons in the world and represents the broad spectrum of the specialty of plastic surgery – both reconstructive surgery and cosmetic surgery. The ASPS works closely with the Plastic Surgery Educational Foundation, the education, research, and service arm of the society.

Plastic Surgery Educational Foundation (PSEF) - The PSEF, founded in 1948, funds directed and non-directed research and educates members to ensure patient safety and improve outcomes. As a result of the FDA's call for manufacturers' PMAs for silicone gel implants in 1991 and the clearly identified need for additional clinical research, the PSEF established a 3 million dollar breast implant research fund. It has provided initial funding of three grants plus 15 projects on breast implants, including: autoimmune disorders, biochemistry of silicone gel implants, quality of life, device integrity, local complications, explanation and implant rupture.

American Society for Aesthetic Plastic Surgery (ASAPS) - The ASAPS, founded in 1967, is the only plastic surgery organization devoted entirely to the advancement of cosmetic plastic surgery. Its 2,100 active-member plastic surgeons are certified by the American Board of Plastic Surgery or the Royal College of Physicians and Surgeons of Canada. The ASAPS works closely with the Aesthetic Surgery Education and Research Foundation, the education and research arm of its society.

Aesthetic Surgery Education and Research Foundation (ASERF) – The ASERF identifies and pursue issues relevant to the effectiveness and safety of aesthetic surgery techniques and technology through funding directed research and development of educational programs for plastic surgeons.



Reviews of Selected Articles on Silicone and Saline Breast Implants April 2004 Update

Entries are listed alphabetically by the first author's last name.

Adams, W.P. Jr., Conner, W.C., Barton, F.E. Jr, and Rohrich, R.J. Optimizing breast pocket irrigation in the post-betadine era. *Plast Reconstr Surg.* 107: 1596, 2001.

Breast pocket irrigation with various antibiotic solutions is supported by good literature and extensive clinical practice amongst most plastic surgeons. Unfortunately, recent restrictions on the usage of Betadine for breast pocket irrigation have left many plastic surgeons confused regarding their surgical protocol for aesthetic and reconstructive breast surgery. The purpose of this study was to examine the in vitro efficacy of alternative non-Betadine containing solutions for breast pocket irrigation and to subsequently give recommendations for breast pocket irrigation in the post-Betadine era.

Bacitracin, cefazolin, gentamycin, vancomycin were tested as single agents and in combination against the organisms, which have been most commonly cultured around breast implants and implanted in capsular contracture and peri-procedural infection. An established in vitro method was used for this testing. The single antibiotic agents were ineffective at controlling many of the tested bacteria. The combination of bacitracin, cefazolin and gentamycin and vancomycin, cefazolin and gentamycin both demonstrated excellent control of all the bacteria except for allowing a 9% and 6% growth of pseudomonas respectively. We conclude a combination breast irrigant of bacitracin, cefazolin and gentamycin is an effective alternative to Betadine containing breast irrigants and is recommended for clinical practice. Clinical implications are discussed.

Alderman, A.K., Wilkins, E.G., Lowery, J.C., Kim, M., and Davis, J.A. Determinants of patient satisfaction in postmastectomy breast reconstruction. *Plast Reconstr Surg.* 106: 769, 2000.

As part of the Michigan Breast Reconstruction Outcome Study, patients undergoing first-time mastectomy reconstruction were prospectively evaluated, including cohorts of women choosing expander/implant, pedicle TRAM flap, and free TRAM flap procedures. A total of 212 patients were followed during the period of 1994 to 1997, including 141 immediate and 71 delayed reconstructions. The study population consisted of 49 expander/implant, 102 pedicle TRAM flap, and 61 free TRAM flap reconstruction patients. The analysis showed a significant association between procedure type and patient satisfaction. TRAM flap patients (both free and pedicle) appeared to have significantly greater general and aesthetic satisfaction compared with expander/implant patients ($p = 0.03$ and 0.001 , respectively). Furthermore, pedicle TRAM flap patients were more aesthetically satisfied than those with free TRAM flaps ($p = 0.072$). The other independent variables of age and procedure timing did not appear to significantly affect either general or aesthetic satisfaction. However, preoperative physical activity was positively correlated with general satisfaction at the $p = 0.034$ level. The choice of procedure seems to have a significant effect on both aesthetic and general patient satisfaction with breast reconstruction. In this study, autogenous tissue reconstructions produced higher levels of patient aesthetic and general satisfaction compared with implant techniques. Pedicle and free TRAM flap patients do not seem to differ significantly in general satisfaction. However, women receiving pedicle

TRAM flaps reported greater aesthetic satisfaction compared with patients undergoing free TRAM flaps. Furthermore, patient age and procedure timing may not have an effect on patient satisfaction with breast reconstruction.

Ajmal, N., Riordan, C.L., Cardwell, N., Nanney, L.B., and Shack, R.B. Chemically assisted capsulectomy in the rabbit model: a new approach. *Plast Reconstr Surg.* 112: 1449, 2003.

Capsular contracture remains the most common adverse sequela of aesthetic and reconstructive breast surgery when breast implants are used. Capsulectomy may be technically difficult and can result in damage to the neighboring tissues. The aim of this study was to verify the efficacy of sodium 2-mercaptoethane sulfonate (mesna) as a facilitator of periprosthetic dissection when instilled locally at the time of capsulectomy. Two 40-cc textured saline implants were placed dorsally into each of 20 rabbits. After 5 months, capsulectomy was performed after the removal of the implants. Mesna was used to highlight the junction between scar and normal tissue and to help separate the tissues during the capsulectomy in one of the two capsules in each rabbit. Saline was used for the same purpose in the other. The blood loss, duration of operation, and difficulty of dissection as experienced by the surgeon were recorded during the course of the operation. The capsules were also examined histologically for their thickness and graded according to their degree of intactness at the conclusion of the procedure. The histological grading based on the intactness of the removed capsule ($p = 0.005$), the operating time ($p = 0.003$), and the subjective evaluation of the difficulty of the procedure ($p = 0.003$) were significantly better in the mesna group. There was no significant difference in the blood loss between the two groups. Because of its ability as a chemical dissector, mesna may be a useful aid in capsulectomy. Clinical studies to confirm this evidence are required.

Austad, E.D. Breast implant – related silicone granulomas: the literature and litigation. *Plast Reconstr Surg.* 109: 1724, 2002.

The author reviews the relative literature related to silicone granuloma formation. The conclusions are that clinically apparent silicone granulomas are a rare complication of breast implant placement and surgical resection is indicated when they are asymptomatic a diagnostic dilemma. The author found no evidence in any peer reviewed scientific literature to support any claim or theories (i.e., in litigation) that silicone granulomas play a role in the ill conceived implant related systemic disease.

Azavedo, E., and Bone, B. Imaging breasts with silicone implants. *Eur Radiol.* 9: 349, 1999.

Over the last two decades, the use of breast implants both for breast augmentation and for breast reconstruction following mastectomy has increased substantially. Different materials have been used for breast implants, but silicone gel implants have been used most frequently. Imaging is important in detecting problems with these implants. Imaging modalities such as ultrasound, computed tomography and magnetic resonance imaging offer greater possibilities to assess a failing implant, as well as surrounding breast tissue.

Baack, B. R. and Wagner, J.D. Silicone gel breast implant rupture presenting as a fluctuant back mass after latissimus dorsi breast reconstruction. *Ann Plast Surg.* 51: 415, 2003.

Patient presented with acute onset of a lower back fluctuant mass 12 years after breast reconstruction with a latissimus dorsi musculocutaneous flap and silicone gel implant. The mass was aspirated and subsequent surgical exploration revealed this mass to be free-flowing silicone gel within a cavity that was confluent with the breast implant capsule through an axillary tunnel. Excision of the back cavity, explantation with subtotal capsulectomy, and implant replacement resolved the problem. The authors believe this the first report of distant migration from a silicone gel to the lower back.

Bacilious, N., Cordeiro, P.G., Disa, J.J., and Hidalgo, D.A. Breast reconstruction using tissue expanders and implants in Hodgkin's patients with prior mantle irradiation. *Plast Reconstr Surg.* 109: 102, 2002.

This study relates a retrospective, single-center, case series review of the reconstructive treatment of women previously treated with mantle irradiation for Hodgkin's Disease. From review of the Memorial Sloan-Kettering Cancer Center breast reconstruction database between 1992 and 1999, 7 patients receiving 11 implants in a two-staged breast reconstructive protocol were identified whom had received prior mantle irradiation for Hodgkin's Disease. A high rate of patient satisfaction with a zero re-operation rate and a low complication rate is related with a review of the literature related to the use of breast implants in an irradiated surgical field.

Baeke, J.L. Breast deformity caused by anatomical or teardrop implant rotation. *Plast Reconstr Surg.* 109: 2555, 2002.

This retrospective, single surgeon, case series investigation relates the identification and description of breast deformities as a result of anatomic breast implant malposition and rotation on three potential axes. Retrospective review of the author's personal case series from February 1995 and October 1999 identified 159 patients for retrospective study (199 retromammary, 40 subpectoral; 158 elective augmentations, 1 reconstruction). Patients were then prospectively contacted either by a mail-in survey, e-mail survey, telephone interview or routine follow-up office interview with regard to overall satisfaction with the surgical intervention. Diagnosis of malposition and rotation of anatomic implants and perioperative risk factors associated with its occurrence dominate the remainder of the publication.

Bar-Meir, E., Eherenfeld, M., and Shoenfeld, Y. Silicone gel breast implants and connective tissue disease - a comprehensive review. *Autoimmunity.* 36: 193, 2003.

Silicone breast implants have been in use for breast reconstruction and breast augmentation for a long time. In the late 80's anecdotal reports describing a possible association between silicone-gel filled breast implants, and autoimmune diseases were accumulating. Due to the growing concern about the safety of silicone-gel implants, the Food and Drug administration (FDA) restricted their use to participants in controlled clinical trials, including women having reconstructive surgery. This literature

Baxter, R.A. Intracapsular allogenic dermal grafts for breast implant-related problems. *Plast Reconstr Surg.* 112: 1692, 2003.

Despite advances in surgical techniques and breast implant design, certain problems unique to breast implant surgery remain. Historically, the most difficult problem, capsular contracture, is relatively uncommon now. However, problems related to thin capsules and periprosthetic atrophy are becoming more common; these problems include rippling, symmastia, implant malposition, and bottoming out. Options for treatment of these conditions remain extremely limited, particularly with saline implants. Allogenic dermal grafting provides one satisfactory option. Techniques for use of allogenic dermal grafts and early results from 10 patients are summarized in this article, along with histologic analysis confirming viability of the grafts at 6-month follow-up in one patient. No graft-related complications were identified.

Beekman, W.H., van Straalen, W.R., Hage, J.J., Taets van Amerongen, A.H., Mulder, J.W. Imaging signs and radiologists' jargon of ruptured breast implants. *Plast Reconstr Surg.* 102: 1281, 1998.

Silicone gel leakage problems are central to the furor over the complications alleged to be caused by breast implants. Because clinical examination may not reveal confirmatory signs of gel bleed or rupture, radiologists are often requested by plastic surgeons to evaluate the integrity of the implant's

envelope. The findings of the various imaging investigations are reported in terms such as "teardrop," "linguini," and "snowstorm." To interpret the radiologist's report correctly, the plastic surgeon should be familiar with these terms and the findings they represent. In this article, we present an explanation of the radiologists' vocabulary in these matters, as well as an indication as to the significance of the various signs.

Berg, W.A., Caskey, C.I., Hamper, U.M., Kuhlman, J.E., Anderson, N.D., Chang, B.W., Sheth, S., and Zerhouni, E.A. Single and double-lumen silicone breast implant integrity: prospective evaluation of MR and US criteria. *Radiology*. 197: 45,1995.

This article evaluates the accuracy of magnetic resonance (MR) and ultrasound (US) criteria for breast implant integrity with MR imaging correlation. MR imaging depicts implant integrity more accurately than US but neither method reliably depicts minimal leakage with shell collapse. Mammography is useful in screening bi-lumen implant integrity.

Blackburn, W.D. Jr, and Everson, M.P. Silicone-associated rheumatic disease: an unsupported myth. *Plast Reconstr Surg*. 99:1362, 1997.

Anecdotal reports have raised the issue of an association between silicone breast implants and the development of rheumatic diseases. Fortunately, this issue has now been extensively addressed by controlled studies, which demonstrate no association between breast implants and rheumatoid arthritis, systemic lupus erythematosus, and scleroderma. Moreover, several studies that now have addressed the issue of "atypical connective tissue disease" indicate no association between a number of rheumatic complaints and silicone breast implants. Additionally, several controlled studies show no evidence of chronic inflammation in patients with silicone breast implants. These observations should be reassuring to women with breast implants and the individuals who care for them.

Blackburn, W., Grotting, J.C., and Everson, M. Lack of evidence of systemic inflammatory rheumatic disorders in women with breast implants. *Plast Reconstr Surg*. 99: 1054, 1997.

This is a prospective review that looked at 70 consecutive women for concerns that were thought to be potentially associated with the patient's silicone breast implants. History and physical exams were done, blood samples were analyzed for: complete blood counts, sed-rates, antinuclear antibody and rheumatoid factors. Interleukin 6, Interleukin 8, tumor necrosis factor-alpha soluble intercellular adhesion molecule 1 (sim-1) insoluble interleukin 2 receptor were also assessed.

A clinical diagnosis was made based on the American College of Rheumatology criteria for osteoarthritis, fibromyalgia, systemic lupus, erythematosus and rheumatoid arthritis. Women with isolated soft tissue complaints and compatible physical findings for disorder such as bursitis or tendonitis were considered to have soft tissue rheumatism. Results indicate that the implants have been present for an average of 10.2 years. Most of them placed for cosmetic reasons. The patients related that their implants had been present for an average of 4.8 years prior to the onset of the symptoms. Twenty-seven out of 70 women had fibromyalgia, 21 had soft tissue rheumatism, 11 had osteoarthritis, 3 had inflammatory rheumatoid disease and 8 were considered miscellaneous. There were no consistent abnormalities in routine chemistries with complete blood counts. Twenty-one patients had detectable antinuclear antibodies the majority of low titers with only five samples detectable with dilutions of greater than 1 in 40. There is no significant elevation on a clinical basis or on the serologic markers of systematic inflammatory conditions resulting from the implants.

Brandberg, Y., Malm, M. and Blouqvist, L. A prospective and randomized study, "SVEA," comparing effects of three methods for delayed breast reconstruction on quality of life, patient-defined problem areas of life, and cosmetic result. *Plast Reconstr Surg*. 105: 66, 2000.

This prospective randomized trial compares three methods of delayed breast reconstruction on patient psychosocial and cosmetic outcomes at 6 months and 1 year post-operative. Patients referred from Stockholm County (941201-961231) between 1995 and 1995 were asked to participate. Patients completed a standardized health-related quality-of-life questionnaire (SF-36) prior to randomization to either Lateral Thoracodorsal Flap (n=16), Latissimus dorsi flap (n=30), or Pedicle TRAM (n=29). Just prior to six months post-operative, patients were interviewed by a participating psychologist and completed a SF-36 in addition to a patient-response questionnaire with a focus on satisfaction with the result of the reconstruction. One-year follow-up included a mail-in combination of the two questionnaires.

Brandon, H.J., Jerina, K.L., Wolf, C.J., and Young, V.L. Biodurability of retrieved silicone gel breast implants. *Plast Reconstr Surg.* 111: 2295, 2003.

This study analyzed the shells of single-lumen silicone gel breast implants within the general context of device durability in vivo. The investigation included the major types of gel-filled implants that were manufactured in the United States in a 30-year period. The implants analyzed were Cronin seamed (two explants and one control), Silastic 0 and Silastic I (18 explants and seven controls), and Silastic II (22 explants and 43 controls). The biodurability of the explants was investigated with measurements of the mechanical and chemical properties of the various types of silicone gel control and explanted shells, with implantation times ranging from 3 months to 32 years. The shell properties measured for the controls and explants included the stress-strain relationships, tensile strength, elongation, tear resistance, moduli, cross-link density, and amount of extractable material in the shell. In addition, the mechanical properties of shells that had been extracted with hexane were analyzed for both explants and control implants. The silicone gel explants investigated in this study included some of the oldest explants of the various major types that have been tested to date. For assessment of long-term implantation effects, the data obtained in this study were combined with data from all known other institutions for various types of gel implants. This study shows that silicone gel implants have remained intact for 32 years in vivo and that degradation of the shell is not a primary mechanism for implant failure.

Brandon, H.J., Young, V.L., Watson, M.E., Wolf, C.J., and Jerina, K.L. Protocol for retrieval and analysis of breast implants. *J Long Term Eff Med Implants.* 13: 49, 2003.

The Center for Implant Retrieval and Analysis has been established at Washington University's Division of Plastic and Reconstructive Surgery for the purpose of studying implantable devices retrieved after surgery or autopsy and assessing their condition after implantation. Since the early 1990s, significant experience has been gained in testing and analyzing silicone gel breast implants and, to a lesser extent, saline-filled devices. However, there has been no systematic method reported for collecting and evaluating these implants in a way that would permit different laboratories to compare their data. This article offers the plastic and reconstructive surgery community a standardized protocol for analyzing explanted silicone gel and saline-filled breast implants. The protocol gives surgeons a clearly defined approach for removing, handling, documenting, and shipping explanted breast implants. At the same time, biomaterials researchers can use the protocol to acquire implant data with reliable and reproducible methods. Because the study of saline implants has lagged behind the study of silicone gel implants, the article concludes with a demonstration of how this protocol can be applied to obtain mechanical properties data and use scanning electron microscopy to illuminate failure mechanisms of saline devices, including three implants removed after 20+ years in vivo.

Bridges, A.J. Rheumatic disorders in patients with silicone implants: a critical review. *J Biomater Sci Polym Ed.* 7: 147,1995.

More than 1000 patients with rheumatic disorders and silicone implants have been reported. In this review, the clinical features of patients with scleroderma, inflammatory myositis, systemic lupus erythematosus and silicone implants are discussed. The clinical features of the most common rheumatic disorder associated with silicone implants, the "Silicone Implant Associated Syndrome", are introduced. Other neurological symptoms are discussed as well.

Brinton, L.A., Lubin, J.H., Burich, M.C., Colton, T., Brown, S.L., and Hoover, R.N. Cancer risk at sites other than the breast following augmentation mammoplasty. *Ann. Epidemiol.* 11: 248, 2001.

PURPOSE: There has been limited investigation of cancer risk other than breast cancer among patients with breast implants, despite some clinical and laboratory evidence suggesting links with certain cancer sites, including hematopoietic and connective tissue malignancies. **METHODS:** A retrospective cohort study of 13,488 patients who received cosmetic breast implants at 18 plastic surgery practices in six geographic areas was conducted to assess long-term health effects. After an average of 12 years of follow-up, questionnaires were administered to subjects located and alive (78% of eligible population). Attempts were made to obtain death certificates for deceased subjects and medical verification for all reported cancers. **RESULTS:** A total of 359 malignancies was observed versus 295.95 expected based on general population rates, resulting in a standardized incidence ratio (SIR) of 1.21 [95% confidence interval (CI) 1.1-1.4]. Individual malignancies for which incidence was significantly elevated included cancers of the stomach (SIR = 2.65), cervix (SIR = 3.18), vulva (SIR = 2.51), brain (SIR = 2.16), and leukemia (SIR = 2.19). No excess risks were observed for other hematopoietic malignancies, including multiple myeloma. The internal analyses, however, based on cancer rates derived among the comparison patients, showed no increased cancer risk among the implant patients [relative risk (RR) = 1.00, 95% CI 0.8-1.2], as well as no statistically significant elevations for most individual sites. Cervical cancer continued to be elevated (RR = 1.78), although to a lesser extent than in the external analyses, while the risk for respiratory cancers was higher (RR = 2.40). Non-significant elevations in risk persisted in this analysis for liver cancer (RR = 2.65), brain cancer (RR = 2.83), and leukemia (RR = 1.83). Many of the cancers showing excesses were defined on the basis of death certificates, requiring caution in interpretation. The histologies of the leukemias were quite varied, which makes a biologic relationship appear unlikely. However, respiratory cancers showed some evidence of increasing risk with follow-up time and both respiratory and brain cancers were elevated in the mortality analyses. **CONCLUSIONS:** Although excesses of cervical and vulvar cancer among implant patients might be attributable to lifestyle factors, reasons for excesses of respiratory and brain cancers were less apparent.

