Journal of Long-Term Effects of Medical Implants, 21(3): 241–250 (2011)

Prosthetic Mammoplasty Sensitivity Syndrome: A Case for Causation

*S. A. Audino & S. V. M. Maharaj**

Center for Research on Environmental Medicine, New Market, MD 21774, U.S.A.

*Address all correspondence to: Dr. S. V. M. Maharaj, Center for Research on Environmental Medicine, P.O. Box 224, New Market, MD 21774, U.S.A.; Tel.: (301) 829-4184; Fax: (301) 829-4911; svmm@environmed.org (preferred for communication).

ABSTRACT: Treatment of patients experiencing adverse health effects following prosthetic mammoplasty has suffered from a lack of an acknowledgment of a causal relationship to their breast prosthetic devices. Case reports and case series showing an association between adverse health effects and breast implants have been routinely dismissed as anecdotal, and epidemiological studies have been considered necessary to prove causality. We show that epidemiological research is not necessary for establishing a causal relationship, and one properly documented case can be, in fact, all that is needed to show causation. Presently in the peer-reviewed literature there exists a substantial scientifically sound body of data showing an association between breast implants and adverse health effects. Ample evidence has shown that exposure to the five common types of breast implants outlined, i.e., silicone gel filled, saline filled, double lumen, polyurethane coated, and cohesive silicone, has caused adverse health effects in humans. Prosthetic mammoplasty sensitivity syndrome (PMSS) is the proposed term to describe the disease processes documented in the literature that has a causal relationship to breast implants.

KEY WORDS: adverse health effects, breast implants, causation, medical devices, PMSS, silicone

I. INTRODUCTION

I.A. Background

Prosthetic mammoplasty is plastic surgery on the breast by insertion of an artificial part, a breast implant, for reconstruction or augmentation. Five types of breast implants that have been placed are: silicone gel filled, saline filled, double lumen, polyurethane coated, and cohesive silicone. Silicone gel–filled implants contain silicone gel enclosed in a silicone elastomer envelope. Saline-filled breast implants contain saline fluid enclosed also in a silicone elastomer envelope. Double-lumen implants usually contain silicone gel surrounded by a smaller outer pocket of saline fluid, with each filler material enclosed in a silicone elastomer envelope. Polyurethane-coated implants contain silicone gel enclosed in a silicone elastomer envelope coated with polyurethane foam. Cohesive silicone implants are anatomically shaped, and contain a more highly cross-linked form of silicone gel (than traditional, round silicone gel–filled implants) enclosed in a silicone elastomer envelope.

I.B. Experimental Studies

Silicones are cross-linked synthetic polymers of alternating silicon and oxygen atoms with organic groups attached to the silicon atoms.[1] Earlier studies suggested that silicones were physiologically inert,[1,2] and therefore biocompatible.[3–5] However, physiologically or chemically inert does not mean that no immune response is mounted. Indeed, the experimental literature has since shown that silicones induce protein adsorption,[6–9] activation of macrophages,[7,10] macrophage-rich inflammation,[11,12] fibrosis,[12] activation of human monocytes,[13] estrogenic activity,[14] reactive synovitis,[15] hypergammaglobulinemia,[10] exacerbation of autoimmune disease,[16] and autoantibodies.[17,18] Moreover, approximately 200,000 adverse event reports about breast implants have been submitted to the U.S. Food and Drug Administration from 1985 to 2005.[19]

I.C. Epidemiological Studies

A number of epidemiological studies have been conducted in an attempt to elucidate a possible link between breast implants and adverse health effects in humans. Epidemiological studies have shown a small increased risk in the frequency of connective-tissue autoimmune diseases with breast implants,[20] or no significant increase with breast implants in general[21–23] or with silicone gel–filled implants in particular.[22,24,25] Limitations of the above studies include an ability to detect an increase in only classically defined connective-tissue diseases,[20] inadequate sample size[21,23–25] to assess the occurrence of uncommon connective-tissue diseases, and inadequate follow-up[21–25] given the long latency period between exposure and connective-tissue autoimmune disease development.