Brinton, L.A., Lubin, J.H., Burich, M.C., Colton, T., Brown, S.L., and Hoover, R.N. Mortality among augmentation mammoplasty patients. *Epidemiol.* 12: 231, 2001.

Much attention has focused on disease risks among women receiving silicone breast implants, but there has been little evaluation of their mortality experience. The authors undertook a retrospective cohort study of 13,488 women receiving cosmetic implants and 3,936 patients with other types of plastic surgery at 18 plastic surgery practices. After an average of 13 years of follow-up, deficits in overall mortality were found as compared with the general population (U.S. rates) for both implant [255 deaths; standardized mortality ratio (SMR) = 0.69, 95% confidence interval (CI) = 0.6-0.8] and comparison subjects (125 deaths; SMR = 0.58, 95% CI = 0.5-0.7). These findings indicate that patients seeking plastic surgery are in general healthier than their peers. Implant patients, however, experienced excess risks of death compared with the general population for brain cancer (SMR = 2.45) and suicide (SMR = 1.54). Internal analyses showed a higher overall mortality among the implant than among the comparison patients (relative risk = 1.27, 95% CI = 1.0-1.6). This overall excess reflected

increases for respiratory tract (SMR = 3.03) and brain (SMR = 2.25) cancers and for suicide (SMR = 4.24).

Brinton L.A., Brown, S.L., Colton, T., Burich, M.A., and Lubich, J. Characteristics of a population of women with breast implants compared with women seeking other types of plastic surgery. *Plast Reconstr Surg.* 105: 919, 2000.

Several previous studies have shown that breast implant patients demonstrate a number of differences compared with the general population. However, studies have not compared patients with breast implants with women receiving other types of plastic surgery, of interest because this latter group has been proposed as a comparison group for assessing the long-term health effects experienced by breast implant patients. Questionnaire data obtained from 7447 breast implant patients and 2203 patients with other types plastic surgery were collected during the course of a retrospective cohort study, to determine whether implant patients demonstrate different characteristics compared with a more restricted group of patients. In contrast to previous investigations that compared implant patients with the general population, distinctive differences with respect to family income, number of pregnancies, alcohol consumption, cigarette smoking, or histories of previous gynecologic operations or operations for benign breast disease were not found. However, implant patients were significantly more likely than other plastic surgery patients to be white, have low levels of education, have early ages at first birth, be thin, and be screened frequently for breast disease. Furthermore, implant patients reported somewhat greater use of exogenous hormones and familial histories of rheumatoid arthritis. These results support the notion that other plastic surgery patients are a more appropriate comparison group than women in the general population for studies of the health effects of breast implants; however, there continue to be distinctive characteristics possessed by breast implant patients, which need to be taken into account in an assessment of what disease effects can be uniquely attributed to silicone breast implants.

Brinton, L.A., Lubin, J.H., Burich, M.C., Colton, T., Brown, S.L., and Hoover, R.N. Breast cancer following augmentation mammoplasty (United States). *Cancer Cause Control*: 9: 819, 2000.

Although clinical reports have raised concern that breast implants may either increase the risk of breast cancer or delay its diagnosis, epidemiologic studies have generally shown implant recipients to be at a reduced risk of subsequent breast cancer. A large retrospective cohort study was undertaken to clarify effects of cosmetic breast implantation. A total of 136 breast cancers were observed among the breast implant patients. External analyses, using general population rates from the Surveillance, Epidemiology and End Results (SEER) program, resulted in 152.2 cases expected and a standardized incidence ratio (SIR) of 0.9 (95% CI 0.8-1.1). A comparable SIR was found for the other plastic surgery patients (SIR = 1.0, 95% CI 0.7-1.2). Internal analyses, directly comparing the implant patients with the other plastic surgery patients, showed a RR of 0.8 (95% CI 0.6-1.1). In neither the external nor internal analyses was there any systematic variation in risk by age or calendar year of initial implant. Risk also did not vary by years of follow-up or by type of implant. Risk was not affected by exclusion of patients who received their implants following surgery for benign breast disease. Although breast tumors tended to be detected at a somewhat later stage among the breast implant than the comparison patients, the difference was not statistically significant, nor was there any significant difference in breast cancer mortality between the two groups. Breast implants do not appear to alter the risk of subsequent breast cancer.

Bronz, G. How reliable are textured implants used in breast surgery? A review of 510 implants. *Aesth Plast Surg.* 23: 424, 1999.

This is a single-center, single-surgeon, retrospective case series of 273 patients (510 implants) was reviewed with a focus on capsular contracture with reported patient satisfaction. Patients having undergone subglandular (n=419) or subpectoral (n=91) breast augmentation with textured gel-filled implants between 1988-1996 were reported with regard to Baker Classification post-operatively at 3 months, 6 months and then annually with a cohort follow-up reported as a range from 3 months to 8 years. Of the 383 (94.7%) of the subglandular patients evaluated at 3 months, 98.3% were found to have Baker Class I/II capsular contracture based on the operative surgeons single examination (397 Class I, 78 Class II). 5 patients were Class III and 3 patients were Class IV for a total of 1.7% with poor outcomes at 3 months.

Brown, S.L., Langone, J. J. and Brinton, L.A. Silicone breast implants and autoimmune disease. *J Amer Med Women's Assn.* 53: 22, 1998.

In 1992, the Food and Drug Administration requested a voluntary moratorium on the sale and implantation of silicone-gel-filled breast implants because of growing concern over the lack of scientific and clinical data supporting their safety and effectiveness. Breast implants had been reported to cause serious local complications, and new questions about breast implants and increased risk for autoimmune disease, including the rare but sometimes fatal connective tissue disease scleroderma, were also raised. Since that time, clinical studies have focused on the adjuvant effect of silicone and of potential autoantibody production. Epidemiologic studies have ruled out a large increased risk for connective tissue disease overall in women with breast implants, but samples were too small to rule out an increase in rare connective tissue diseases. Nor were studies properly designed to address whether an atypical syndrome might develop in women with breast implants. Meta-analyses of these studies cannot remedy their underlying methodologic weaknesses. While the question of whether rare connective tissue disease is associated with breast implants may never be answered definitively, recent progress in identifying new syndromes such as fibromyalgia and chronic fatigue syndrome may provide an insight into methodology for evaluating the existence of a silicone-related syndrome in women with breast implants.

Brown, S.L., Duggirala, H.J., and Pennello, G. An association of silicone-gel breast implant rupture and fibromyalgia. *Curr Rheumatol Rep.* 4: 293, 2002.

Silicone-gel breast implant rupture is common. Silicone-gel from ruptured implants may escape the scar capsule that forms around breast implants and become "extracapsular silicone." The authors' previously published study found that women with extracapsular silicone gel were at higher risk of reporting that they were diagnosed with fibromyalgia. This review calls for additional study of this possible relationship.

Brown, S.L., Pennello, G., Berg, W.A., Soo, M.S., and Middleton, MS. Silicone gel breast implant rupture, extracapsular silicone, and health status in a population of women. *J Rheumatol.* 28: 996, 2001.

This study was done to assess whether breast implant rupture or extracapsular silicone is associated with selected symptoms of self-reported physician-diagnosed connective tissue disease (CTD). It was found that women with breast implant rupture diagnosed by MRI were no more likely to report a diagnosis of selected CTD than those with intact implants or those with implants of indeterminate status. Women with extracapsular silicone (silicone gel outside of the fibrous scar that forms around breast implants) were more likely to report having fibromyalgia (FM, $p = 0.004$) or other CTD, which included dermatomyositis, polymyositis, Hashimoto's thyroiditis, mixed CTD, pulmonary fibrosis, eosinophilic fasciitis, and polymyalgia ($p = 0.008$) than other women in the study. This data suggests

an association between extracapsular silicone from ruptured silicone breast implants and FM. If this association persists in other studies, women with silicone gel breast implants should be informed of the potential risk of developing fibromyalgia if their breast implants rupture and the silicone gel escapes the fibrous scar capsule.

Brown, S. L., Epidemiology of silicone breast implants. *Epidemiology*. 13: S34, 2002.

Silicone breast implants have been marketed in the United States since 1963. However, concerns about the safety of these medical devices have been raised in the last several years. In 1992, the Food and Drug Administration restricted the availability of silicone-gel breast implants to women requiring them for reconstruction after breast cancer or for other medical indications. Inflatable saline breast implants have remained available for either reconstruction or for cosmetic augmentation while manufacturers completed studies addressing issues of safety and effectiveness. The Food and Drug Administration (FDA) has less concern today regarding a putative association between breast implants and autoimmune disease because of epidemiologic studies that have indicated that there is not a large increase in risk for connective tissue disease in women with breast implants. These studies have not ruled out a small increase in risk of connective tissue disease to these women nor have they addressed the issue of an atypical syndrome related to silicone. This review provides a brief discussion of the regulatory history of silicone implants and of FDA concerns over breast implants.

Brown, S.L., Middleton, M.S., Berg, W.A., Soo, M.S., and Pennello, G. Prevalence of rupture of silicone gel breast implants revealed on MR imaging in a population of women in Birmingham, Alabama. *AJR Am J Roentgenol*. 175: 1057, 2000.

Silicone gel breast implants have been reported to rupture, but the prevalence of implant rupture in the general population of women with implants is not known. The objective of this study was to assess the prevalence of implant rupture and the presence of extracapsular silicone gel in this population.

Women identified as part of a National Cancer Institute cohort study on breast implants, living in the Birmingham, AL., area were invited to undergo MR imaging of their current silicone gel breast implants at the Kirklin Clinic at the University of Alabama, at Birmingham. Three radiologists independently examined and rated all MR images for signs of implant rupture and extracapsular silicone. 344 women with silicone gel breast implants underwent MR imaging. Implant rupture was reported by at least two of three radiologists for 378 (55.0%) of the 687 implants in this study. Another 50 implants (7.2%) were rated as indeterminate (suspicious) for rupture.

A majority of women in this study, 265 (77.0%) of 344, had at least one breast implant that was rated as ruptured or indeterminate. Radiologists also agreed that silicone gel could be seen outside the fibrous capsule that forms around the implant in 85 (12.4%) of the 687 implants affecting 73 women (21.2%). The prevalence of silent or occult silicone gel breast implant rupture is higher than was previously suspected.

Brown, S.L., Silverman, B.G., and Berg, W. A. Rupture of silicone-gel breast implants: causes, sequelae, and diagnosis. *Lancet*. 350: 1531, 1997.

Silicone-gel-filled breast implants have been widely used for breast augmentation and reconstruction after mastectomy. The rate of implant rupture and its sequelae are not known. We review the frequency, causes, sequelae, and detection of implant rupture. Material testing of removed implants provides evidence that as implants age in vivo, they weaken and may rupture. Sequelae of rupture include migration of gel accompanied by inflammation and silicone granuloma formation. The role of free silicone gel in relation to idiopathic or atypical connective tissue disease is not clear. Magnetic resonance imaging is substantially more sensitive in the detection of rupture than is mammography or ultrasonography.

Cash, T.F., Duel, L.A., and Perkins, L.L. Women's psychosocial outcomes of breast augmentation with silicone gel-filled implants: a 2-year prospective study. *Plast Reconstr Surg.* 109: 2112, 2002.

The authors present a prospective, quantitative, case series investigation that examines multiple psychosocial aspects of breast augmentation utilizing textured and smooth gel-filled mammary implants. A patient population (n=360 patients) was studied using a pre-operative questionnaire addressing patient expectations of surgery, reasons for proceeding with surgery, and personal concerns for safety (surgical and related to implant placement). Outcomes analysis was performed at 6, 12 and 24 months in the form of subsequent questionnaires focused on psychosocial outcomes (body-image improvement, self-image improvement, and sexual/social improvement), persistent patient safety concerns, and benefit to risk appraisals. Further examination of the effects of surgical complications on patient satisfaction is addressed in addition to the potential effect of the FDA moratorium on breast implants on patient overall satisfaction.

Chandler, P.J. Jr., and Kasper, C.S. Frequency and distribution of talc contamination in patients with silicone gel-filled breast implants. *Ann Plast Surg.* 51: 358, 2003.

This study examines contamination of breast implant patients with talc. Peri-implant scar tissue, obtained from a population with breast implants, was evaluated for talc. Patients were considered positive if more than two talc particles were seen intracellularly in more than two microscopic fields. Patients were grouped to demonstrate the difference in talc exposure in Texas after the manufacturer stopped using talc in gloves. This occurred in 1983. Of those receiving implants before 1984, 136 of 140 were positive for talc. Of those receiving implants after 1983, 24 of 54 were positive ($p < 0.000$; RR = 42.5; CI: 13.7-131.6). Widespread prevalence of contamination was evidenced by findings of talc in patients from various facilities, different surgeons, and multiple sites within Texas.

Cher, D.J., Conwell, J.A., and Mandel, J.S. MRI for detecting silicone breast implant rupture: meta-analysis and implications. *Ann Plast Surg.* 47: 367, 2001.

The objective of this study was to assess the accuracy of magnetic resonance imaging (MRI) in detecting silicone breast implant rupture, and to explore implications of the use of MRI for screening and estimating the prevalence of rupture among asymptomatic women. The study consisted of a meta-analysis of published studies with the calculation of sensitivity and specificity as independent parameters, the summary receiver operating characteristic (ROC) curve, and other clinically important values such as positive predictive value (PPV) and negative predictive value. Among lower prevalence populations, PPV appeared to be insufficient to warrant use as a screening tool. MRI is moderately accurate in detecting silicone breast implant rupture. However, MRI should remain a confirmatory diagnostic test and should not be used to screen asymptomatic women.

Chung, K.C., Greenfield, M.L., and Walters, M. Decision-analysis methodology in the work-up of women with suspected silicone breast implant rupture. *Plast Reconstr Surg.* 102: 689, 1998.

Despite numerous studies advocating ultrasonography and magnetic resonance imaging (MRI) in the evaluation of women with possible silicone breast implant rupture, an appropriate algorithm has not been published for the optimal use of these tests. To derive a diagnostic algorithm using ultrasonography and MRI, we applied a decision-analytic model using Bayes theorem to calculate the probabilities of implant rupture for three representative patient characteristics. This diagnostic algorithm will assist plastic surgeons in counseling women who are worried about the integrity of their silicone breast implants.

Clough, K.B., O'Donoghue, J.M., Fitoussi, A.D., Vlastos, G., and Falcou, M.C. Prospective evaluation of late cosmetic results following breast reconstruction: I. implant reconstruction. *Plast Reconstr Surg.* 107: 1702, 1997.

This prospective, consecutive case series examines the long-term cosmetic results of a 360 immediate implant breast reconstructive patient series performed from 1989 to 1997 at a single institution by two surgeons with an early complication rate of 9.2%, late complication rate of 23%, a symmetrization rate of 92.5%, and a revisional surgery rate of 30.2%. The cosmetic outcomes were judged on a 5 point global scale by 3 independent observers routinely at serial 6-month follow-up examinations on 334 available patients with a median follow-up of 4.2 years (range 1 to 9 years). A distinct linear decrease in aesthetic satisfaction was noted from an initial 86% acceptable at 2 years to 54% at 5 years with an author highlighted study limitation analysis of the potential effects of patient attrition. The decline in cosmetic outcome was independent of implant type, volume of implant reconstruction, age of patient, type of mastectomy incision, or radiotherapy. Capsular contracture was significantly associated with lessened cosmesis, however, it did not account for the only variable of causation. The authors hypothesize that asymmetric contralateral ptosis progression over time was a contributing factor to decreased cosmesis over time.

Collis, N., Coleman, D., Foo, I.T., and Sharpe, D.T. Ten-year review of a prospective randomized controlled trial of textured versus smooth subglandular silicone gel breast implants. *Plast Reconstr Surg.* 106: 786, 2000.

This prospective randomized controlled trial presents its 10 year follow-up of an original cohort of 53 patients whom underwent subglandular silicone gel-filled (Mentor) breast implant augmentation (24 smooth, 27 textured) at a single center in 1989. Patients without significant capsular contracture at 3 years were contacted for 10 year examination (11/14 smooth, 18/24 textured). Smooth implant contracture rate had increased from 6% at 3 years to 65% at 10 years which was significantly different from textured implants of 11% which was constant from the time period addressed. Additional information regarding the protective effect of submuscular placement is presented. Smoking is reported to increase capsular contracture rates in augmented patients. Data relative to Nator smooth and Meme polyurethane breast implants is also presented. Follow-up of patients is discussed relative to the phenomena that once capsular contracture occurs, it is difficult to correct i.e. "Prevention is better than cure as far as capsular contracture is concerned."

Collis, N., Coleman, D., Foo, I.T., and Sharpe, D.T. An analysis of telephone interview data collected in 1992 in 820 women who reported problems with their breast implants to the Food and Drug Administration. *Plast Reconstr Surg.* 109: 2043, 2002.

The authors present an applied qualitative method of analytic induction to describe "salient themes, recurring ideas, patterns that occurred across subjects and within subgroups, and any relationships within the data" derived from the telephone interview of women who reported breast implant problems to the FDA in 1992. A 108 item questionnaire focusing on 9 categories of implant safety and patient medical history was designed based on the study of the transcripts of original telephone calls from patients who reported local implant and/or systemic problems after breast implant surgery to the Problem Reporting Program in collaboration with the Postmarket Product Management of the FDA and the Surveillance Program of the NCI. This questionnaire was then administered by female representatives of Westat (Rockville, Md.), a survey research firm, to a group of these participants and results were reported.

Cunningham, B.L., Lokeh, A., and Gutowski, K.A. Saline-filled breast implant safety and efficacy: a multicenter retrospective review. *Plast Reconstr Surg.* 105: 2143, 2000.

The authors present an industry-funded, outcomes-based, multi-center, retrospective review of the safety and patient satisfaction of saline breast implants with a mean follow-up of 13 years. This study

extends from a prior investigation with a focus on improved patient tracking, stronger biostatistical support with a minimum of 10 year follow-up. Physician and patient-reported data on 450 patients are represented with statistical analysis for complication rates, implant actuarial survival, and patient satisfaction.

de la Torre, J.I., Fix, R.J., Gardner, J.M., and Vasconez, L.O. Reconstruction with the latissimus dorsi flap after skin-sparing mastectomy. *Ann Plast Surg.* 46: 229, 2001.

This retrospective, single-center, case series reviews the application of immediate breast reconstruction utilizing latissimus dorsi flaps in combination with saline implants after skin-sparing mastectomy. Eighteen patients (23 breasts) reconstructed between September 1996 and October 1998 with a range of follow-up from 22 to 48 months are reviewed in addition to a description of the surgical technique. Post-operative surgeon evaluation of cosmesis and patient subjective appraisal is included.

De Jong, W.H., Kallewaard, M., Goldhoorn, C.A., Verhoef, C.M., Bijlsma, J.W., Schouten, J.S., and Van Loveren, H. Long-term exposure to silicone breast implants does not induce antipolymer antibodies. *Biomaterials.* 25: 1095, 2004.

This study examined whether antipolymer antibody assay (APA) as an objective laboratory assay could contribute to the diagnosis in women with a silicone breast implant (SBI) and complaints/symptomatic disease. The authors investigated whether there is a large number of symptomatic SBI recipients in the Netherlands. The number of APA positive responses in our study population was low. In addition, also in the normal population a similar low percentage of positively reacting women were observed. Hence, we cannot recommend the use of the APA assay for diagnostic purposes in the clinical evaluation of SBI recipients with severe complaints/symptoms.

De Jong, W.H., Kallewaard, M., Goldhoorn, C.A., Geertsma, R.E., Van Loveren, H., Bijlsma, J.W.J., and Schouten, J.S.A.G. Study to determine the presence of antipolymer antibodies in a group of Dutch women with a silicone breast implant. *Clin Exper Rheum* 20: 151, 2002.

The purpose of this study was to determine if there is a population of women with silicone breast implants (SBI) with a high prevalence of antipolymer antibodies and severe health complaints/symptoms. The population was chosen from a voluntary registry of SBI recipients and selection was based on the severity of self-reported complaints in a questionnaire. Blood samples from 42 SBI women and 12 female lab workers (controls) were analyzed. 7% of the SBI women and 17% of the controls had positive APA assay. 21% of SBI women and 8% of controls had weakly positive samples. Another interesting finding was that the SBI women reported quite high incidence of symptoms (example: 95% with fatigue, 81% with arthralgia, 48% with morning stiffness) yet the general assessment performed for all the women by a physician placed 85% of the women's disease activity into "no or mild disease activity".