II. CAUSATION

II.A. Case Reports and Series

Case reports and case series have been dismissed as anecdotal[26,27] and inferior quality[28,29] to epidemiological research, and the latter has been frequently cited as required to infer causality,[30–33] essential to establish ill effects,[34] or needed to assess risk factors.[28,35] However, epidemiological evidence may show only whether there is an increase in the incidence or prevalence of the specific diseases studied, and their magnitudes. They have not shown, therefore, that breast implants have caused no adverse health effects in humans, as in our experience, laypersons and experts alike have commonly misunderstood their results to mean. Furthermore, studies showing similar rates of disease in breast implant populations and control groups do not preclude that for an individual case in the study, the prosthetic device did not cause the morbidity. In other words, no amount of epidemiological studies failing to find an association of disease risk precludes it for the study patient, and much less so for the presenting patient that was not part of the group being followed. If we cannot use case reports and case series to infer association or causation for a similarly exposed population,[36] the converse is also true. We must not use epidemiological study results to infer risk for presenting patients. Epidemiological evidence, therefore, is not necessary for establishing a causal relationship.[37]

Medical inference of causation should be based on an evaluation of multiple lines of evidence.[38] The best evidence to determine whether causation exists for the presenting individual comes from the clinical observations of a carefully conducted case study. Contrary to what many experts seem to think,[27,33,39–42] one properly documented case can be, in fact, all that is needed to show causation.

II.B. Peer-Reviewed Literature

Fifteen years ago, the body of literature on this subject was already almost too large to deal with.[43] Indeed, a recent PubMed database search,[44] using a number of search terms, produced more than 2000 results linking breast implants and adverse effects. An all-encompassing review of the literature, therefore, is beyond the scope of this work. However, a first-pass read reveals many peer-reviewed journal publications where authors have associated adverse health effects in humans with breast implants. Adverse health effects, as defined here, do not include aesthetic complications (e.g., capsular contracture), or complications associated with breast implant surgery. When it was not clear whether a

publication was peer-reviewed, an inquiry was sent to the journal or corresponding author for clarification. Discussions on study limitations and critical appraisals may be included in the original references and/or the literature.

Many different research groups have reported on a wide range of clinical data showing adverse health effects directly or indirectly attributable to the five common breast implant types outlined, for example: silicone gel filled,[45–69] saline filled,[50,56,70–77] double lumen,[56,78,79] polyurethane coated,[56,79–85] and cohesive silicone.[86–88] Adverse health effects attributable to silicone gel–filled breast implants include: rheumatic manifestations,[53,58,59] chronic fatigue syndrome,[52,66] gel migration to the liver[54,60] and as far as the shins,[68] systemic tissue damage,[51] adult Still's disease-like illness,[63] a scleroderma-like process,[61] precipitated or aggravated scleroderma,[50,69] multiple sclerosis–like syndrome,[62] systemic lupus erythematosus–like disorder,[49] and an enhanced spread of cancer.[48] Adverse health effects attributable to saline breast implants include: late intracapsular hematoma,[76] synovial metaplasia,[72] atypical chest pain syndrome,[56] hypersensitivity,[75] unclassified[71] and defined connective tissue disease,[70] systemic sclerosis,[50] and anaplastic large-cell lymphoma.[77] Inflammation and foreign-body tissue reactions have been caused by double-lumen,[78] polyurethane-coated,[80] and cohesive-silicone implants,[86] with late breast pain,[81] synovial metaplasia,[82,85] polyurethane migration to lymph nodes,[83] atypical chest pain syndrome,[56] and hypersensitivity[84] in individuals exposed to polyurethane-coated breast implants, and gel migration to lymph nodes[87] and hypersensitivity[88] in individuals exposed to cohesive silicone implants.

There is a consistency of adverse health effect results across different researchers in different locations using different methods with patients from different cultures involving different implant types. Authors have come to the same conclusions, i.e., that breast implants play a role in the etiology of adverse health effects in humans, with many concluding that the role is one of causation, e.g., "there is strong clinical and pathological evidence for a causative role."[77] Indeed, a critical review[37] of the criteria necessary to establish medical causation[38] concludes that the criteria, for example, the large number of patients and reports, the temporal relationship of breast implant exposure and response, biological plausibility, and that disease is increased by presence and decreased by absence of the devices, have been met.

1. Additional Evidence

Data from toxicology, animal studies, other silicone implanted devices,[89] silicone injections, as well as non-peer-reviewed editorials,[90,91] letters to the editor,[92,93] and abstracts[94] also support a causal relationship between breast implants and disease. Additionally, many peer-reviewed epidemiological studies where authors did not conclude that there was a causal association between breast implants and disease contained data that could be interpreted as additional evidence for causation; for example: higher prevalence of unusual symptoms in breast implant patients,[21,23] laboratory abnormalities among breast implant patients consistent with disease,[95] higher rates of connective tissue disorders and other conditions in implant patients vs. controls,[96] other adverse health conditions,[25,97] including cancer[98–103] in women who received breast implants, and an increased risk for suicide in women opting for breast augmentation[104,105] and reconstruction.[101]

Likewise, in many peer-reviewed case reports authors did not conclude that a causal relationship exists, but evidence in the future may show causation to breast implants for additional, e.g., hypersensitivity reactions,[106,107] automimmune disease,[108–110] including adult-onset Still's disease,[111] and cancer,[112] including anaplastic large-cell lymphoma.[113,114] Therefore, we must remain cognizant that both the peer-reviewed and non-peer-reviewed literature presently contain invaluable data that after additional careful study will most likely reveal further or as-yet-undetermined morbidity causally linked to breast implants. Also, given that latency periods of more than 30 years are possible before immunopathological disease develops,[115] we can expect that the literature will continue to evolve to support a causal relationship.

II.C. Prosthetic Mammoplasty Sensitivity Syndrome

The term *prosthetic mammoplasty sensitivity syndrome* (PMSS) is proposed to describe the disease processes characterized in the literature that have been (and those expected to be) associated with these medical devices. Previous terms reflect an emphasis on disease associated with silicone gel–filled breast implants, and include (chronologically): silicone reactive disorder,[116] adjuvant breast disease,[57] silicone-related disorders,[117] siliconosis,[51] silicone implant associated syndrome,[58] human adjuvant disease,[62] silicone breast implant adjuvant syndrome,[118] and silicone-related symptom complex.[119]

PMSS is preferred as more accurate. "Prosthetic" qualifies mammoplasty, as the procedure may also be performed using autogenous tissue, and "prosthetic mammoplasty" may be used for either reconstructive or augmentative mammoplasty. "Prosthetic" is also more inclusive than "silicone," reflecting the different types of implants that have been proposed as plausible to cause illness,[106] and those documented in the literature to have done so. "Sensitivity" may be used for local or systemic, immediate or delayed, cell-mediated or humoral, and allergic or toxic responses.

II.D. Patient Population

Compared to the total number of individuals that have had breast implants placed, the number of individuals that have developed adverse health effects of clinical concern following prosthetic mammoplasty is relatively small. However, adverse health effects following prosthetic mammoplasty are more widespread than is commonly appreciated. Most of the population with breast implants have been lost to follow-up;[120] therefore, the true incidence and prevalence of disease, including autoimmune,[121] in this population is not known.

In addition, it is commonly assumed[122] that what is reported in the literature represents the prevalence of a disease. However, far fewer than the actual number of patient case reports, series, etc., are published. For example, we have medical reports of many individuals, and know of many more, suffering adverse health effects most likely as a result of their breast (or testicular) implants, of which there is no record in the literature; and this situation is true for other researchers as well.[115] The literature, therefore, represents the minimal number of affected cases. That much more evidence exists than is published, makes the case for a causal relationship between breast implants and adverse health effects in humans even stronger than is readily apparent.

II.E. Possibility of Chance

Adverse health effects following prosthetic mammoplasty would occur in some individuals based on chance alone. Just as it is a fallacy to conclude that all adverse health effects that occur following prosthetic mammoplasty should be attributed to the devices, it is equally fallacious to conclude that none are, though this is what is routinely suggested when case reports and case series are dismissed.[28] Following prosthetic mammoplasty, the likelihood that breast implants will cause adverse health effects is obviously much smaller compared to the likelihood that they have when there has been documented illness; however, critics often use the likelihood of the former as evidence against the likelihood of the latter.