Duffy, M.J., and Woods, J.E. Health risks of failed silicone gel breast implants: a 30-year clinical experience. *Plast Reconstr Surg.* 94: 295, 1994.

The purpose of this paper is to assess the clinically evident systemic health problems associated with failed silicone gel breast implants. A computer search of the medical records of 2033 patients receiving implants from 1962-1992 revealed that between 1970 and 1992, 200 women 14 to 75 years of age underwent secondary silicone gel breast implant procedures by a single surgeon. This allowed determination of the exact integrity status of 681 implants collectively placed in these 200 patients. The common indications for surgical re-exploration in these 200 patients were capsulectomy, open capsulotomy, or implant exchange/removal. All patients had a minimum clinical follow-up of 6 months. Surgical findings revealed that 577 (85 percent) implants were intact in 135 (67.5 percent)

patients and that in 65 (32.5 percent) patients, 104 (15 percent) implant failures were found. The patients' medical records were reviewed with specific attention to diagnoses suggesting immune-related disorders, siliconoma, acquired non-breast malignancies, metachronous breast cancer, and recurrent breast carcinomas. In this very select subgroup of 65 patients with silicone gel breast implants which had failed or were deteriorating, no excess of expected immune-related disorders or malignancies was identified. Our 30-year clinical experience with silicone gel breast implants for augmentation mammoplasty or breast reconstruction failed to demonstrate that clinically evident adverse health problems are incurred by those women who subsequently experience a silicone gel breast implant failure.

Englert, H., Joyner, E., McGill, N., Chambers, P., Horner, D., Hunt, C., Makaroff, J., O'Connor, H., Russell, N., and March, L. Women's health after plastic surgery. *Intern Med J.* 31: 77, 2001.

This is a population-based retrospective cohort study where Australian women who had received augmentation mammoplasty for cosmetic reasons during 1979 and 1983 were compared with other Australian women who had non-silicone associated plastic surgery. Allegations that exposure to endogenous silicone, especially related to breast implants, might be causally related to connective tissue disease originated from case studies.

Both groups were matched for age plus or minus five years; and year of plastic surgery plus or minus two years. There was no difference in the occurrence of connective tissue diseases or connective disease related parameters, thyroid disorders, fibromyalgia or multiple sclerosis between the cohorts. Axillary adenopathy and low titer positive anti-nuclear antibody occurred with significantly greater frequency in the exposed cohort. Axillary adenopathy correlated with capsular contracture and also self-reported development of digital vasospasm after breast augmentation. No association was found between the augmentation mammoplasty exposure and various connective tissues disease and/or their related features.

Fagrell, D. Beggren, A. and Tarpila, E. Capsular contracture around saline-filled fine textured and smooth mammary implants: a prospective 7.5 year follow-up. *Plast Reconstr Surg.* 108: 2108, 2001.

This prospective randomized controlled clinical trial investigates the potential effect of small pore size (30 to 70 micrometer) texturization on capsular contracture in the clinical setting of submammary saline-filled breast implants. Siltex Model 2800 and Smooth Model 1800 Mentor saline-filled breast implants were blindly randomized to individual patient side, right vs. left, in a patient cohort (n=20) and followed at 6mo, 1yr and mean of 7.5 yrs (range 5 yrs 11 mo to 8 yrs 4 mo) with regard to capsular contracture and patient satisfaction. Patients were blinded up until the 1 year evaluation and then followed for implant preference. Capsular contracture was evaluated by physician physical examination and subjective Baker Classification. No significant difference was found in capsular contracture with smooth vs. texturized implants. Patients did report that augmentation had a positive effect on the quality of life.

Flassbeck, D., Pfeleiderer, B., Klemens, P., Heumann, K.G., Eltze, E., and Hirner, A.V. Determination of siloxanes, silicon, and platinum in tissues of women with silicone gel-filled implants. *Anal Bioanal Chem.* 375: 356, 2003.

Silicone gel used in breast implants has been known to migrate through intact silicone elastomer shells, resulting in the clinically observable "gel bleed" on the implant surface. Although silicon concentration in capsular tissues of women with silicone prostheses have been measured with element-specific silicon analyses, no silicone-specific investigation of these tissues has been performed as yet. A combination of element-specific inductively coupled plasma high-resolution isotope dilution mass spectrometry (ICP-HR-IDMS) and species-specific gas chromatography

coupled mass spectrometry (GC-MS) was used to analyze silicon, platinum, and siloxanes in prosthesis capsule, muscle, and fat tissues of women (n=3) who had silicone gel-filled breast implants and in breast tissue of non-augmented women (n=3) as controls. In all tissues of augmented women, siloxanes, in particular octamethylcyclotetrasiloxane (D4), decamethylcyclopentasiloxane (D5), and dodecamethylcyclohexasiloxane (D6) were identified. Depending on the siloxane species and type of tissue analyzed, siloxane levels in the range of about 10-1,400 ng g⁻¹ were detected; total silicon was found in all tissue samples in the range of about 8,900-85,000 ng g⁻¹. Higher platinum levels ranging from 25-90 ng g⁻¹ were detected in fibrin layer and fat tissue of two patients with prostheses. No siloxanes were detected in control breast tissue samples. This investigation of human tissues by a combination of element-specific and species-specific analytical techniques clearly demonstrates for the first time that platinum and siloxanes leak from prostheses and accumulate in their surrounding tissues.

Fodor, L., Ramon, Y., Ullmann, Y., Eldor, L., and Peled, I.J. Fate of exposed breast implants in augmentation mammoplasty. *Ann Plast Surg.* 50: 447, 2003.

Exposure of silicone breast implants usually leads to infection and extrusion. According to the literature, implant extrusion rates are not higher than 2% and removal of the implant is recommended. During the past 3 years, the authors dealt with eight implant exposures (six women: two cases of bilateral exposure and four cases of unilateral exposure). All the pockets were infected. Patients were offered two alternatives: immediate removal of the implant and reimplantation after a few months or conservative treatment with an effort to close the exposed area after the discharge stopped. All the patients in this study chose the latter alternative. Four out of eight implants were saved. The authors had to remove the other four. The average follow-up of these women was 2 years and there were no signs of capsular contracture or any other problems. According to this series, 50% of eight exposed breast implants could be saved with conservative treatment.

Food and Drug Administration. Breast Implants - An Information Update - 2000. Rockville, MD: Office of Device Evaluation of General, Restorative and Neurological Devices. 2000.

This 80-page booklet is an update of the FDA's earlier consumer publication on silicone gel-filled and saline-filled breast implants and is a resource for patients and others interested in breast implants. It presents information on availability of breast implants, current research, answers frequently asked questions about implants, reviews potential risks, and covers regulatory issues related to the device. It includes a chronology of FDA activities related to breast implants.

Friis, S., Mellekjaer, L., McLaughlin, J.K., Breiting, V., Kjaer, S.K., Blot, W., and Olsen, J.H. Connective tissue disease and other rheumatic conditions following breast implants in Denmark. *Ann Plast Surg.* 39: 1, 1997.

Researchers investigated the risk of connective tissue diseases (CTDs) following breast implants by using Danish Hospital Discharge Register (HDR) to identify 2,570 women who received breast implants, either for cosmetic reasons (N = 1,135) or for breast reconstruction (N = 1,435), between 1977 and 1992. Two additional cohorts of women having either breast reduction surgery (N = 7,071) or breast cancer without implants (N = 3,952) were identified for comparison. Observed-to-expected (O/E) cases of CTDs and other rheumatic conditions were calculated based on national hospital discharge rates. No CTD excesses were seen in the breast reduction or breast-cancer-without-implant cohorts. Statistically significant risks for muscular rheumatism (a nonspecific discharge diagnosis) were observed in all four patient cohorts: cosmetic (O/E ratio, 2.5; 95% CI, 1.7-3.6), breast reconstruction (O/E ratio, 2.5; 95% CI, 1.7-3.4), breast reduction (O/E ratio, 2.0; 95% CI, 1.6-2.3), and breast cancer without implants (O/E ratio, 1.4; 95% CI, 1.0-1.9). Breast implants showed little association with definite CTDs. Breast surgery however, was associated with an apparent increase in

muscular rheumatism.

Fryzek, J.P., Signorello, L.B., Hakelius, L., Feltelius, N., Ringberg, A., Blot, W.J., McLaughlin, J.K., and Nygren, O. Self-reported symptoms among women after cosmetic breast implant and breast reduction surgery. *Plast Reconstr Surg.* 107: 206, 2001.

A retrospective cohort study was performed in Sweden to evaluate the possibility that an individual symptom or constellation of illness symptoms related to silicone occurs in women after breast implant surgery. A random sample (n = 2500) of all women in the Swedish national implant registry who underwent breast augmentation surgery with alloplastic breast implants during the years 1965 through 1993 was compared with a sample (n = 3500) of women who underwent breast reduction surgery during the same period, frequency matched to the implant patients for age and calendar year at the time of surgery. In total, 65 percent of the breast implant patients (n = 1546) and 72 percent of the breast reduction patients (n = 2496) completed a self-administered questionnaire covering 28 rheumatologic and other symptoms and lifestyle and demographic factors. Practically all of the 28 symptoms inquired about were reported more often by women in the breast implant cohort, with 16 (57 percent) significantly more common in breast implant recipients. In contrast, few significant differences or consistent patterns were observed in the length of time since the implant and in the type (silicone or saline) or volume of the implant. Although women with breast implants report a multitude of symptoms more often than women who have breast reduction surgery, the lack of specificity and absence of dose-response relationships suggest that the excess of reported symptoms is not causally related to cosmetic implants.

Fryzek, J.P., Signorello, L.B., Hakelius, L., Lipworth, L., McLaughlin, J.K., Blot, W.J., and Nyren O. Local complications and subsequent symptom reporting among women with cosmetic breast implants. *Plast Reconstr Surg.* 107: 214, 2001.

This clinical study was a retrospective cohort that looked at the local complications after cosmetic breast augmentation and subsequent symptoms reported by cosmetic augmentation patients. The augmentation group that was compared was a similar control cohort of breast reduction patients the average follow-up was 13 and 12 years respectively.

The author found that 31% of cosmetic augmentation patients had implant change, implant leakage or capsulotomy. When they compared the amount of symptoms reported by this group of patients, they found there were excess systemic complaints in the cosmetic augmentation patients compared with the breast reconstruction group that was not fully explained by the presence of local complications.

Gabriel, S.E., Woods, J.E., O'Fallon, W.M., Beard, C.M., Kurland, L.T., and Melton, L.J. 3rd. Complications leading to surgery after breast implantation. *N Engl J Med.* 336: 677, 1997.

This article is a retrospective cohort out of the Mayo Clinic. A total of 749 women were studied for a follow-up period of 7.8 years. The conclusions were that local complications were frequent including a capsular contracture rate of 17.5%, reoperation rate of 27% over the follow-up period. The most common reason for reoperation was size change. When the data was stratified there was a significantly lower rate of complications (less than 0.001) in the subgroup of patients receiving implants for cosmetic reasons. Overall complication rate of 6.5% in one year and 12% at five years compared to the reconstructed patients 17.3% at one year and 30.4% at five years.

Gabriel, S.E., O'Fallon, W.M., Kurland, L.T., Beard, C.M., Woods, J.E., and Melton, L.J. 3rd. Risk of connective-tissue diseases and other disorders after breast implantation. *N Engl J Med.* 330: 1697, 1994.

This is a retrospective study looking at the possible association between connective tissue disease and silicone breast implant. All women in Olmsted County, Minnesota, who received a breast implant between January 1, 1964, and December 31, 1991, were studied. For each case subject, two women of the same age (within three years) from the same population who had not received a breast implant and who underwent a medical evaluation within two years of the date of the implantation in the case subject were selected as control subjects. Each woman's inpatient and outpatient medical record was reviewed for the occurrence of various connective-tissue diseases, certain other disorders thought to have an autoimmune pathogenesis (e.g., Hashimoto's thyroiditis), and cancer other than breast cancer, as well as related symptoms and abnormal results of laboratory tests. No association was found between breast implants and connective tissue disease or other diseases studied.

Gui, G.P., Tan, S.M., Faliakou, E.C., Choy, C., A'Hern, R., and Ward, A. Immediate breast reconstruction using biodimensional anatomical permanent expander implants: a prospective analysis of outcome and patient satisfaction. *Plast Reconstr Surg.* 111: 125, 2003.

This prospective, single-center, case series design investigation addresses clinical and patient satisfaction outcomes after immediate breast reconstruction utilizing the McGhan 150 permanent expander implant. A study population of 107 consecutive patients (129 breast reconstructions) performed between April 1997 and October 1999 were studied for postoperative breast reconstructive shape and symmetry, patient satisfaction with cosmesis, physician perception of aesthetic outcome and the impact on the quality of life related to the surgical intervention.

Gutowski, K.A., Mesna, G.T., and Cunningham, B.L. Saline-filled breast implants: a Plastic Surgery Educational Foundation multicenter outcomes study. *Plast Reconstr Surg.* 100: 1019, 1997

In 1993, the Plastic Surgery Educational Foundation commissioned an 11-center retrospective cohort outcomes study to obtain physician- and patient-reported data on saline-filled breast implants. Data were obtained from 504 patients with 995 saline-filled breast implants placed between January 1, 1980 and December 31, 1989, with a mean follow-up of 6 years. Most (93.8 percent) saline-filled breast implants were placed for breast augmentation. Of the 504 patients, 104 (20.6 percent) required reoperation for open capsulotomy or for replacement or removal of a deflated implant. Complications occurred in 22 patients (4.4 percent), with hematoma being most common. Implant deflation occurred in 55 implants (5.5 percent) and affected 51 patients (10.1 percent) but was underreported by chart abstraction alone. Overall patient satisfaction with saline-filled breast implants was rated as high by 94.2 percent, and 94.8 percent of patients would choose saline-filled breast implants again. In conclusion, saline-filled breast implants are a safe alternative to silicone gel-filled breast implants and demonstrate a high rate of patient satisfaction. Underfilling of saline-filled breast implants should be avoided because it contributes to deflation. Although intraluminal antibiotics and steroids protect against capsular contracture, they also contribute to saline-filled breast implant deflation. The incidence of capsular contracture is decreased by placing the saline-filled breast implant in the subpectoral position. Finally, patients should be aware of the possible need for reoperations related to their implants.

Hadden, W.E. Silicone breast implants: a review. *Australas Radiol.* 42: 296, 1998.

The diagnostic imaging procedures used to evaluate silicone prostheses used for breast augmentation are reviewed. The nature of silicone and the types of prostheses used are discussed, as are the complications and risks from use of these prostheses. For each imaging type: mammography, ultrasound, and magnetic resonance imaging, criteria for rupture with examples of silicone leak into adjacent tissues are given.

Handel, N., Jensen, J.A., Black, Q., Waisman, J.R., and Silverstein, M.J. The fate of breast implants: A critical analysis in complications in outcomes. *Plast Reconstr Surg.* 96: 1521, 1995.

This is a retrospective review of 1655 breast implants. The study posed several conclusions, the primary one being that capsular contracture was a progressive phenomenon that increased over time independent of other variables. There was no difference in contracture based on filler material. This study is significant because capsular contracture is the most significant local complication reported in multiple studies. Given this finding, studies with saline implants that reduce local complications would apply this benefit to all implants in general.

Hennekens, C.H., Self-reported breast implants and connective-tissue diseases in female health professionals. A retrospective cohort study. *JAMA.* 275: 616, 1996.

The purpose of this article is to examine the association of breast implants with connective tissue diseases. Compared with women who did not report breast implants, the relative risk (RR) of the combined end point of an connective-tissue disease among those who reported breast implants was 1.24 (95% confidence interval, 1.08 to 1.41, $P = .0015$). With respect to the individual diseases, the finding for other connective-tissue diseases (including mixed) was statistically significant ($P = .017$), the findings for rheumatoid arthritis, Sjogren's syndrome, dermatomyositis or polymyositis, or scleroderma were of borderline statistical significance ($.05 < P < .10$), and the finding for systemic lupus erythematosus was not statistically significant ($P = .44$). There were no clear trends in RR with increasing duration of breast implants.

Henriksen, T.F., Holmich, L.R., and Fryzek, J.P. Incidence and severity of short-term complications after breast augmentation: Results from a nationwide breast implant registry. *Ann Plast Surg.* 51: 531, 2003.

The frequency and severity of local complications remain the primary safety issues with silicone breast implants. The Danish Registry for Plastic Surgery of the Breast (DPB), established in 1999, prospectively collects pre-, peri- and postoperative information regarding Danish women undergoing breast augmentation. Through DPB, the authors conducted a prospective follow-up study of short-term local complications among 1090 women who underwent cosmetic breast implantation from June 1999 through October 2002. Nineteen percent of women who underwent initial implantation developed at least 1 adverse effect. Forty percent of the adverse effects occurred within 3 months of implantation; 79%, within 6 months. Capsular contracture grade II-IV was observed among 4.1% of women in the 2-year follow-up period. Overall, 97 (29%) of the 344 adverse effects among 55 (6%) of the 971 women required surgical intervention. A higher incidence of adverse effects typically occurred after subsequent implantations. According to the DPB experience, we conclude that most short-term postoperative adverse effects following cosmetic implantation are clinically insignificant and do not require treatment and that short-term complications requiring adjuvant treatment are rare.

Hidalgo, D. A., Breast augmentation: choosing the optimal incision, implant and pocket plane. *Plast Reconstr Surg.* 105: 2202, 2000.

Author relates a retrospective case series with a technical operative focus on breast augmentation related to the incision site, implant selection and pocket plane selection. Conclusions regarding patient satisfaction, long-term effects of capsular contracture, implant rupture/deflation and re-operation rates were not the primary intent of the publication. A total of 220 patients having undergone surgery between 1991 and 1998 were reviewed (primary augmentation (n=77), unilateral augmentation for symmetry in the setting of breast reconstruction (n=80) and secondary aesthetic augmentations (n=63) with a follow-up range of 1mo. to 6 years.

Holmich, L.R., Friis, S., Fryzek, J.P., Vejborg, I.M., Conrad, C., Sletting, S. Kjoller, K., McLaughlin, J.K., and Olsen, J.H. Incidence of silicone breast implant rupture. *Arch Surg.* 138: 801, 2003.

These authors examined whether the incidence of silicone breast implant rupture varies with implantation time and type of implant. In 1999, 271 women who had received breast implants at least 3 years before, and who were randomly chosen from a larger cohort of women with cosmetic breast implants, underwent a baseline MRI. A second MRI was performed in 2001; 317 silicone implants (in 186 women) that were intact at the baseline MRI (n = 280) or were intact at baseline but removed before the second MRI (n = 37) were included in the rupture incidence analyses. When implants were found to have definite or possible rupture, crude and implant age-adjusted incidence rates were calculated, and implant survival was estimated based on the observed rupture rates. It was found that 33 definite ruptures (10%) and 23 possible ruptures (7%) occurred during the 2-year period. The overall rupture incidence rate for definite ruptures was 5.3 ruptures/100 implants per year (95% confidence interval, 4.0-7.0). The rupture rate increased significantly with increasing implant age. Double-lumen implants were associated with substantially lower rupture risk than single-lumen implants. For modern implants intact 3 years after implantation, it is estimated rupture-free survival of 98% at 5 years and 83% to 85% at 10 years.

Holmich, L.R., Kjoller, K., Fryzek, J.P., Hoier-Madsen, M., Vejborg, I., Conrad, C., Sletting, S., McLaughlin, J.K., Breiting, and V., Friis, S. Self-reported diseases and symptoms by rupture status among unselected Danish women with cosmetic silicone breast implants. *Plast Reconstr Surg.* 111:723, 2003.

Epidemiologic evidence does not support an association between silicone breast implants and connective tissue or other rheumatic diseases. However, a recent study has suggested that women with ruptured implants may be at increased risk of developing fibromyalgia. An analysis of adverse health outcomes according to breast implant rupture status was conducted in 238 unselected Danish women with cosmetic silicone breast implants. Ninety-two of the women had definite implant rupture, and 146 had intact implants as determined by magnetic resonance imaging. Before undergoing imaging, the women provided blood samples and completed a self-administered questionnaire. Women with ruptured implants overall, and the subgroup with extracapsular ruptures (n = 23), were compared with women with intact implants regarding a number of self-reported diseases and symptoms and the presence of specific autoantibodies, such as antinuclear antibodies, rheumatoid factor, and cardiolipin immunoglobulin G and M antibodies. Overall, there were no differences in the occurrence of self-reported diseases or symptoms or in the presence of autoantibodies between women with intact implants and women with ruptured implants, including extracapsular rupture. The only exception was capsular contracture, which was reported six times more frequently by women with extracapsular ruptures than by women with intact implants (OR, 6.3; 95 percent CI, 1.7 to 23.5). In conclusion, this study of unselected women with silicone breast implants could establish no association between silicone implant rupture and specific diseases or symptoms related to connective tissue disease or other

rheumatic conditions, except for an excess of capsular contracture among women with extracapsular rupture.

Holmich, L.R., Mellekjaer, L., Gunnarsdottir, K.A., Tange, U.B., Krag, C., Moller, S., McLaughlin, J.K., and Olsen, J.H. Stage of breast cancer at diagnosis among women with cosmetic breast implants. *Br J Cancer*. 88: 832, 2003.

Concern has been raised about the potential delay in breast cancer diagnosis in the augmented breast. The authors linked a cohort of 2955 women, who received cosmetic breast implants in Denmark during the period 1973-1997 with the Danish Cancer Registry and the Danish Breast Cancer Cooperative Group register. They identified 23 incident cases of invasive breast cancer diagnosed subsequent to breast implantation. The authors found that women with breast implants on average were diagnosed with breast cancer at the same stage as controls. Significantly more women with breast implants had tumor cells in the surgical margins according to the Danish Breast Cancer Cooperative Group's data. There was no significant difference in overall survival between the two groups after an average of 6.4 years of follow-up. Based on this limited number of women with breast cancer subsequent to breast augmentation, breast implants do not appear to delay the diagnosis of breast cancer, and no evidence of impaired survival after breast cancer diagnosis in augmented women was found.

Holmich, L.R., Kjoller, K., Vejborg, I., Conrad, C., Sletting, S., McLaughlin, J.K., Fryzek, J., Breiting, V., Jorgensen, A., and Olsen, J.H. Prevalence of silicone breast implant rupture among Danish women. *Plast Reconstr Surg*. 108: 848, 2001.

The durability of silicone gel-filled breast implants is of concern, but there are few epidemiological studies on this issue. To date, most of the relevant findings are derived from studies of explantation, which suffer from bias by including women with symptoms or concerns about their implants. As part of a long-term magnetic resonance imaging study of the incidence of rupture, this study involved 271 women with 533 cosmetic breast implants who were randomly selected from among women who underwent cosmetic breast implantation from 1973 through 1997 at one public and three private plastic-surgery clinics in Denmark. The prevalence of rupture was determined from the first magnetic resonance screening. The images were evaluated by four independent readers, using a standardized, validated form. The outcomes under study were rupture, possible rupture, and intact implant. Ruptures were categorized as intracapsular or extracapsular. Overall, 26 percent of implants in 36 percent of the women examined were found to be ruptured, and an additional 6 percent were possibly ruptured. Of the ruptured implants, 22 percent were extracapsular. In multiple regression analyses, age of implant was significantly associated with rupture among second- and third-generation implants, with a 12-fold increased prevalence odds ratio for rupture of implants that were between 16 and 20 years of age, compared with implants between 3 and 5 years of age. Surgitek implants (Medical Engineering Corporation, Racine, Wis.) had a significantly increased prevalence odds ratio of 2.6 for rupture, compared with the reference implants. No significant association was found with the position (subglandular or submuscular) or the type of implant (single- or double-lumen). Extracapsular ruptures were significantly associated with a history of closed capsulotomy ($p = 0.001$). In the future, the authors plan to examine the women in their cohort with a second magnetic resonance imaging scan to establish the incidence of rupture, a parameter unknown to date in the literature, and to further characterize those factors associated with the actual risk of rupture.

Hoshaw, S.J., Klein, P.J., Clark, B.D., Cook, R.R., and Perkins, L.L. Breast implants and cancer: causation, delayed detection, and survival. *Plast Reconstr Surg*. 107: 1393, 2001.

Concern for many women with breast implants has been focused on three topics: cancer (both breast and other cancers), delayed detection of breast cancer, and increased breast cancer recurrence or

decreased length of survival. In this study, a qualitative review of the literature on these subjects was conducted, coupled with a meta-analysis of the risk for breast cancer or other cancers (excluding that of the breast). Researchers have consistently found no persuasive evidence of a causal association between breast implants and any type of cancer. The meta-analysis results obtained by combining the epidemiology studies support the overall conclusion that breast implants do not pose any additional risk for breast cancer (relative risk, 0.72; 95% confidence interval, 0.61 to 0.85) or for other cancers (relative risk, 1.03; 95% confidence interval, 0.87 to 1.24). This analysis suggests that breast implants may confer a protective effect against breast cancer. Women with implants should be reassured by the consistency of scientific studies which have uniformly determined that, compared with women without implants, they are not at increased risk for cancer, are not diagnosed with later-stage breast malignancies, are not at increased risk for breast cancer recurrence, and do not have a decreased length of survival.

Hudson, D.A., and Skoll, P.J. Complete one-stage, immediate breast reconstruction with prosthetic material in patients with large or ptotic breasts. *Plast Reconstr Surg.* 110: 487, 2002.

This retrospective case series reports the clinical outcome of immediate prosthetic breast reconstruction at a single surgical center. Eighteen patients (19 implants) underwent single stage gel-filled prosthetic breast reconstruction utilizing a modified Wise pattern breast reduction skin incision with either total muscle coverage of the implant (n=8) or subcutaneous placement of the implant (n=11). Surgical techniques of the skin design and nipple/areolar grafting are presented.

Independent Review Group (United Kingdom). Silicone gel breast implants: report of the independent review group. 1998. www.silicone-review.gov.uk. (accessed 9/18/2003).

This report looks at the scientific literature, areas of concern regarding silicone gel breast implants, and makes recommendations to assist women in making decisions about implants; assure that surgeons have relevant information available; and assure that ongoing data collection on the health effects of implants is done.

International Agency for Research on Cancer. Surgical implants and other foreign bodies. IARC Monograph on the Evaluation of Carcinogenic Risks to Humans, Vol. 7. Lyon: IARC Press, 1999.

This is a summary report on various chemicals and other substances that are found in medical devices. Animal and human carcinogenic data is reviewed, as well as other relevant data. There is a section that reviews breast implants. This review indicates that an analysis of 18,000 women with implants found no evidence of increased risk of breast cancer. A combination of four cohort studies on the same topic found a 24% reduction in risk.

Institute of Medicine. Safety of Silicone Breast Implants. Washington, DC: National Academies Press, 2000.

The landmark IOM study, which reviewed more than 1,000 research reports and held public and private meetings, found that women with silicone breast implants are no more likely than the rest of the population to develop cancer, immunologic diseases, or neurological problems, nor do implants pose a threat in breastfeeding or to unborn babies. The 440 page report notes problems associated with the use of silicone implants, most notably capsular contracture and implant rupture, but states that "there is no plausible evidence of a novel autoimmune disease because of implants." It estimates that in 1997 some 1.5-1.8 million American women had implants, 70 percent of them placed for augmentation. It noted that more than 10 million people in the U.S. have some type of implant, including finger joints and pacemakers, and that many of these are also made, at least in part, from silicone. The committee found no evidence of a health risk from silicone breast implants, but noted that local and perioperative complications occur with a frequency to be cause for concern. These

include overall reoperations, ruptures or deflations, contractures, infections, hematomas and pain. Addressing concerns over a health risk from exposure to silicone, the report summary states "a review of 17 epidemiological reports of connective tissue disease in women with breast implants was remarkable for the consistency in finding no elevated relative risk or odds ratio for an association of implants with disease."

The study was funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases following a 1997 appropriations bill request from Congress. The report was created by an independent panel of 13 scientists under the auspices of the IOM, a private, non-profit organization that provides governmental health policy advice.

Institute of Medicine. Information for Women about Safety of Silicone Breast Implants. Washington DC: National Academies Press, 2000.

The 30 page booklet is a consumer version of the Institute of Medicine's key findings on the safety of silicone breast implants.

Janowsky, E.C., Kupper, L.L., and Hulka, B.S. Meta-analyses of the relation between silicone breast implants and the risk of connective-tissue diseases. N Engl J Med. 16: 781, 2000.

The alleged connection between silicone breast implants and the risk of connective-tissue and autoimmune diseases has generated intense interest during the past decade. The salience of the issue persists, despite the fact that a great deal of research has been conducted on this subject. To provide a stronger quantitative basis for addressing the postulated relation, we applied several techniques of meta-analysis that combine, compare, and summarize the results of existing relevant studies. There was no evidence that breast implants were associated with a significant increase in the summary adjusted relative risk of individual connective-tissue diseases. On the basis of our meta-analyses, there was no evidence of an association between breast implants in general, or silicone-gel-filled breast implants specifically, and any of the individual connective-tissue diseases, all definite connective-tissue diseases combined, or other autoimmune or rheumatic conditions.

Jensen, B., Hechmann, W.I., Friis, S., Kjoller, K., McLaughlin, J.K., Bliddal, H., Danneskiold-Samsoe, B., and Olsen, J.H. Self-reported symptoms among Danish women following cosmetic breast implant surgery. Clin Rheumatol. 21: 35, 2002.

The aim of this study was to examine self-reported symptomatology and to identify distinctive characteristics among women with silicone breast implants (SBI). Women with SBI and women with breast reduction with no previous diagnosis of muscular rheumatism had similar patterns of reporting for most symptoms and characteristics. They reported significantly more somatic symptoms and psychological distress, including somatisation, obsessive-compulsiveness and depression, than women with no breast surgery. No significant differences in self-reported symptomatology and characteristics were observed among the three groups of women with a previous diagnosis of muscular rheumatism. Overall, women with prior muscular rheumatism reported more symptoms than those without. We concluded that self-reported somatic symptoms among women with SBI were similar to those of controls. Women with cosmetic breast surgery appear to have distinctive psychological characteristics. Our study emphasises the importance of taking the psychological profile and previous history of rheumatic diseases into account when examining women with SBI.

Jensen, B., Bliddal, H., Kjoller, K., Wittrup, H., Friis, S., Hoier-Madsen, M., Rogind, H., McLaughlin, J.K., Lipworth, L., Danneskiold-Samsoe, B., and Olsen, J.H. Rheumatic manifestations in Danish women with silicone breast implants. Clin Rheumatol. 20: 345, 2001.

The purpose of this study was to investigate whether women with silicone breast implants (SBI) present with a unique rheumatic symptomatology. The authors assessed the profile of rheumatic disease in six groups of women identified through Danish hospital and population registers, three groups of women with a prior hospital diagnosis of muscular rheumatism (a non-specific diagnostic code) who had previously undergone SBI surgery (n = 28), breast reduction surgery (n = 29) or no breast surgery (n = 27); and three groups of women without a diagnosis of muscular rheumatism who had undergone SBI surgery (n = 21), breast reduction surgery (n = 27) or no breast surgery (n = 56). Women with a prior diagnosis of muscular rheumatism but no prior breast surgery had a significantly higher prevalence of soft-tissue rheumatism than those with breast implant or reduction surgery. No significant differences in the frequencies of rheumatic diseases were observed among the three groups of women without previous muscular rheumatism. No specific pattern of inflammatory rheumatic disorders or soft-tissue complaints was identified among the women with SBI, and blood tests for autoimmunity revealed no unique pattern. Overall, women with earlier rheumatism had significantly increased frequencies of rheumatic conditions than did those without. We found no evidence of a rheumatic symptomatology unique to women with silicone breast implants. Our study emphasises the need for consideration of prior rheumatic disease when evaluating rheumatic manifestations in women with SBI.

Jensen, B., Wiik, A. Wittrup, I.H., Friis, S. Shen, G-Q., Bliddal, H. McLaughlin, J.K., Thomsen, B.L., Danneskiold-Samsoe, B., and Olsen, J.H. Silicate antibodies in Danish women with silicone breast implants. *Rheumatology (Oxford)*. 42:1032, 2003.

This article reviews the use of a new immunological assay to evaluate silicate antibody levels in women with and without silicone breast implants (SBIs). Women (n=186) were identified through Danish population-based registers and categorized into six groups defined by prior breast surgery (breast implantation/breast reduction/no breast surgery) and by the presence or absence of prior hospital diagnoses of soft-tissue rheumatism (muscular rheumatism, ICD-8 codes 717.90 and 717.99). The women underwent blood tests, a silicate antibody assay and a clinical examination. No significant correlations were observed between silicate antibody levels and symptom severity scores. Silicate antibodies were not consistently associated with silicone breast implants and were not correlated with rheumatic symptoms. The clinical relevance of these antibodies remains questionable.

Kallenberg, C.G. Overlapping syndromes, undifferentiated connective tissue disease and other fibrosing conditions. *Curr Opin Rheumatol*. 7: 568, 1995.

Connective tissue diseases (CTDs) frequently present with one or only a few symptoms, which does not allow prompt diagnosis. Raynaud's phenomenon is one of those symptoms. However, only a minority of patients who present with Raynaud's phenomenon develop a CTD. Prognostic factors for the future development of CTD in such patients are older age at presentation, more severe Raynaud's phenomenon, the presence of antinuclear antibodies, and abnormal patterns on nailfold capillary microscopy. Some patients have overlapping symptoms of various CTDs. Mixed connective tissue disease (MCTD) is the prototype of such an overlapping syndrome. Fibrotic conditions related to silicone exposure still evoke much interest. However, most recent data does not substantiate a role for silicone gel breast implants in the development of autoimmune CTDs.

Karlson, E.W., Hankinson, S.E., Liang, M.H., Sanchez-Guerrero, J., Colditz, G.A., Rosenau, B.J., Speizer, F.E., and Schur, P.H. Association of silicone breast implants with immunologic abnormalities: a prospective study. *Am J Med*. 106:11, 1999.

Authors studied immunologic markers (ANA, rheumatoid factor, Ig, complement, C-reactive protein, anticardiolipin, antithyroglobulin, antithyroid, and antisilicone antibodies) in silicone breast implant patients and control group women from the Nurses Health Study, an ongoing prospective cohort study of women.

	+ ANA(>1:40)	RF
200 SBI patients	14%	5%
100 no SBI, definite connective tissue disease	39%	17%
100 no SBI, 1 CTD symptom		
100 no SBI, diabetes	15%	2%
200 no SBI, healthy controls	20%	2%

Karlson, E.W., Lee, I.M., Cook, N.R., Buring, J.E., Hennekens, C.H., and Bloch, K.J. Serologic evaluation to breast implants. *J Rheumatology*. 28:1523, 2001.

Serologic test on women with and without breast implants and diabetic patients (presumed silicone exposure through needles) from the Women's Health Study (randomized trial testing aspirin and Vitamin E in preventing Cardiovascular disease) to look for possible activation of the immune system.

298 women without breast implants
 298 women with breast implants
 52 diabetic patients diagnosed before age 30

In 14 of 16 serologic tests, there was no statistically significant difference between the three groups. For the C3 level, 7.4% of breast implant patients compared to 2.7% of patients without BI showed a decreased C3 levels. For C4, 16.1% of BI patients vs. 10.4% of patients without BI showed a decrease in C4. No higher monoclonal Ig by electrophoresis in breast implant patients. Little evidence for activation of the immune system in breast implant patients. The isolated reduction of C3 and C4 is of unknown significance.

Kent, J. Lay experts and the politics of breast implants. *Public Underst Sci*. 12:403, 2003.

This paper discusses the controversy around breast implants in the United States and Europe. It focuses on the emergence of consumer and support groups for women. It discusses the political environment in which this debate takes place highlighting the fact that lay women are at a disadvantage when arguing with scientists. This paper attempts to provide understanding for consumers, manufacturers and scientists involved in this debate.

Kjoller, K., Holmich, L.R., and Fryzek, J.P. Self-reported musculoskeletal symptoms among Danish women with cosmetic breast implants. *Ann Plast Surg*. 52:1, 2004.

No clinical evidence exists to support the alleged connection between breast implants and rheumatic diseases. This study evaluates rheumatic symptoms reported between 1977 and 1997. The patients were drawn from 2 private clinics in Denmark. The authors found no statistically significant differences in mild moderate or severe musculoskeletal symptoms when women with breast implants were compared with women with other cosmetic surgery. Compared with women from the general population, women with breast implants were statistically significantly less likely to have mild or moderate musculoskeletal symptoms. For severe symptoms the deficit was not statistically significant either. The authors not find an excess of rheumatic symptoms or symptom clusters among women with breast implants. In fact, the occurrence of mild, moderate, and severe musculoskeletal symptoms was generally lower among women with implants compared with women with other cosmetic surgery and women in the general population.

Kjoller, K., Holmich, L.R., Jacobsen, P.H., Friis, S., Fryzek, J., McLaughlin, J.K., Lipworth, L., Henriksen, T.F., Jorgensen, S., Bittmann, S., and Olsen, J.H. Epidemiologic investigation of local complications after cosmetic breast implant surgery in Denmark. *Ann Plast Surg*. 48: 229, 2002.

In contrast to the previous study this recent clinical study is a much better overall design and provides more meaningful data. This is a retrospective cohort of 754 cosmetic augmentation patients being

followed for seven years. The study design was basically two geographically distinct plastic surgeons in Denmark. All surgeries were done by these two surgeons. The follow-up and methods were much more consistent. The data retrieval was also well documented and well controlled. In this group of patients the overall complication rate was 17.8%. Hematoma 2.3%, infection 2.0%, most common complication that led to additional surgery was a capsular contracture (11.4%). The authors also noted that of the complications only 3.4% required subsequent general anesthesia. Overall, there were low incidences of complications and much of these were mild and did not lead to additional hospitalization.

Holmich, L.R., Kjoller, K., Vejborg, I., Conrad, C., Sletting, S., McLaughlin, J.K., Fryzek, J., Breiting, V., Jorgensen, A., and Olsen, J.H. Prevalence of silicone breast implant rupture among Danish women. *Plast Reconstr Surg.* 108: 848, 2001.

The durability of silicone gel-filled breast implants is of concern, but there are few epidemiological studies on this issue. To date, most of the relevant findings are derived from studies of explantation, which suffer from bias by including women with symptoms or concerns about their implants. As part of a long-term magnetic resonance imaging study of the incidence of rupture, this study involved 271 women with 533 cosmetic breast implants who were randomly selected from among women who underwent cosmetic breast implantation from 1973 through 1997 at one public and three private plastic-surgery clinics in Denmark. The prevalence of rupture was determined from the first magnetic resonance screening. The images were evaluated by four independent readers, using a standardized, validated form. The outcomes under study were rupture, possible rupture, and intact implant. Ruptures were categorized as intracapsular or extracapsular. Overall, 26 percent of implants in 36 percent of the women examined were found to be ruptured, and an additional 6 percent were possibly ruptured. Of the ruptured implants, 22 percent were extracapsular. In multiple regression analyses, age of implant was significantly associated with rupture among second- and third-generation implants, with a 12-fold increased prevalence odds ratio for rupture of implants that were between 16 and 20 years of age, compared with implants between 3 and 5 years of age. Surgitek implants (Medical Engineering Corporation, Racine, Wis.) had a significantly increased prevalence odds ratio of 2.6 for rupture, compared with the reference implants. No significant association was found with the position (subglandular or submuscular) or the type of implant (single- or double-lumen). Extracapsular ruptures were significantly associated with a history of closed capsulotomy ($p = 0.001$). In the future, the authors plan to examine the women in their cohort with a second magnetic resonance imaging scan to establish the incidence of rupture, a parameter unknown to date in the literature, and to further characterize those factors associated with the actual risk of rupture.

Kjoller K., Friis S., Mellemkjaer L., McLaughlin J.K., Winther J.F., Lipworth L., Blot W.J., Fryzek J., and Olsen J.H. Connective tissue disease and other rheumatic conditions following cosmetic breast implantation in Denmark. *Arch Intern Med.* 161: 973, 2001.

This study examined the occurrence of connective tissue diseases and other rheumatic conditions among Danish women with cosmetic silicone breast implants. The findings of this study support previous investigations and independent review panel conclusions that an association between silicone breast implants and definite CTDs is unlikely. The observation of an excess of unspecified rheumatism among women with implants and among control women suggests that women undergoing cosmetic plastic surgery have hospitalization rates for this condition in excess of those from the general population.

Kjoller, K., Holmich, L.R., Jacobsen, P.H., Friis, S., Fryzek, J., McLaughlin, J.K., Lipworth, L., Henriksen, T.F., Jorgensen S, Bittmann, S., and Olsen, J.H. Capsular contracture after cosmetic breast implant surgery *Ann Plast Surg.* 47: 359, 2001.

The authors investigated the association between the occurrence of capsular contracture and implant and patient characteristics. All women with breast implants from 1977 to 1997 were identified from the files of two private plastic surgery clinics in Denmark. Information on implant and patient characteristics, surgical procedure, and complications was obtained through medical records and self-administered questionnaires. Of 754 women (1,572 implants), average age at implantation was 32 years. In summary, capsular contracture typically occurs within the first 2 years of implantation. Individual body chemistry may be a factor because more than half the capsular contractures in the current study were bilateral. Occurrence of capsular contracture did not appear to be associated with implant surface or placement, occurrence of local complications, or patient characteristics, although these findings should be interpreted cautiously.

Kjoller, K., Friis, S., Signorello, L.B., McLaughlin, J.K., Blot, W.J., Lipworth, L., Mellekjaer, L., Winther, J.F., and Olsen, J.H. Health outcomes in offspring of Danish mothers with cosmetic breast implants. *Ann Plast Surg.* 48: 238, 2002.

This article examines whether maternal breast implants are related to adverse health outcomes in offspring. This was done by conducting a retrospective cohort study of esophageal disorders, rheumatic disease, and congenital malformations among 2,854 children born to women with breast implants and among 5,805 children born to a comparison group of women who underwent breast reduction or other plastic surgery. Statistics were calculated using both hospitalization and outpatient data. The risk of malformations overall was not statistically significantly higher than expected among children born after maternal breast implant surgery. The elevated risks of adverse health outcomes appear unrelated to breast implants per se, because similar findings were observed among children born both before and after the mother's implant surgery, as well as among children born to mothers in the comparison cohort.

Koot, V.C.M., Peeters, P.H.M., Granath, F., Grobbee, D.E., and Nyren, O. Total and cause specific mortality among Swedish women with cosmetic breast implants: prospective study. *BMJ.* 326: 527, 2003.

For the last several years, there has been discussion about the adverse effects of silicone breast implants. Questions regarding long-term mortality of breast implant patients have been raised within this debate. This prospective study of 3,000 Swedish women reviews the apparent increase in suicide rates among breast implant patients. It shows an increased rate of suicide among breast implant patients (5.2 expected suicides vs. 15 actual suicides). Other causes of mortality, most notably, lung cancer was also higher than expected. This authors speculate that patient personality may be a factor in the increased suicide rate.

Kossovsky, N., Conway, D., Kossovsky, R. and Petrovich, D. Novel anti-silicone surface-associated antigen antibodies (anti-SSAA(x)) may help differentiate symptomatic patients with silicone breast implants from patients with classical rheumatological disease. *Curr Top Microbiol Immunol.* 210: 327, 1996.

The frequency of novel autoreactive antibodies to silicone surface associated antigens (anti-SSAA(x)) was measured in healthy control patients, symptomatic patients with breast implants, asymptomatic patients with breast implants, and control patients with classical rheumatological diseases. The frequencies of elevated anti-SSAA(x) antibodies in 310 symptomatic breast implant patients were 17.4% anti-SSAA(fn), 12.9% anti-SSAA(coll), and 7.4% anti-SSAA(coI3) and 7.1 % anti-SSAA(fbg) [Normal (n = 173) = 0.6% for all four tests] (p < .005). In 11 asymptomatic breast implant patients, the frequencies of elevated values for the same anti-SSAA's were 0%, 9%, 0%, and 0% respectively, while in 50 patients with rheumatoid arthritis, the frequencies were 4%, 0%, 6% and 2% respectively. The anti-SSAA(x) profile for symptomatic patients with breast implants was

different than the profile for control healthy patients ($p < .005$ on all eight tests) but differed significantly by two measures, anti-SSAA(fbg) and anti-SSAA(coI3), from the profile for the 19 patients with systemic lupus erythematosus. We conclude that anti-SSAA(x) antibodies levels in symptomatic patients with breast implants are elevated, that the antibodies are associated with symptoms and that they differ both qualitatively and quantitatively from healthy control asymptomatic patients with breast implants, and symptomatic patients with classical rheumatological diseases.

Lewy, R.I., and Ezrailson, E. Laboratory studies in breast implant patients: ANA positivity, gammaglobulin levels, and other autoantibodies. *Curr Top Microbiol Immunol.* 10: 337, 1996.

Silicone polymers when used in augmentation prosthesis in breast surgery have been associated in the medical literature with various systemic clinical manifestations and abnormal laboratory testing suggestive of an atypical autoimmune disease. The most frequently cited abnormal test result is the antinuclear antibody. The literature regarding this test is reviewed in general, and then specific previous studies analyzed. The present study then compares the rate of positive antinuclear antibody tests in a case series of 3380 breast implant recipients with historical normal controls, and finds a six-fold increase in relative risk of a positive test. Analysis of the data show that this increased tendency is at least partially a function of duration of implant exposure to a significant degree ($p < 0.001$), and the same data shows it is not patient age related. Possible explanations of this phenomenon are discussed, including animal studies suggesting that silicone serves as an adjuvant, and therefore might have an effect on immune tolerance in the subject population.

Liang, M.H. Silicone breast implants and systemic rheumatic disease. Some smoke but little fire to date. *Scand J Rheumatol.* 26: 409, 1997.

For over 20 years silicone breast implants have been used for cosmetic and breast reconstruction purposes. They have recently been banned by the American Food and Drug Administration other than for reconstruction or in the setting of a study. Complications of rupture, leaking, bleeding, capsular thickening and contracture are acknowledged but the potential of silicone implants in causing classic rheumatic diseases or a new syndrome has caused much controversy; there are millions of dollars at stake in legal suits. The biological plausibility of silicone breast implants causing disease is not without merit. The epidemiological evidence linking the two is reviewed.

Lipworth, L., Tarone, R.E., and McLaughlin, J.K. Breast implants and fibromyalgia: a review of the epidemiologic evidence. *Ann Plast Surg.* 52:284, 2004.

The literature does not support evidence of a connection between breast implants and fibromyalgia. However, this remains a concern in some circles. This article examines 16 studies that have evaluated the incidence of fibromyalgia in women with breast implants. The studies are based on data from Sweden and Denmark. . They found relative risks for fibromyalgia of 1.0 (95% confidence interval [CI] 0.3 to 3.0) and for unspecified rheumatism (including fibromyalgia and myalgia) of 1.2 (95% CI 0.9 to 1.5), respectively. Similarly, both a case-control and a cross-sectional study conducted within rheumatic disease clinics reported no association between silicone breast implants and the subsequent development of fibromyalgia. This is a single positive finding, of a greater than 2-fold excess of self-reported fibromyalgia among women with magnetic resonance imaging-diagnosed extracapsular ruptures in one study. It can be explained by selection bias and the use of an inappropriate reference group in the analyses. There have been other well defined studies over the years that also do not substantiate this connection. However, a recent study, 5 does raise this issue again.

Losken, A., Carlson, G.W., Bostwick, J. III, Jones, G.E., Culbertson, J.H., and Schoemann, M. Trends in unilateral breast reconstruction and management of the contralateral breast: the Emory experience. *Plast Reconstr Surg.* 110: 89, 2002.

This retrospective case series examines the practice trends from January 1975 to December 1999 regarding the management of unilateral breast reconstruction and the treatment trends of the contralateral breast for symmetry. A total of 1394 patients were reviewed and categorized regarding the reconstructive method of the unilaterally involved breast to include the timing of the reconstruction (immediate vs. delayed) and the method of excision (non- skin sparing mastectomy vs. skin-sparing mastectomy). Treatment of the contralateral breast, immediate and delayed, included augmentation, mastopexy, augmentation/mastopexy, and reduction. Any type of reconstruction including an implant, i.e. latissimus dorsi with implant, was categorized as "implant" reconstruction, not autologous (n=349: 36% (n=149) from 1997-1989, 20% (n=200) from 1990-2000). Implant reconstructions required contralateral symmetry procedures 66% of the time with augmentation being most common compared to autologous requiring 37%, namely reduction.

Lugowski, S., Smith, D.C., Bonek, J., Lugowski, W. Peters, W. and Semple, J. Analysis of silicon in human tissues with special reference to silicone breast implants. *J Trace Elem Med Biol.* 14: 31, 2000.

Silicon levels in blood, urine, tissue and breast milk and formula.

	(Means)	Blood	urine	2 nd study
30 SBI pts(before 1986)	38.5ug/kg	6.043		103.8
(after 1986)	39.16	5.276		
24 controls, no BI	24.23	6.191		74.3

Statistically significant increase in silicone concentration in blood of breast implant patients vs controls (p=0.046) but no significant difference in urine silicone.

No statistical significant difference in silicon in breast milk between nursing mothers with SBI (58.7ug/kg) and nursing mothers without silicone breast implants (51.5ug/kg). Cow's milk and formula (4.40 mg/kg) were found to have silicone levels a few orders of magnitude higher than breast milk. A second study of silicone blood levels also done. It showed no statistical difference.

Mean concentration of silicone in control tissue (reduction) Mean=0.235 vs. saline capsules M= 20.04 vs. silicone capsules M=39312.7(before 1986) and M= 22773.3(after 1986)

Lykissa, E.D., Kala, S.V., Kurtey, J. B. and Lebovitz, R.M. Release of low molecular weight silicones and platinum from silicone breast implants. *Anal Chem.* 69: 4912, 1997.

We have conducted a series of studies addressing the chemical composition of silicone gels from breast implants as well as the diffusion of low molecular weight silicones (LM-silicones) and heavy metals from intact implants into various surrounding media, namely, lipid-rich medium (soy oil), aqueoustissue culture medium (modified Dulbecco's medium, DMEM), or an emulsion consisting of DMEM plus 10% soy oil. LM-silicones in both implants and surrounding media were detected and quantitated using gas chromatography (GC) coupled with atomic emission (GC-AED) as well as mass spectrometric (GC/MS) detectors, which can detect silicones in the nanogram range. Platinum, a catalyst used in the preparation of silicone gels, was detected and quantitated using inductive argon-coupled plasma/mass spectrometry (ICP-MS), which can detect platinum in the parts per trillion range. Our results indicate that GC-detectable low molecular weight silicones contribute approximately 1-2% to the total gel mass and consist predominantly of cyclic and linear poly-(dimethylsiloxanes) ranging from 3 to 20 siloxane [(CH₃)₂-Si-O] units (molecular weight 200-1500). Platinum can be detected in implant gels at levels of approximately 700 micrograms/kg by ICP-MS. The major component of implant gels appears to be high molecular weight silicone polymers (HM-silicones) too large to be detected by GC. However, these HM-silicones can be converted almost quantitatively (80% by mass) to LM-silicones by heating implant gels at 150-180 degrees C for several hours. We also studied the rates at which LM-silicones and platinum leak through the intact implant outer shell into the

surrounding media under a variety of conditions. Leakage of silicones was greatest when the surrounding medium was lipid-rich, and up to 10 mg/day LM-silicones was observed to diffuse into a lipid-rich medium per 250 g of implant at 37 degrees C. This rate of leakage was maintained over a 7 - day experimental period. Similarly, platinum was also observed to leak through intact implants into lipid-containing media at rates of approximately 20-25 micrograms/day/250 g of implant at 37 degrees C. The rates at which both LM-silicones and platinum have been observed to leak from intact implants could lead to significant accumulation within lipid-rich tissues and should be investigated more fully *vivo*.

Macdonald, P., Plavac, N., Peters, W., Lugowski, S., and Smith, D. Failure of ^{29}Si NMR to detect increased blood silicon levels in silicone gel breast implant recipients. *Anal Chem.* 67: 3799, 1995.

The authors have compared directly the results atomic absorption (AA) spectroscopy and a ^{29}Si magic angle spinning (MAS) nuclear magnetic resonance (NMR) technique reported in the literature by Garrido et al.(Garrido, L.; et al. *Magn. Reson. Med.* 1994, 31, 328-330) for analyzing blood silicon levels in control patients versus patients with silicone gel breast implants. AA spectroscopy yielded blood silicon levels in the nanogram per milliliter range for control patients, while somewhat higher values were found in patients with implants. The ^{29}Si MAS NMR technique applied to the identical blood samples was unable to detect silicon in any of the samples. Sensitivity calculations demonstrate that ^{29}Si MAS NMR should not be expected to detect silicon at the levels determined by AA spectroscopy under the spectroscopic conditions employed and that the concentration of silicon-containing compounds would need to 10(4) times the level detected by AA in order to be detected by this NMR method.

Marotta, J.S., Goldberg, E.P., Habal, M.B., Amery, D.P., Martin, P.J., Urbaniak, D.J., and Widenhouse, C.W. 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.* 49: 227, 2002.

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 intact 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. The 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; $p < 0.001$). 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, SGB

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.

Martin-Mareno, J., Gorgojo, L., Gonzalez, J. and Wisbaum, W. Health Risks posed by silicone implants in general, with special attention to breast implants. Luxembourg: European Parliament. June, 2000. www.europar.eu.int.

Gorgojo, L. Update Report (study) Health Risks posed by silicone implants in general, with special attention to breast implants. May, 2003.

This is a report commissioned by the European parliament in 1998. In 2000, a ban was not placed on silicone breast implants in Europe, but a system for tracking patients and surveillance was implemented. This report presents an update on the scientific literature on silicone breast implants; reviews the opinions of interested parties. The 2003 update concludes that the parties may always be at variance but that the ongoing well being of the patient is of primary importance. Ongoing tracking and surveillance, as well as scientific research, will continue.

Mason, W.T., and Hobby, J.A. Immediate rupture of breast implant following trauma. *Plast Reconstr Surg.* 111: 2432, 2003.

This is a case report of a ruptured silicone gel breast implant following trauma. The author also cites two previous studies in which a series of 32 patients with rupture, 21 had a history of trauma. In another series, trauma was responsible for 4 of 27 ruptures. No direct conclusions can be drawn to determine rupture rates.

McCain, L.A. A review of autoimmune disorders anecdotally linked to mammary implants. *Plast Surg Nurs.* 15: 68, 1995.

Autoimmune disorders lead to a sequence of tissue reactions and damage that may produce diffuse, systemic signs and symptoms. Litigants in many breast implants trials have claimed their autoimmune disorders (rheumatoid arthritis, scleroderma, and SLE) were from a causal relationship with mammary implants. Science suggests environmental factors, such as vinyl chloride, and hereditary factors may account for some of the prevalence of these disorders, however the exact cause remains a mystery and brings into question the claims being brought by litigants regarding implants.

McConnell, J.P., Moyer, T.P., Nixon, D.E., Schnur, P.L., Salomao, D.R., Crotty, T.B., Weinzwieg, J., Harris, J.B., and Petty, P.M. 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.* 107: 236, 1997.

A method for analysis of silicon in tissue was developed to determine silicon content in breast parenchymal and periprosthetic capsular tissues of patients with silicone or saline implants and to compare levels in tissues from normal (nonaugmented) breasts. It is of interest to determine whether increased silicon content in tissues can be associated with morbidity in patients who have received silicone implants. This manuscript addresses the issues involved in analysis of breast tissue samples for silicon and compares silicon levels with tissue histologic findings and patient morbidity. One hundred sixty tissue samples were obtained for silicon analysis from 72 patients during augmentation, capsulectomy with or without replacement mammoplasty, mastectomy, or biopsy procedures and were frozen in acid-washed polystyrene tubes at 220 degrees C until analysis. Samples were thawed, sectioned to approximately 0.1 g (dry weight), and digested in nitric acid before analysis by inductively coupled plasma emission spectroscopy, monitoring emission intensity at 251.6 nm. Tissue silicon levels (breast parenchymal and periprosthetic capsular tissue) in patients with silicone gel implants were much higher (mean, 9,287 micrograms/g, n = 106) than in patients with saline implants

(mean, 196 micrograms/g, n = 37) or non-augmented breasts (mean, 64 micrograms/g, n = 17). Histologic examination was performed on 54 tissue samples stained with hematoxylineosin. Tissue samples were rated as to degree of inflammation and calcification, and amount of giant cells, foamy histiocytes, and vacuoles containing a colorless refractory material. Vacuolization and foamy histiocyte ratings correlated significantly with tissue silicon concentration. No correlations were found between tissue silicon concentration and inflammation, calcification, or giant cell rating. Implant age (number of years an implant was in place before sampling) correlated with capsular tissue silicon concentration in patients with intact implants but not in those with ruptured implants. No difference in tissue silicon concentration was found between patients with or without signs or symptoms of morbidity.

McGregor, J.C., and Brown, D.T. Observations on a consecutive series of patients who have had Trilucent breast implants removed as recommended by the MD. Hazard Notice. *Br J Plast Surg.* 55: 231, 2002.

A prospective study of 25 female cosmetic-surgery patients who had a total of 50 Trilucent breast implants forms the basis of this paper. All but one patient elected to have new implants, of which all but three patients had silicone implants (the others selected glucose saline implants). The Trilucent implants were more difficult to remove than expected because of a 'Velcro-like' attachment to the internal surface of their capsules. As a result, several implants were ruptured on removal (though none were ruptured on initial exposure). The sites of rupture suggest a structural weakness, possibly related to the microchip panel or folds in the implant shell. Only three patients in this series had problems with their Trilucent implants that required additional surgery. One of these remains a significant and unsolved problem.

McLaughlin, J.K., and Lipworth L. Brain cancer and cosmetic breast implants: a review of the epidemiologic evidence. *Ann Plast Surg.* 52: 115, 2004.

The authors examine the results of four existing large-scale incidence follow-up studies regarding the possible occurrence of brain cancer. More than 10,000 women with cosmetic implants followed for as long as 29 years. Overall, there were 12 observed incident cases of brain cancer compared with 9.6 cases expected, yielding a nonstatistically significant summary standardized incidence ratio of 1.25 (95% confidence interval, 0.7-2.2). This data does not support an association of brain cancer with breast implants.

McLaughlin, J.K. Do cosmetic implants cause suicide? *Plast Reconstr Surg.* 112: 1721, 2003.

This editorial addresses the number of recent reports highlighting a possible association between breast implants and suicide. It examines characteristics of those who commit suicide. This article calls for well-designed studies to examine any potential association.

McLaughlin, J.K., Lipworth, L., and Tarone, R.E. Suicide among women with cosmetic breast implants: a review of the epidemiologic evidence. *J Long Term Eff Med Implants.* 13: 445, 2003.

Recent studies of women with cosmetic breast implants suggest a statistically significant increase in suicide risk when compared with the general population. But an association of suicide with cosmetic breast implants based on comparisons with the general population does not by itself support a cause-and-effect relationship regarding the role of implants. Well defined, controlled studies looking at all aspects of social-psychological issues are necessary in order to thoroughly investigate this claim.

Mellemkjaer, L., Kjoller, K., Friis, S., McLaughlin, J.K., Hogsted, C., Winther, J.F., Breiting, V., Krag, C., Kruger Kjaer, S., Blot, W.J., and Olsen, J.H. Cancer occurrence after cosmetic breast implantation in Denmark. *Int J Cancer.* 88:301, 2000.

This article examines the incidence of cancer in sites other than the breast after breast augmentation. Based on information from the Danish Cancer Registry the authors found that no significant excess of cancer was observed among women who received implants in public. The overall findings from this study of 2 implant cohorts and results from other investigations indicate that the risk of cancer does not increase in women with breast implants. There were some inconsistencies between private clinics and public hospitals. They are likely related to selection bias and other issues among the private clinic patients, but this data did not permit exploration of these possibilities. Further research into the determinants of these inconsistencies is warranted.

Middleton, M.S. Magnetic resonance evaluation of breast implants and soft-tissue silicone. *Top Magn Reson Imaging*. 9: 92, 1998.

Concern for the safety of silicone gel-filled breast implants remains an issue. Although systemic effects of silicone are debated, there is growing consensus that implant rupture and other local breast complications from implants are very real concerns. This paper reviews the history of breast augmentation with an emphasis on the great variety of implants manufactured during the last generation. A classification scheme consisting of 14 breast implant categories is described, and the MR appearance of many is illustrated.

Miglioretti, D.L., Rutter, C.M., Geller, B.M., Cutter, G., Barlow, W.E., Rosenberg, R., Weaver, D.L., Taplin, S.H., Ballard-Barbash, R., Carney, P.A., Yankaskas, B.C., and Kerlikowske, K. Effect of breast augmentation on the accuracy of mammography and cancer characteristics. *JAMA*. 291: 442, 2004.

Breast augmentation is not associated with an increased risk of breast cancer; but there is concern that implants may interfere with the detection of breast cancer in women who have implants. This study was designed to investigate that concern. It was determined that among asymptomatic women, the sensitivity of screening mammography based on the final assessment was lower in women with breast augmentation vs women without (45.0% [95% confidence interval [CI], 29.3%-61.5%] vs 66.8% [95% CI, 60.4%-72.8%]; $P = .008$), and specificity was slightly higher in women with augmentation (97.7% [95% CI, 97.4%-98.0%] vs 96.7% [95% CI, 96.6%-96.7%]; $P < .001$). Among symptomatic women, both sensitivity and specificity were lower for women with augmentation compared with women without but these differences were not significant. Breast implants do decrease the sensitivity of screening in asymptomatic women but that does not adversely effect overall outcome.

Montalto, M., Vastola, M., Santoro, L., La Regina, M., Curigliano, V., Manna, R., and Gasbarrini, G., Systemic inflammatory diseases and silicone breast prostheses: Report of a case of adult Still disease and review of the literature. *Am J Med Sci*. 327: 102, 2004.

This is a single case study reporting an adult with Still disease in a patient with breast implants. The disease improved with steroid treatment. The implant remained in the patient. This adds to the concerns about breast implants and autoimmune diseases.

National Institutes of Health. Breast implants: status of research at the National Institutes of Health. May, 2003.

The six-page NIH report to Congress provides an update on the status of its research on the long-term health effects of silicone breast implants. Issued in response to the Medical Device User Fee and Modernization Act of 2002, the NIH report summarizes studies currently being conducted or supported by NIH.

The report includes key results from a long-term retrospective National Cancer Institute (NCI) study of women who elected to have breast augmentation surgery. This study is one of the longest and largest studies to date on the health effects of breast implants and was part of the fiscal year 1992 Senate Appropriations Report, which asked the NCI to develop a strategy for conducting longitudinal studies of women with various types of silicone breast implants.

The participants include 13,500 women who had implant surgery for cosmetic reasons in both breasts before 1989 and compares them to 4,000 women similar in age who had some other type of plastic surgery. NCI researchers found no significant increase in breast cancer incidence or mortality among women with implants compared to controls, and women with implants showed a slight decrease in breast cancer risk during the initial 10-year follow-up period. Patients in the study also experienced lower rates for nearly every cancer and for total mortality when compared to the general population, except for an elevation in mortality from brain cancer and suicide. While the reasons for these excesses are unclear, it is possible that the higher risks observed are due either to chance or to factors common to women who choose to have implants, such as smoking in relation to the lung cancer excesses. A follow-up analysis will evaluate the relationship of breast implants to connective tissue diseases and will continue to follow mortality rates among study participants.

The NIH report also described a study currently underway at the Mayo Clinic to evaluate the efficacy of prophylactic mastectomy in preventing breast cancer. Investigators have also collected clinical information on reconstructive surgery, breast implants, and complications in women with hereditary breast cancer risk who undergo prophylactic mastectomy. The NIH reported that the additional data about reconstructive surgery and implant use may provide information about long-term outcomes and effects of breast implants in the highly select group of women studied.

National Organization for Women. Research indicates long-term risk to women's health not fully addressed in FDA clinical trials. Conclusions from symposium on the safety and effectiveness of silicone gel-filled breast-implants. July, 2003.

The National Organization for Women convened a symposium in spring 2003 to highlight recent research on the safety and effectiveness of silicone gel-filled breast implants and encourage dialogue on these devices. NOW states that the conclusions of the 1999 Institute of Medicine report were misinterpreted by the popular press and erroneously suggested that past research had definitely proven the safety of these devices. The organization states that new research has raised additional questions on the long-term safety of these devices and the need for frequent surgeries to correct complications. The NOW and Public Citizen Health Research Group released the symposium report at a July 22, 2003 press conference on Capitol Hill and called on the FDA to delay reviewing applications for approval of silicone gel-filled devices.

Noone, R.B. A review of the possible health implications of silicone breast implants. *Cancer*. 79:747, 1997.

This article is a literature review looking at possible health hazards of the silicone gel implant. The review is reasonably comprehensive and concludes that silicone gel breast implants may rupture and cause local symptoms but they have not been documented to be systemic health hazard for patients undergoing cosmetic or reconstructive breast surgery.

Nahabedian, M.Y., Tsangaris, T., Momen, B., and Manson, P.N. Infectious complications following breast reconstruction with expanders and implants. *Plast Reconstr Surg*. 112: 467, 2003.

The incidence of infection following breast reconstruction with expanders and implants ranges from 1 to 24 percent. Numerous factors associated with infection have been described; however, a one-variable

at time setting and multifactorial analysis have not been performed. The purpose of this study was to analyze a set of factors that may predispose women to infection of the expander or implant. Between 1997 and 2000, a total of 168 implant reconstructions were performed in 130 women at a single institution. The mean age for all women was 48.2 years (range, 25 to 77 years). The factors that were analyzed included axillary lymph node dissection, chemotherapy, radiation therapy, tumor stage, timing of implant insertion, number of sides (unilateral versus bilateral), tobacco use, and presence or absence of diabetes mellitus. Statistical analysis was performed with stepwise logistic regression. Mean time to follow-up for all patients was 29 months (range, 12 to 47 months). Infectious complications occurred in 10 women (7.7 percent) and in 10 expanders or implants (5.9 percent). Infected implants were removed an average of 116 days following insertion (range, 14 to 333 days). Cultured bacteria included *Staphylococcus aureus* and *Serratia marcescens*. A significant association ($p < 0.04$) was detected between implant infection and radiation therapy. The chance for implant infection was 4.88 times greater for implants that were exposed to radiation therapy compared with those that were not. In addition, there was suggestive ($p < 0.09$) evidence that the chance of implant infection following lymph node dissection was 6.29 times higher than when no lymph nodes were removed. No significant association between implant infection and age, diabetes, tobacco use, tumor stage, timing of implant insertion, or chemotherapy was found.

Nyren, O., Yin, L., Josefsson, S., McLaughlin, J.K., Blot, W.J., Engqvist, M., Hakelius, L., Boice, J.D. Jr, and Adami, H.O. The risk of connective tissue disease and related disorder among women with breast implants. *Brit Med J.* 316: 417, 1998.

This is a large nationwide retrospective cohort study of all women in the Swedish National Inpatient Registry who underwent breast augmentation surgery with artificial implants during 1964 to 1993, compared to women who underwent breast reduction surgery in the same period. It identifies subsequent hospitalization for definite connective tissue disease (rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, dermatomyositis, and Sjogren's syndrome) or related disorders. Twenty-nine women with implants were hospitalized for definite connective tissue disease compared with 25.5 expected based on general population rates (standardized hospitalization ratio 1.1 (95% confidence interval 0.8 to 1.6)). There was no excess in risk for polymyalgia rheumatica, fibromyalgia, and several related disorders. Among women who underwent breast reduction surgery, 14 were hospitalized for definite connective tissue disease compared with 10.5 expected (standardized hospitalization ratio 1.3 (0.7 to 2.2)). Compared with the breast reduction group, women with breast implants showed a slight reduction for all definite connective tissue disease (relative risk 0.8 (95% confidence interval 0.5 to 1.4)).

Oliver, D., Walker, M.S., Wlaters, A.E., Chatrath, P., and Lamberty, B.G.H. Anti-silicone antibodies and silicone containing breast implants. *Brit J Plast Surg.* 53: 410, 2000.

Detection of anti-silicone antibodies in silicone breast implants (SBI) patients has been studied primarily in the United States. This study looks at a British population. Mann-Whitney U-test was used for statistical analysis. Findings were:

	Mean
20 SBI patients	1.54 U/ml
20 women without SBI	1.86
20 women with AI disease (+ANA/RF)	7.29
20 anonymous blood donors	21.5

Blood samples of the first three groups had been frozen and stored 1-14 days before evaluation. The anonymous blood donors had been stored frozen between one and two years. The significant elevation in this blood donor group is thought to be related to storage. There was no significant difference

between silicone breast implant patients and normal controls. There was a significant difference between silicone breast implant patients and patients with autoimmune disease.

Peacock, D.J., and Cooper, C. Epidemiology of the rheumatic diseases. *Curr Opin Rheumatol.* 7: 82, 1995.

Both retrospective and prospective population studies have been used to describe the relationship between silicone gel breast implants and connective tissue disease. These and other studies have helped to define the important role of epidemiologic research in the understanding of rheumatic diseases.

Peters, W., Smith, D., Fornasier, V., Lugowski, S., and Ibanez, D. An outcome analysis of 100 women after explantation of silicone gel breast implants. *Ann Plast Surg.* 39: 9, 1997.

This is a retrospective outcome analysis of 100 consecutive women who requested explantation of their silicone gel breast implants from January 6, 1992 through 1995. Eighteen patients were referred by rheumatologists with a diagnosis of autoimmune or rheumatic disease. Six had autoimmune disease (systemic lupus, rheumatoid arthritis, multiple sclerosis, and Raynaud's). Twelve had rheumatic disease (fibromyalgia, in 10 patients; inflammatory arthritis in 2). All of these 18 patients had developed symptoms of the disease after they had received implants.

All 100 patients were extensively evaluated pre- and post-operatively by interviews, clinical assessment, and by assay of the following laboratory tests: rheumatoid factor, ESR, ANA, and anti-Ro/SSA, La/SSP, Sm, RNP, double-stranded deoxyribonucleic acid, Sci-70, centromere, and cardiolipin. The patients were also evaluated by a questionnaire that was sent at a mean time of 2.7 years post-explantation range 1 to 5 years that had a 75% response rate. Thirty-six percent of the patients had undergone at least one closed capsulotomy and 54% at least one open capsulotomy.

The main reasons for explantation were suspected silicone related health problems in 76%; suspected rupture 59%; breast firmness 36%; breast pain 36%; and musculoskeletal pain 23%. A total of 186 implants were removed. Only 3.2% demonstrated extravasation extracapsularly. The prevalence of class III-IV capsular contracture was 61%. Only 43 of the 100 women elected to have saline implants reinserted. At a mean time of 2.7 years after the explantation, 45% out of the 75 questionnaire respondees felt that their implants had caused permanent health problems and 56% felt that they had not been given adequate informed consent by their original surgeon. Forty-three percent were involved in litigation against implant manufacturers. Twenty-four percent had undergone professional psychological support.

Of the 75 respondees, those who had no proved rheumatic or autoimmune disease responded most favorably to explantation. In those patients, more than 80% related "major improvement" in their symptoms and more than 93% related significantly improved psychological well-being. In patients with fibromyalgia or inflammatory arthritis, most experienced an initial, almost euphoric improvement in symptoms during the first few months after explantation. However, their symptoms subsequently recurred after the following 6 to 12 months. Ultimately, 11 of these 12 patients related no change or further deterioration from their pre-explantation status. Of all 6 patients with autoimmune disease, there was no improvement in clinical or laboratory findings after explantation.

Of the 10 patients with fibromyalgia, all had developed their symptoms after the implants were inserted. The mean implant duration for this group was 12 years ranging 7 to 21. The mean duration of their symptoms was 6.3 years ranging 1 to 16. Of the 100 explanted women 24% had positive tests for ANAs of dilution to 1 to 100 or greater compared to 28% of 100 aged matched control women without exposure to breast implants.

Peters, W., Smith, D., Lugowski, S., McHugh, A., MacDonald, P., and Baines, C. Silicon and silicone levels in patients with silicone implants. *Curr Top Microbiol Immunol.* 210:39, 1996.

Although a potential link between silicone gel breast implants and autoimmune connective tissue disease has been suggested, none has been proven. The potential role of silicone as an immune adjuvant remains very controversial. Currently available techniques do not easily allow precise measurements of silicone in tissues. However, all compounds containing silicon (which would include silicone) can be measured accurately. The present study was designed to measure silicon levels in the fibrous capsules of patients with silicone-gel breast implants, saline breast implants and silicone inflatable penile prostheses. Baseline control silicon levels were obtained from the breast tissue of patients undergoing breast reduction, who had no exposure to breast implants. All silicon measurements were carried out using atomic absorption spectrometry with a graphite furnace. The mean silicon levels in 16 breast tissue control samples from 8 patients undergoing breast reduction varied from 0.046 to 0.742 micrograms/g dry weight, with the median mean being 0.0927. The median silicon level in capsules from 6 patients with saline implants was 7.7 micrograms/g (range 36.6). The median silicon level in capsules from 5 patients with silicone inflatable penile prostheses was 19.5 micrograms/g (range 34.8). Although the levels of silicon in capsules of patients with saline breast prostheses and penile implants were higher than in control samples, they were much lower than those from the capsules of the 58 gel implants (median 9979 micrograms/g). Of the 58 silicone gel breast implants (from 20 patients with bilateral implant removal and 18 patients with unilateral removal) which had been inserted from 1974 to 1990, 28 were intact, 8 had pinhole leaks, and 22 were ruptured. Median capsule silicon levels and ranges for all 58 implants, for intact only, for leaking, and for ruptured were: 9979 (152,000), 10,477 (88,703), 6592 (65,396), and 9922 (152,387) micrograms/g respectively. There were no significant differences in silicon levels associated with implant status, duration in situ, or year of implantation. Capsule contracture was not associated with higher levels of capsule silicon. Capsule silicon levels were about 10(6) times higher than previously assayed blood silicon levels. This may be because silicone released from implants remains localized in capsular tissue, or because blood-borne silicone is quickly excreted. Using ²⁹Si nuclear magnetic resonance spectroscopy, no detectable silicone was found in the blood of 7 control women and 7 women with silicone-gel implants (5 with known implant rupture).

Piccoli, C.W. Imaging of the patient with silicone gel breast implants. *Magn Reson Imaging Clin N Am.* 9: 393, vii-viii, 2001.

There are two reasons for radiologic evaluation of the augmented breast. Because women with implants are at the same risk for breast cancer as other women, imaging is performed to screen for cancer or to work up clinical abnormalities. Additionally, imaging allows assessment of implant integrity. The various methods for imaging implants and breast tissue in the augmented patient are discussed. Imaging findings suggestive of silicone gel implant rupture are presented.

Poblete, J.V., Rodgers, J. and Wolfort, F. G. Toxic shock syndrome as a complication of breast prostheses. *Plast Reconstr Surg.* 96: 1702, 1995.

A case of a 21-year-old woman who developed toxic shock syndrome 6 days after augmentation mammoplasty with saline breast implants is reported. The infecting organism was *S. aureus* that was toxic shock syndrome exotoxin 1-negative and staphylococcal endotoxin B-positive. The causes and etiology of this rare postoperative complication are discussed.

Press R.I., Peebles, C.L., Kumagai, Y., Ochs, R.L., and Tan, E.M. Antinuclear autoantibodies in women with silicone breast implants. *Lancet.* 340: 1304, 1992.

General comparison of symptoms and ANA titers in 24 women referred to rheumatologist for rheumatic complaints. 23 of the 24 women had silicone breast implants. 11 with defined autoimmune

disease, 13 undefined. Results show 10 of the 11 patients had high ANA titers, The other 13 had low titers of ANA. Conclusion: ANA are associated with the development of autoimmune complications in women with silicone breast implants.

Pukkala, E., Kulmala, I., Hovi, S.L., Hemminki, E., Keskimaki, I., Pakkanen, M., Lipworth, L., Boice, J.D. Jr, McLaughlin, J.K. Causes of death among Finnish women with cosmetic breast implants, 1971-2001. *Ann Plast Surg.* 51: 339, 2003.

Mortality patterns among women with cosmetic breast implants have become a concern recently. These investigators examined cause-specific mortality among women who underwent cosmetic breast implantation at major public hospitals and private clinics in Finland from 1970 through 2000. Causes of death through 2001 were identified through the national mortality register. The level of validity of the use of this registry is not given. Among the 2166 women with cosmetic breast implants, 31 deaths were observed versus 32.1 expected. Overall disease mortality was below expectation. Mortality from cancer was close to expectation. There was a statistically significant excess of suicide, based on 10 deaths, which was most pronounced during the first 5 years of follow-up. Questions remain regarding the nature of the suicides, accidents and deaths due to violence that could affect their significance. The authors conclude that, although based on small numbers, women with cosmetic breast implants did not experience higher mortality overall than women in the general population.

Pukkala, E., Boice, J.D. Jr, Hovi, S.L., Hemminki, E., Asko-Seljavaara, S., Keskimaki, I., McLaughlin, J.K., Pakkanen, M., and Teppo, L. Incidence of breast and other cancers among Finnish women with cosmetic breast implants, 1970-1999. *J Long Term Eff Med Implants.* 12: 271, 2002.

To examine cancer risk among women with silicone breast implants, the authors conducted a cohort study of 2,171 women. Nationwide Finnish population and health outcomes registries were used to track patients. The authors concluded that breast implants do not cause cancer, nor do they appear to delay the detection of cancer.

Racano, C., Fania, P.L., Motta, G.B., Belloni, C., Lazzarini, E., Isoardi, R., Boccu, C., Duodeci, S., D'Agosto, M., and Ragni, L. Immediate and delayed two-stage post-mastectomy breast reconstruction with implants. *Minerva Chirurgica.* 57: 135, 2002.

This article reports an Italian study on breast reconstruction post-mastectomy using breast implants. It presumes that reconstruction provides the best quality of life after mastectomy. These authors focus on the aesthetic result of reconstruction and report a 78% satisfaction rate among those receiving implants. This rate takes includes patients who had complications with their implants. The overall satisfaction rate is attributed to the reduced operative time in reconstruction with implants versus other techniques as well as the immediate psychological and physical benefits due to the breast restoration.

Rice, D.C., Agsthan, T., Clay, R.P., and Deschamps, C. Silicone thorax: a complication of tube thoracostomy in the presence of mammary implants. *Ann Thorac Surg.* 60:1417, 1995.

Rupture of silicone breast implants is usually either iatrogenic or due to trauma. The authors present a case of blunt chest wall trauma in a patient with bilateral breast implants. Emergency chest tube thoracotomy resulted in rupture of one of the prostheses and caused subsequent migration of silicone into the chest cavity, where it led to emphysema. The patient ultimately required a thoracotomy to evacuate the silicone and decorticate the lung. Review of the literature and methods to avoid this complication are described.

Richardson, D.C., Long, M., Schroeder, L.W. and Kisielewski, R.W. An in vitro study of the effect of in-folds on the durability of mammary implants. *J Long Term Eff Med Implants*. 12: 281, 2002.

The concern is that in-folding shortens the life of the mammary prosthesis due to failure under tensile fatigue. Samples were taken from various parts of different implants. It was determined that it is possible that in-folding causes reduced fatigue time and may be a factor in developing silicone on silicone abrasive wear and the generation of debris.

Rizkalla, M., Duncan, C., and Matthews, R.N. Trilucent breast implants: a 3-year series. *Br J Plast Surg*. 54: 125, 2001.

The use of Trilucent breast implants in the UK dates back to 1995 and their introduction coincided with the medium-term effects of the silicone-implant controversy. The authors present a review of 3 years' experience of the Trilucent implant (1996-1998) during which 29 patients with a mean age of 39.4 years had a total of 50 implants. The aim of the study was to analyze the results in these patients in terms of complications, reoperation rate and patient satisfaction. Using a combination of retrospective chart analysis and postal survey, the authors found an incidence of implant deflation of 10% (5/50). The overall reoperation rate was 20% (10/50). The postal survey yielded a mean satisfaction score of 7.1 (on a scale of 0-10) from the 20 respondents out of the 29 patients (68.9%). In view of the high complication rate, the authors discontinued the use of Trilucent implants in advance of their withdrawal by the Medical Devices Agency (MDA) in March 1999. However, these findings may now be considered of added interest, particularly with regard to patients who are opting to keep their Trilucent implants despite the recommendation of the MDA in June 2000 that such implants should be removed.

Rizkalla M., Webb, C.B., Chuo, C. and Matthews, R.N. Experience of explantation of Trilucent breast implants. *Br J Plast Surg*. 55: 117, 2002.

In June, 2000 the British Medical Devices Agency (MDA) recommended that all Trilucent (soya-bean-oil filled) breast implants should be removed from patients. This study is a follow-up to a previous study on this topic by these authors. This report includes, 44 patients (82 implants) underwent explantation. 34 were cosmetic cases and 10 were reconstructive. Implant rippling was the most common problem reported (25%), followed by pain (18%), implant deflation (9.1%) and capsular contracture (4.5%). Free oil was seen around the implant in 15 cases; four of these presented with clinical deflation, and three with rippling. The remaining eight patients were asymptomatic. The authors concluded that these implants tend to bleed, as evidenced by the presence of free oil around the implant in 34% of patients. The absence of free oil in 73% of the patients who presented with rippling suggests that the leaking oil is often metabolised and absorbed. This is an important study for women in whom free oil was found around the implant during explantation, and for those who still have Trilucent implants in place, despite the MDA recommendation.

Robinson, O.G. Jr, Bradley, E.L., and Wilson, D.S. Analysis of explanted silicone implants: a report of 300 patients. *Ann Plast Surg*. 34: 1, 1995.

Breast implants from 300 consecutive patients during the 35-month period from February 1, 1991 to January 1, 1994 were examined. Of these, 214 (71.3%) patients had disruption (frank rupture or severe silicone bleed or both) of one or both implants. Of the 592 implants removed, 376 (63.5%) had disruption. No difference was found in disruption rates between those patients relating symptoms to their implants and those who did not (71.8% vs. 70.9%). However, disruption was directly related to time since implantation. A Kaplan-Meier survival curve for mammary implants based on this study has proven very helpful and effective in communicating with patients and has served as a guideline in predicting the presence or absence of implant disruption.

Rohrich, R.J., Kenkel, J.M., Adams, W.P., Jr., Beran, S. and Conner, W.C.H. A prospective analysis of patients undergoing silicone breast implant explantation. *Plast Reconstr Surg.* 105: 2529, 2002.

This prospective, single-center, cohort study was designed to quantitatively investigate whether there are any pre-operative parameters which can be used to identify patients who will have improvement in satisfaction of physical functioning, physical role, bodily pain, general health, physical appearance, appearance orientation and body-area satisfaction after removal of silicone-filled breast implants. An experimental cohort (n=38) was matched with a control volunteer population with no prior history of, nor future interest in breast augmentation. No participants were known to have any documented rheumatologic disease prior to enrollment. An extensive preoperative questionnaire was performed by all subjects and repeated postoperatively at 6 weeks and 6 months. Preoperative physician questionnaires were also administered regarding the general health of the experimental surgical group.

Sahoo, S., Rosen, P.P., Feddersen, R.M., Viswanatha, D.S., Clark, D.A., and Chadburn, A. Anaplastic large cell lymphoma arising in a silicone breast implant capsule: a case report and review of the literature. *Arch Pathol Lab Med.* 127: e115, 2003.

Anaplastic large cell lymphoma is a rare type of primary breast lymphoma. The authors report a case of anaplastic large cell lymphoma, T-cell phenotype, occurring in the periprosthetic capsule of a silicone breast prosthesis 9 years after implantation for augmentation mammoplasty. This case is unique for its unusual presentation.

Sanchez-Guerrero, J., Colditz, G.A., Karlson, E.W., Hunter, D.J., Speizer, F.E., Liang, M.H. Silicone breast implants and the risk of connective-tissue diseases and symptoms. *NEJM.* 332: 1666, 1995.

Silicone breast implants have been linked to a variety of illnesses. This study looked at data from 14 years of follow-up of the Nurses' Health Study cohort. Among 87,501 women who were eligible for follow-up, 516 were confirmed as having definite connective-tissue diseases and 1183 as having breast implants. For women with silicon-gel-filled implants, the comparable relative risk was 0.3 (95 percent confidence interval, 0 to 1.9). The relative risk of self-reported signs or symptoms of connective-tissue disease for women with implants was 1.5 (95 percent confidence interval, 0.9 to 2.4); the risk of having any 1 of 41 signs, symptoms, or laboratory features of connective-tissue disease was 0.7 (95 percent confidence interval, 0.3 to 1.6). The authors did not find an association between silicone breast implants and connective-tissue diseases.

Sarwer D.B., LaRossa, D., Bartlett, S.P., Low, D.W., Bucky, L.P., and Whitaker, L.A. Body image concerns of breast augmentation patients. *Plast Reconstr Surg.* 112: 83, 2003.

This study investigated the body image concerns of women who sought cosmetic breast augmentation. Thirty breast augmentation candidates completed several measures of body image before their initial surgical consultation. Thirty physically similar women who were not interested in breast augmentation were recruited from the medical center and university community and also completed the measures. Breast augmentation candidates, as compared with women not seeking augmentation, reported greater dissatisfaction with their breasts. Augmentation candidates rated their ideal breast size, as well as the breast size preferred by women, as significantly larger than did controls. In addition, women interested in breast augmentation reported greater investment in their appearance, greater distress about their appearance in a variety of situations, and more frequent teasing about their appearance. Finally, breast augmentation candidates also reported more frequent use of psychotherapy in the year before the operation as compared with women not seeking augmentation. These results replicate and extend

previous studies of body image in cosmetic surgery patients.

Semple, J.L., Lugowski, S., Baines, C.J., Smith, D., and McHugh, A. Breast milk contamination and silicone implants: preliminary results using silicon as a proxy measurement for silicone. *Plast Reconstr Surg.* 102: 528, 1998.

In response to concerns about contamination of human breast milk from silicone gel-filled breast implants, and because silicon levels are assumed to be a proxy measurement for silicone, we compared silicon levels in milk from lactating women with and without implants. Two other sources of infant nutrition, cow's milk and infant formulas, were also analyzed for silicon. The survey took place at the Breast-feeding Clinic at Women's College Hospital in Toronto. A convenience sample of lactating women, 15 with bilateral silicone gel-filled implants and 34 with no implants, was selected. Women with foam covered or saline implants or with medically related silicone exposures were ineligible. Collection of samples was scrupulously controlled to avoid contamination. Samples were prepared in a class 100 "ultraclean" laboratory and analyzed using graphite furnace atomic absorption spectrophotometry.

Silicon levels were analyzed in breast milk, whole blood, cow's milk, and 26 brands of infant formulas. Comparing implanted women to controls, mean silicon levels were not significantly different in breast milk (55.45 +/- 35 and 51.05 +/- 31 ng/ml, respectively) or in blood (79.29 +/- 87 and 103.76 +/- 11 ng/ml, respectively). Mean silicon level measured in store-bought cow's milk was 708.94 ng/ml, and that for 26 brands of commercially available infant formula was 4402.5 ng/ml (ng/ml = parts per billion). We concluded that lactating women with silicone implants are similar to control women with respect to levels of silicon in their breast milk and blood. Silicon levels are 10 times higher in cow's milk and even higher in infant formulas.

Signorello L.B., Fryzek J.P., Blot W.J., McLaughlin J.K., and Nyren O. Offspring health risk after cosmetic breast implantation in Sweden. *Ann Plast Surg.* 46: 279, 2001.

Case reports have suggested that children born to women with silicone breast implants may have an excess risk of rheumatic disease and/or esophageal disorders. In Sweden, the authors conducted a retrospective cohort study of 5,874 children born to women with cosmetic breast implants and 13,274 children born to women who had breast reduction surgery. Using national registers, they computed hospitalization rates for rheumatic and esophageal disorders, incidence rates for cancer, and prevalence rates for congenital malformations and perinatal death. This study provides no evidence that certain hypothesized health outcomes are more likely among the children of women with cosmetic breast implants.

Silverman, S., Gluck, O., Silver, D., Tesser, J., Wallace, D., Neumann, K., Metzger, A. and Morris, R. The prevalence of autoantibodies in symptomatic and asymptomatic patients with breast implants and patients with fibromyalgia. *Curr Top Micro Immun.* 210: 317, 1996.

This is a cohort study that looked at the incidence of antinuclear antibodies in 3,184 consecutive symptomatic patients with breast implants. Subjects included 984 patients from four university affiliated rheumatology practices in Los Angeles and 2,200 from one rheumatology group practice in Phoenix. It compared them to 40 age matched controls, 37 asymptomatic women with breast implants, and 100 consecutive patients who met the ACR criteria for fibromyalgia but who did not have silicone exposure from one Los Angeles site and 100 from the Phoenix site for a total of 200 patients. The overall prevalence of all five sites with a positive ANA at 1:40 was 59.6% and 35.2% at 1:80. The incidence of positive ANA >180 was similar in both the fibromyalgia populations and the symptomatic women with breast implants. Both groups had increased incidence compared to the healthy controls and asymptomatic women with breast implants. However, the mean ANA titer was higher in the symptomatic women with breast implants versus the breast implant patients with

fibromyalgia. The prevalence of fibromyalgia in patients with silicon breast implants was assessed using the ACR criteria in 2 of the Los Angeles sites and the Phoenix site was found to range from 11% to 25%.

Smalley, S.M. Breast implants and breast cancer screening. *J Midwifery Womens Health*. 48: 329, 2003.

Concern about breast prostheses preventing breast cancer detection has become a priority issue. This article provides a review of the literature on the influence of implants on early detection methods of breast cancer, specifically breast self-examination (BSE), clinical breast examination (CBE), and mammography. The literature suggests that implants may be beneficial in BSE and CBE, yet challenge interpretation of mammography. However, there is no evidence that these women will have a later stage diagnosis or a poorer prognosis if diagnosed with breast cancer.

Smith, H.R. Do silicone breast implants cause autoimmune rheumatic diseases? *J Biomater Sci Polym Ed*. 7: 115, 1995.

Current estimates are that up to a million women in the U.S. have breast implants with the predominant type being the silicone gel implant. Concerns have been raised regarding the safety of silicone gel breast implants with focus upon whether escaped gel might cause inflammatory and immune responses that subsequently lead to autoimmune rheumatic. Our understanding of the relationship between the presence of autoimmune rheumatic diseases and silicone breast implants is limited. The available data indicate that silicone elicits a minimal immunological response as compared to conventional antigens. The histological, immunological and epidemiological experimental data derived from patients with silicone implants, as well as those from animal studies, are reviewed. These data do not convincingly demonstrate that there is a cause and effect relationship between silicone breast implants and autoimmune diseases.

Smith, B.K., Cohen, B.E., Biggs, T.M. and Suber, J. Simultaneous bilateral breast reconstruction using latissimus dorsi myocutaneous flaps: a retrospective review of an institutional experience. *Plast Reconstr Surg*. 108: 1174, 2001.

A retrospective, single institution, multiple surgeon, case series is reviewed with regard to the safety of bilateral breast reconstruction utilizing latissimus dorsi myocutaneous (LDM) flaps. Twenty-four patients were reconstructed between 1979 and 1999 with mean age 47 years (range 19-64 years) with 13 delayed, 6 immediate, and 5 secondary reconstructions. 92% of reconstructions utilized implants with the remaining reconstructions using and extended LDM in the setting of moderate obesity. Implants used included smooth silicone (9/22, 41%), polyurethane covered (5/22, 23%), textured silicone (1/22, 5%) and textured saline (7/22, 32%) with one conversion of the textured saline to textured silicone. A mean implant volume of 300cc was reported with a range of 150cc-525cc. Operative time of 5.25 hours, estimated blood loss of 360 cc with a mean 1.1 unit packed red blood cell transfusion requirement per patient and a mean hospital stay of 4.6 days is disclosed. Re-operation rates for implants and patient satisfaction specifically addressed.

Spear, S. and Spittler, C.J. Breast reconstruction with implants and expanders. *Plast Reconstr Surg*. 107:177, 2001.

This article is well-organized and written descriptive representation of the authors' approach to breast reconstruction with implants and expanders. Patient selection, surgical techniques and a thoughtful discussion are presented.

Spear, S.L. and Wolfe, A.J. The coincidence of TRAM flaps and prosthesis in the setting of breast reconstruction. *Plast Reconstr Surg*. 110: 478, 2002.

This retrospective single-center case series reviews 32 women with 50 combinations of TRAM flap breast reconstruction with an associated breast implant between 1989 and 2000. Six distinct study groups were identified as follows:

- a. Group I: Elective implant beneath TRAM (n=14)
- b. Group II: TRAM flap with contralateral implant reconstruction (n=10)
- c. Group III: Contralateral breast augmentation (n=8)
- d. Group IV: TRAM placed over or to replace prior implant reconstruction (n=11)
- e. Group V: Implant used to augment prior TRAM (n=4)
- f. Group VI: Implant used to salvage failed TRAM (n=3)

Discussion includes

- Disclosure of implant types (not manufactures)
 - 23 (55%) anatomic saline
 - 9 (21%) round saline
 - 3 (7%) anatomic gel
 - 7 (17%) round gel
 - Disclosure of radiation exposure (n=17, 41%, all to TRAM site)
 - 50% of Group I with irradiation (to TRAM + implant)
 - Only 45% of Group IV (TRAM to salvage implant) received radiation
- Re-Operation rates were reported as follows:
- 8 patients with 12 complications (4 related to implants, 8 related to TRAM flaps)
 - 4 (10%) of implants removed because of infection
 - All on same side as TRAM (3 Group I, 1 Group IV)
 - 3 eventually replaced
 - No ruptures
 - No capsular contractures

Soubirac L., Jouglu, E., Hezard, L., Grolleau, J.L. and Chavoïn, J.P. Deflation of breast implants, pre-filled with saline or hydrogel. Results and analysis of 650 treated patients. *Annales de Chirurgie Plastique et Esthétique*. 47: 273, 2002.

This study reports on a retrospective chart review of patients who underwent breast implant surgery at this university hospital between 1993 and 2000. The charts of 650 patients were reviewed and 1117 implants identified in this cohort. All results on implant failure were reported by number of implants rather than by number of patients affected. Over the course of the time period studied, 4 different styles of implants were used:

1. PIP pre filled saline implants
2. PIP pre filled hydrogel implants
3. McGhan saline implants
4. Mentor saline implants

The PIP implants were used between 1993 and 1998 and the McGhan/Mentor implants were used 1998-2000. Both reconstructive and cosmetic cases were included in the review and the authors report that 53% of the reconstructive cases had postop radiation. The authors also report that >97% of the cosmetic augmentations were retropectoral with 63% inserted transaxillary and 37% via the inframammary approach.

The report is a descriptive summary of the deflation rates in those patients charts that had adequate information documented at various time points post- surgery. The authors excluded patients who had secondary surgery at other institutions.

Strom, S.S., Baldwin, B.J., Sigurdson, A.J. and Schusterman, M. A. Cosmetic saline breast implants: a survey of satisfaction, breastfeeding experience, cancer screening, and health. *Plast Reconstr Surg.* 100: 1553, 1997.

Saline breast implants have been used for the past 30 years for cosmetic and reconstructive purposes. Data based on a large number of patients are needed to evaluate patient satisfaction, cancer screening practices, problems associated with breast-feeding, and health effects. We conducted a follow-up study of 292 cosmetic saline breast implant patients from Texas and Louisiana who consented to a telephone interview. Using a Likert scale, we measured the patients' degree of satisfaction with the implants. The results indicated that 80.5 percent were satisfied, 73.3 percent would recommend saline breast implants to others, and 65.1 percent felt that implants improved their quality of life. The extent of satisfaction was independent of the number of additional surgeries, age at implant, and follow-up time. Mammography use and breast self-examination was reported with high frequency in this survey. Ninety-one percent of study participants who were between 40 and 49 years of age at time of interview and 94 percent of those 50 or older reported having had at least one mammogram. Breast self-examination was practiced by 75 percent of the women, and 61 percent reported checking their breasts at least once a month. Of the 46 women who had children after augmentation, 28 reported breastfeeding and 8 (28.6 percent) reported having implant-related problems. The patients were asked to provide information regarding a series of conditions for which they sought medical attention. They reported: atypical rheumatoid syndrome (n = 1), Sjogren syndrome (n = 1), atypical autoimmune disorder (n = 1), and chronic fatigue syndrome (n = 2). Overall, women who elected to have saline breast implants were satisfied with their augmentations, had mammograms and performed breast self-examinations more often than nonaugmented women. A few had problems when breast-feeding that could be related to their implants. There were no reports of breast cancer, but five women reported autoimmune conditions.

Tebbetts, J.B. Patient evaluation, operative planning and surgical techniques to increase control and reduce morbidity and re-operations in breast augmentation. *Clin Plast Surg.* 28: 501, 2001.

Current rates of reoperations and complications in augmentation mammoplasty are unacceptably high and can be improved. Risks, trade-offs, complications, morbidity, time to recovery, and reoperation rates in breast augmentation can be improved substantially by stringent patient selection, thorough tissue evaluation, implant selection based on tissue characteristics, and selection of pocket location and surgical techniques.

Tebbetts, J.B. Achieving a predictable 24-hour return to normal activities after breast augmentation: Part I. Refining practices by using motion in time study principles. *Plast Reconstr Surg.* 109: 273, 2002.

This article is the first of a two-part series that looks at achieving a more predictable recovery for breast augmentation. For purposes of this review the study is important because it is extremely well controlled. One surgeon did all the procedures. The 627 patients were followed prospectively for up to 36 months. The local complications reported include: grade 3 to 4 capsular contracture, fold revisions, deflations, infections, hematoma, implant size change and mal-position. The overall complication rate was 0.3% over 36 months.

Tebbetts, J. B. Achieving a predictable 24-hour return to normal activities after breast augmentation: Part II. Patient preparation refined surgical techniques and instrumentation. *Plast Reconstr Surg.* 109: 293, 2002.

The second part of this article focuses on patient education, preoperative planning, and surgical technique modifications that were identified in part I. These modifications, based on motion and time study video analyses, reduced surgical trauma and bleeding, reduce perioperative morbidity, and

allowed 96 percent of 627 breast augmentation patients to return to full, normal activities in 24 hours or less.

Tenenbaum, S.A., Rice, J.C., Espinoza, L.R., Cuellar, M.L., Plymale, D.R., Sander, D.M., Williamson, L.L., Haislip, A.M., Gluck, O.S., and Tesser, J.R. Use of antipolymer antibody assay in recipients of silicone breast implants. *Lancet*. 349: 449, 1997.

Article reports on a double blind study to assess difference, if any, in silicone breast implant patients and controls in the proportions positive for serum antibodies directed against polymeric substances.

Findings included:

5 groups tested for positive antipolymer antibody (APA).	
34 SBI patients with limited symptoms	3%
26 SBI patients with mild problems	8%
16 SBI patients with moderate symptoms	44%
19 SBI patients with classic CTD	68%
23 healthy nonSBI	17%
20 nonSBI with classic autoimmune disease	10%

Silicone breast implant patients with moderate or severe symptoms were significantly more likely to have APA than those with limited to mild symptoms. However, healthy patients without silicone breast implants also had a significantly higher rate of antipolymer antibody than limited to mild symptom silicone breast implant group. Antinuclear (ANA) looked at as well. Higher ANA for women with classic autoimmune disease (70%) than any silicone breast implant group (0-33%).

Teuber, S. S. Rowley, M. J., Yoshida, S.H., Ansari, A. and Gershwin, M.E. Anti-collagen autoantibodies are found in women with silicone breast implants. *J Autoimm*. 6: 367, 1993.

This study tested 46 women with silicone breast implants, who were self-referred to rheumatology clinic, for anti-collagen antibodies, antinuclear antibodies and rheumatoid factor. 34.7% of silicone breast implant patients vs. 8.8% controls tested positive for collagen antibodies. There is no difference on age of implant or if intact or ruptured. 35% of silicone breast implant patients had ANA titer greater or equal to 1:80. ANA levels were not reported for normal group. Rheumatoid factor not significantly elevated.

Teuber, S.S. Reilly, D.A., Howell, L., Oide, C. and Gershwin, M. E. Severe migratory granulomatous reactions to silicone gel in three patients. *J Rheumatology*. 26: 679, 1999.

This is a case report review article that documents severe local complications caused by migration of silicone gel in a 3 patient case report. The article has 3 patients that have migration of silicone gel into their upper extremity causing multiple symptoms including pain, neurological issues and deformity. The article also reviewed some literature and cited other local complications resulting from gel migration to the axilla, arm and abdominal wall. The authors conclude that silicone gel once it leaves the implant is not biologically inert and some persons can elicit profound pathologic response.

Tugwell, P., Wells, G., Peterson, J., Welch, V., Page, J., Davison, C., McGowan, J., Ramroth, D., and Shea, B. Do silicone breast implants cause rheumatologic disorders? A systematic review for a court-appointed national science panel. *Arthritis Rheum*. 44: 2477, 2001. Comment in: *Arthritis Rheum*. 46: 2545, 2002.

This article is written to assist in evaluating expert testimony and scientific evidence presented in law suits brought against silicone breast implant manufacturers. The US District Court Order established a National Science Panel to assess whether existing studies provide scientific evidence of an association between silicone breast implants and systemic classic/accepted connective disease, atypical connective disease, and certain signs and symptoms identified by plaintiffs in the law

suits. The authors performed a systematic review of published studies on the association between silicone breast implants and systemic connective tissue disorders. The panel found no evidence to support expert testimony suggesting an association between silicone breast implants and connective diseases. Discordance for symptoms may reflect differences in symptoms included in various categories, the small number of cases, and the effect of having single subjects with > 1 symptom represented in analyses of each symptom reported. The process presented here is an early example of the use of independent scientific panels to help courts clarify scientific evidence in legal proceedings.

Tzafetta, K., Ahmed, O., Bahia, H., Jerwood, D., and Ramakrishnan, V. Evaluation of the factors related to postmastectomy breast reconstruction. *Plast Reconstr Surg.* 107: 1694, 2001.

This retrospective, case series report characterizes 73 breast reconstructions relative to the mode of reconstruction including post-operative complications, aesthetic quality as graded by a non-invested observer and patient psychosocial assessment of the reconstruction with regard to overall satisfaction, comfort within a brassiere, effect on sexual life and effect on social life. Consecutive breast reconstructions performed by a single surgeon underwent objective demographic and clinical outcome review revealing a mean age of 48 years (range 28-65), average of 3.6 operations for complete reconstruction to include nipple/areolar reconstruction and contralateral symmetry, and a minimum of 6 months follow-up. Effects of patient age, body fat index, smoking, steroid administration, pre-operative radiation, pre-operative medications and aggregated operative time were studied between reconstructive groups as related to aesthetic outcome and patient satisfaction with an overall 28% post-operative complication rate.

Vandeweyer, E., and Deraemaeker, R. Radiation therapy after immediate breast reconstruction with implant. *Plast Reconstr Surg.* 106: 56, 2000.

The authors present a retrospective case series of 124 cases of expander/implant breast reconstruction at a single center between January 1990 and 1997. Six of the patients in this series subsequently received external beam radiation for locally advanced disease immediately post-operative at 6 weeks (n=4) or for local recurrence months after their reconstruction (n=2, time to recurrence not documented). Significant differences between patients receiving and not receiving radiation related to capsular contracture, implant displacement, breast symmetry and final placement of the inframammary fold is discussed. Overall patient satisfaction between the two study groups was not statistically significant.

Vermeulen, R.C., and Scholte, H.R. Rupture of silicone gel breast implants and symptoms of pain and fatigue. *J Rheumatol.* 30: 2263, 2003.

The purpose of this study was to compare symptoms of women with silicone gel breast implants and women with chronic fatigue syndrome (CFS) relative to the effect of rupture of the silicone implant. Five hundred readers of the Dutch silicone breast implant support group magazine were asked to respond if they had been informed by the surgeon about the silicone implant status at operation, and to answer questions about symptoms of CFS. Their complaints were compared with those of 100 female patients with CFS and 40 female controls. Women with silicone breast implants often report severe pain and chronic fatigue. Rupture of the implant is associated with an increase in symptoms of pain and chronic fatigue.

Wilkins, E.G., Cederna, P.S., Lowery, J.C., Davis, J.A., Kim, H.M., Roth, R.S., Goldfarb, S., Izenberg, P.H., Houin, H.P., and Shaheen, K.W. Prospective analysis of psychosocial outcomes in breast reconstruction: one-year postoperative results from the Michigan breast reconstruction outcome study. *Plast Reconstr Surg.* 106: 1014, 2000.

This prospective, multi-center cross-sectional study examines the psychosocial outcomes of breast reconstruction. Post-mastectomy breast reconstructive patients utilizing three methods of reconstruction (expander/implant n=56, pedicle TRAM n=128, and free TRAM n=66) were evaluated by 3 patient response questionnaires (Medical Outcome Study Short Form 36, Functional Assessment of Cancer Therapy-Breast (FACT-B), and a study-specific designed Body Image Scale Items) both pre-operatively and to 1-yr post-operative. Assessment of the timing of the reconstruction and the surgical procedure utilized was examined with potential effects on psychosocial outcome.

Winkler, E., Bar-Meir, E., Regev, E., Haik, J., Tamir, J., Orenstein, A. Silicone breast implants with silicone gel and autoimmune disease--are they related? *Harefuah*. 142: 536, 2003.

Silicone breast implants are used for breast reconstruction and breast augmentation. In the late 80's anecdotal literature describing a possible connection between silicone gel filled breast implants and autoimmune disease accumulated. Emerging concern about the safety of silicone gel implants had led the FDA to restrict their use. In recent years, large meta-analyses indicate that there is no association between silicone gel breast implants and autoimmune disease. [Abstract only in English].

Winther, J.F., Friis, S., Bach, F.W., Mellekjaer, L., Kjoller, K., McLaughlin, J.K., Lipworth, L., Blot, W.J., and Olsen, J.H. Neurological disease among women with silicone breast implants in Denmark. *Acta Neurol Scand*. 103: 93, 2001.

The purpose of this study is to analyze the risk of neurological disease among women with cosmetic breast implants. The occurrence of neurological disease in the private clinic implant cohort was comparable to that in the general population. A similar risk pattern was observed in the private clinic comparison cohort. The authors analyzed the data for these private clinic cohorts were combined with updated data for public hospital cohorts. Excess risks for neurological disorders were seen in both implant and comparison cohorts, reaching statistical significance only in the comparison cohort. The authors conclude that there is no causal association between silicone breast implants and neurological disease.

Yoshida, SH., Swan, S., Teuber, S.S., and Gershwin, M.E. Silicone breast implants: immunotoxic and epidemiologic issues. *Life Sci*. 56: 1299, 1995.

Silicone gel implants for breast augmentation and reconstruction have been in use since 1962. Significant local complications as well as histologic findings of foreign body granulomas in the capsular tissue and in lymph nodes have been reported. Well-publicized case reports have raised significant concerns regarding an association between implants and systemic disease. Currently available epidemiologic data are extremely limited. In 1992, due to the unavailability of studies demonstrating the safety of implants, the U.S. Food and Drug Administration advised that silicone breast implants should be used only in reconstructive surgery and as part of clinical trials. This article reviews the adverse immune effects following contact with silicone as well as the epidemiologic data available.

Young, V.L., Nemecek, J.R., and Nemecek, D. A. The efficacy of breast augmentation: breast size increase, patient satisfaction, and psychological effects. *Plast Reconstr Surg*. 94: 958, 1994.

In this study designed to quantify the degree of breast enlargement produced by augmentation mammoplasty, 112 women who underwent breast augmentation were interviewed. The size increase that typically resulted from various implant volumes was measured by comparing preoperative and postoperative bra sizes. For the study group as a whole, the average increase was two bra sizes (either increased cup size or a combination of increased cup size and chest circumference), regardless of the implant volume inserted. Patients also were asked a series of questions to evaluate the impact of the surgery on various psychological parameters, including body image, feelings of self-confidence, and

interpersonal relationships. Along with having a very positive body image, the group reported decreased self-consciousness (86 percent) and heightened self-confidence (88 percent); in addition, 95 percent said they felt better about themselves after surgery. The women's satisfaction with the results of augmentation and the success of surgery in meeting their expectations also were measured. Eighty-six percent reported being completely or mostly satisfied with the postoperative results, 86 percent felt the operation was a complete success, and 95 percent said that augmentation met their expectations.

Young, V.L., Hertl, M.C., Murray, P.R., Jensen, J., Witt, H., and Schorr, M.W. Microbial growth inside saline-filled breast implants. *Plast Reconstr Surg.* 100: 182, 1997.

In vitro and in vivo experiments were conducted to determine whether intraluminal saline in breast implants can support the growth of common wound-infecting microorganisms over a prolonged period of time. The bacteria tested were *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli*, *Corynebacterium jeikeium*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. Three fungal species also were tested: *Aspergillus fumigatus*, *Paecilomyces variotii*, and *Candida albicans*. In the in vitro study, four organisms survived in flasks of sterile saline for the 2 weeks in which serial cultures were performed: *K. pneumoniae*, *C. albicans*, *A. fumigatus*, and *P. variotii*. In the in vivo study, 61 white rabbits (122 implants) received both an experimental implant inoculated with one of the test organisms and a control implant containing only sterile saline. They were sacrificed at 1-, 3-, or 6-month scheduled endpoints. None of the control implants containing sterile saline had positive cultures. In contrast, the intraluminal saline was culture positive for 7 of the 10 inoculated organisms after varying lengths of time: *S. epidermidis*, *E. coli*, *E. cloacae*, *K. pneumoniae*, *P. aeruginosa*, *A. fumigatus*, and *P. variotii*. Samples of capsular tissue also were cultured. Of the 122 capsular tissue specimens, 21 (17 percent) had positive cultures and surrounded both inoculated and sterile implants. In most instances, capsules that were culture positive contained an organism different from the one that had been inoculated in the group. In only 3 cases was the same organism cultured from both the periprosthetic tissue and the intraluminal saline, and these may represent instances of the inoculated organism migrating through the implants filler valves. The data show that several types of bacteria (particularly gram-negative species) and fungi can grow and reproduce in a restricted saline environment for extended periods of time.

Zandman-Goddard, G., Blank, M., Ehrenfeld, M., Gilburd, B., Peter, J., and Shoenfeld, Y. A comparison of autoantibody production in asymptomatic and symptomatic women with silicone breast implants. *J Rheumatology.* 26: 73, 1999.

This study included: 86 silicone breast implant patients without symptoms; 116 silicone breast implant patients with symptoms; and 50 controls. Discussion states that asymptomatic women demonstrated statistically significant increased autoantibodies for 5 of 15 antibodies, but does not explain what group this was compared to. Only 7 of 16 autoantibody percents are given for controls. 5 of 16 autoantibodies in the asymptomatic group are listed as not determined. The asymptomatic group showed a much greater positivity for at least 7 of the 16 autoantibodies. No statistical significance for this is given.

Zion, S.M., Slezak, J.M., Sellers, T.A., Woods, J.E., Arnold, P.G., Petty, P.M., Donohue, J.H., Frost, M.H., Schaid, D.J., and Hartmann, L.C. Reoperations after prophylactic mastectomy with or without implant reconstruction. *Cancer.* 98: 2152, 2003.

The authors discuss unanticipated reoperations after prophylactic mastectomy. 1417 women with a family history of breast carcinoma were included in the study. The women had prophylactic mastectomy with (bilateral, n = 593; contralateral, n = 506) or without reconstruction (n = 318) at the Mayo Clinic (Rochester, MN) between 1960 and 1993. 18 women (6%) required reoperation. Most of these reoperations took place within the first year after prophylactic mastectomy.

Silicone Implant Education Initiative
Evolution and Advances in Breast Surgery – Saline, Gel and Cohesive Gel Implants
Inaugural Session, ASAPS, Vancouver, BC, April 16, 2004

- Faculty:** Brian Kinney, MD, Chair
Dennis Hammond, MD, Co-Chair
Bill Adams, MD
Laurie Casas, MD
Bruce Cunningham, MD
Roxanne Guy, MD
Mark Jewell, MD (ASAPS meeting Co-Chair)
LeRoy Young, MD
- Foad Nahai, MD, (Symposia Chair for PSEF, 2003 – 2004)
Renato Saltz, MD, (Symposia Chair for ASAPS, 2003 – 2004)
- Meetings:** Five meetings to run once each over a yearly cycle
- First meeting after the FDA approval will start the cycle
- Programs to be added to regularly scheduled meetings: Atlanta, GA @ SE Breast Symposium (January), Vail, CO @ PSEF Perspectives Symposium (March), Vancouver, BC @ ASAPS Annual Meeting (April/May), Santa Fe, NM @ PSEF/ASAPS Breast Surgery Symposium (August), Philadelphia, PA @ ASPS Plastic Surgery 2004 (October)
- Course Type:** Comprehensive (not basic or advanced)
- Course Format:** Didactic (not workshop or demonstration, i.e., live surgery)
- Course Features:** Videos required where applicable, standardized curriculum on a national and regional basis, DVD to accompany course materials
- ½ or 1 full day, based on particular meeting
- 6-8 faculty per meeting from a pool of 8-10
- E-learning modules for later study
- Instant testing at the end of each session, patterned after maintenance of certification exams (open book exam?)
- Course Topics:** FDA guidelines and regulatory status, historical review, manufacturing process and mechanical properties of implants and materials (current and planned in the future), informed consent and risk management, implant registry, follow-up information and

guidelines, patient and physician education, reconstructive and cosmetic, primary and secondary, emphasis on rupture and capsulectomy treatment, panel discussions, awareness of manufacturers' plans,

- FDA Conditions:**
- 1) Company will assist in developing a "model" informed consent
 - 2) Company patient education brochure
 - 3) Company will support a ten year follow-up program with physical exam and MRI
 - 4) Company will produce annual reports and independent audit
 - 5) Company will encourage patient follow-up with physicians who have completed education and verification program with assurance of compliance by company
 - 6) Company toll-free number and patient self-monitoring program
 - 7) Company and professional organizations are to develop a surgeon education and verification program
 - 8) Company will participate in maintaining a patient registry to include a good faith effort at follow-up with patients

Features to Include: FDA representative to attend or present?
Company representatives to attend (CME requirements met?)
Company support from Silimed and Mentor
Internet streaming video to offsite viewers?
Foreign company representatives invited?
Coordination with PSEC?
DVD

Literature Review included
FDA Hearing Transcript
Patient Education Brochures
Reporting Forms
Physician Education Bullet Points
Quiz Questions
Web Pages and Links
Company Background and Information
Media clips and summation of coverage
Patient Follow-up Exam Forms
Registry Forms
Rupture Education
Chronology of FDA Breast Implant Proceedings

Comments

This course is different from the Santa Fe or Atlanta in that the emphasis is not the on numerous variations in surgery and diagnoses, i.e., mastopexy, reconstruction, flaps, lifts, nipple-areola reconstruction. Instead, the primary emphasis is on patient education and safety, the implants themselves, the FDA regulations, the reintroduction of silicone vis a vis saline, tracking, silicone complications and outcomes. Therefore, the curriculum is influenced and guided by the FDA recommendations gleaned from panel discussions on October 14 and 15, 2003 and their ruling in January 2004.

Symposium Description

Recent advances and new technology in breast surgery demand an up-to-date knowledge of the latest in breast prostheses. This course will review the latest information from the FDA, informed consent, patient education and provide detailed information on uses of various implants. Emphasis will be placed on precise pre-operative diagnosis of anatomic variations, patient considerations and how they influence the appropriate choice of operation. Over versus under the muscle, textured versus smooth, silicone versus saline, big versus small, single size versus expandable implants, and mastopexy versus augmentation will be compared and contrasted. Implant mechanical properties will be presented and new materials for the future will be explained. Demographic and statistical data on implants will provide a basis for rational surgical planning. Reconstructive experience with silicone, saline and expandable prostheses will provide a foundation for operative design in cosmetic patients.

Symposium Objectives

- Practice smart risk management in breast surgery
- Improve the consultation, discuss staff involvement, manage patient expectations
- Understand implant mechanical properties
- Discern differences in demographic data of various implants and operations
- Appreciate accurate anatomic diagnosis and pre-operative planning
- Learn how to choose over versus under the muscle, smooth versus textured, silicone versus saline
- Be aware of future uses of cohesive gel implants
- Make intelligent choices in implants
- Diagnose and surgically treat gel bleed and implant rupture
- Management of implant complications
- Develop methods for long-term patient follow-up and comply with FDA guidelines

Friday April 16, 2004 Vancouver Symposium

8:00 am – 8:10 am	<p>Welcoming Remarks Necessity of Teaching This Course, Un/Relearning the Procedure with “Best Practices,” FDA Guidelines and Regulatory Status Update Brian Kinney, MD, Dennis Hammond, MD, Mark Jewell, MD</p>
8:10 am – 8:30 am	<p>Silicone Regulatory Issues, Mentor PMA Update on Mentor Study, design of the study, data collection, what implants are being used, restrictions on their use, questions FDA wants to answer: rupture, capsule, gel migration, cancer and connective tissues diseases <i>Bill Adams, MD</i></p>

- 8:30 am – 8:50 am Silicone Regulatory Issues, Inamed PMA
Data submitted by Inamed, design of the study, Data collection, what the FDA didn't like, what else it asked for in January 2004, questions FDA wants to answer: rupture, capsule, gel migration, cancer and connective tissues diseases
Mark Jewell, MD
- 8:50 am – 9:10 am Manufacturing, Materials Science and Mechanical Properties
(Design, assembly line processes, molds, chemistry of silicones, biocompatibility, fillers and shells, testing and quality control, preparation and sterilization, packaging, shipping and tracking)
LeRoy Young, M.D.
- 9:10 am – 9:30 am FDA Patient Education Brochures, Informed Consent
(FDA Brochure, consent forms, exam requirements, risks, company forms and stickers, "recall" and notification methods, truth in marketing, advertising, pathology and biopsies, rippling and folding, erythema and nodularity, slough, contracture, sensory changes, gel bleed, intra-and extracapsular rupture, malposition, adenopathy, seroma and hematoma, calcification, cutaneous changes, symmastia, closed capsulectomy, financial programs, revisional surgery policies)
Roxanne Guy
- 9:30 am – 9:50 am Patient Tracking, Follow-up, FDA Regulations and the ASPS TOPS Program
(Data entry, program features, logging in, HIPAA, data analysis, forms, patient tracking, MRI, follow-up exams and intervals, implant warranty)
Bruce Cunningham, MD
- 9:50 am – 10:00 am *Break***
- 10:00 am – 10:10 am The Breast Implant Registry, FDA Requirements and Worldwide Efforts
(ASPS Registry, coordination with companies, data entry, tracking and retrieval, recall issues, variations in implants and patients)
LeRoy Young, MD
- 10:10 am – 10:30 am Patient Self-Monitoring and Training
(Breast exam in the implanted patient, finding a qualified mammography center, diagnostic versus screening mammograms, reporting to companies and physicians,

when to seek an MRI, what to do if your physician moves, retires or is unavailable, toll-free number, etc.)

Laurie Casas, MD

- 10:30 pm – 10:50 am Primary Breast Augmentation – Safe Choices for Patients, Smart Choices By Surgeons
(Evaluation of anatomy, planning surgery, choosing and placing the implant in a pocket, positioning the patient, irrigating the pocket, postoperative bandages, no touch technique, my favorite technique)
Bill Adams, MD
- 10:50 pm – 11:00 am Augmentation Mastopexy – Additional Features of Management
(Over versus under the muscle, dynamics of mound surface area versus skin surface area, areolar versus vertical versus full incision, laxity of ligaments, implant textures and sizes)
Dennis Hammond, MD
- 11:00 am – 11:20 am Revisional Surgery, Natural History of Augmentation and Implant Complications
(Post-partial involution and subsequent reaugmentation, glandular atrophy and descent with aging, malposition, rippling, implant fold and fatigue, gel bleed versus rupture, patient desire for change in size, implant descent and size, elongation/breast ptosis and submuscular augmentation, etc.)
Brian Kinney, MD
- 11:20 pm – 11:40 am Leaking vs. Ruptured Silicone, Capsulectomy vs. Capsulotomy, How to Decide
(Dense versus soft, thick versus thin capsules, implant collapse versus gel bleed, silicone nodule versus rippled implant, etc.)
Laurie Casas, MD
- 11:40 am – 12:00 am The Future – Shaping, Cohesive Gel and Customization of Implants
(What’s available in other countries, research protocols in US, future technologies, segmentation of implant choices?)
Dennis Hammond, MD,
- 12:00 pm – 12:10 pm Summary, Highlights, Feedback and Discussion
Brian Kinney, MD
- 12:10 pm – 12:30 pm *Self Evaluation and Program Verification***
Moderators: Brian Kinney, MD, Dennis Hammond, MD
- Twenty-question quiz and instant grading

About two questions per lecture, question handed out in advance (or not), may be answered as the day goes on or only at the end, distribution of certificates

12:30 pm

Adjourn

<u>Participant</u>	<u># Lectures</u>	<u>Topic</u>
Brian Kinney, Chair	2	Secondary Surgery, Final Review and Quiz
Dennis Hammond, Co-Chair	2	Aug/Mastopexy, Future and Shaping, Final Review and Quiz
Bill Adams	2	Regulatory/Mentor, Primary Augmentation
Laurie Casas	2	Pt. Monitoring, Leak vs. Rupture
Bruce Cunningham	1	TOPS and Tracking
Roxanne Guy	1	Brochures, Consent and Consultation
Mark Jewell, Co-Chair	1	Regulatory/Inamed
LeRoy Young	2	Materials Science, Registry