The breast implant population is a non-random group. Critics have asserted that it is unacceptable, therefore, to compare non-randomly sampled group results to a normal population,[123] but the possibility that, e.g., the association of connective-tissue disease following silicone implantation is just chance indeed can be negated by statistics.[124]

The possibility that the association of adverse health effects following prosthetic mammoplasty is merely coincidental is also negated by higher incidences of connective tissue disease, e.g., progressive systemic sclerosis,[124] autoimmune diseases,[73] and several humoral parameters[73] in individuals exposed to breast implants vs. respective normal populations. Furthermore, if disease is a random occurrence in the breast implant population, the relative prevalence rates for various rheumatic diseases in the implant population would be similar to the general female population, but it is not.[95,125]

Finally, if the association is just chance, we would not be recommending explantation as a therapeutic approach when symptoms cannot be medically managed[71,107] or explantation in patients with severe connective tissue disease[109,126] or not considering patients at all with symptoms or active connective tissue disease,[126] or those even at risk for autoimmune diseases,[107] for silicone breast implants.

III. CONCLUSIONS

Many research groups have reported on a wide range of clinical data showing adverse health effects attributable to the five major breast implant types outlined: silicone gel filled, saline filled, double lumen, polyurethane coated, and cohesive silicone. There is a consistency of adverse health effect results across the different researchers in different locations using different methods with patients from different cultures involving the different implant types. Many authors have concluded that breast implants play a causative role in the etiology of adverse health effects in humans. Prosthetic mammoplasty sensitivity syndrome is the proposed term for the disease processes documented in the literature that have resulted following prosthetic mammoplasty. It may be used to describe adverse health effects following exposure to at least the five common breast implant types outlined, and may present as pathology as relatively mild as inflammation to as severe as breast cancer. In the interest of presenting patients, we hope that this study will provide the next step in further understanding, defining, and reaching a consensus regarding the diagnostic criteria for PMSS, a syndrome that has a causal relationship to breast implants.

REFERENCES

1. Blocksma R, Braley S. The silicones in plastic surgery. Plast Reconstr Surg. 1965;35:366–70.
2. Rowe VK, Spencer HC, Bass SL. Toxicological studies on certain commercial silicones and hydrolyzable silane intermediates. J Ind Hyg Toxicol. 1948;30:332–52.
3. Ballantyne DL Jr, Rees TD, Seidman I. Silicone fluid: response to massive subcutaneous injections of dimethylpolysiloxane fluid in animals. Plast Reconstr Surg. 1965;36:330–8.
4. Rees TD, Platt J, Ballantyne DL Jr. An investigation of cutaneous response to dimethylpolysiloxane (silicone liquid) in animals and humans—a preliminary report. Plast Reconstr Surg. 1965;35:131–9.
5. Homsy CA. Bio-compatibility in selection of materials for implantation. J Biomed Mater Res. 1970;4:341–56.
6. Roggendorf E. The biostability of silicone rubbers, a polyamide, and a polyester. J Biomed Mater Res. 1976;10:123–43.
7. Anderson JM, Ziats NP, Azeez A, Brunstedt MR, Stack S, Bonfield TL. Protein adsorption and macrophage activation on polydimethylsiloxane and silicone rubber. J Biomater Sci Polym Ed. 1995;7:159–69.
8. Butler JE, Lü EP, Navarro P, Christiansen B. Comparative studies on the interaction of proteins with a polydimethylsiloxane elastomer. I. Monolayer protein capture capacity (PCC) as a function of protein pI, buffer pH and buffer ionic strength. J Mol Recognit. 1997;10:36–51.
9. Backovic A, Huang HL, Del Frari B, Piza H, Huber LA, Wick G. Identification and dynamics of proteins adhering to the surface of medical silicones in vivo and in vitro. J Proteome Res. 2007;6:376–81.
10. Naim JO, Satoh M, Buehner NA, Ippolito KM, Yoshida H, Nusz D, Kurtelawicz L, Cramer SF, Reeves WH. Induction of hypergammaglobulinemia and macrophage activation by silicone gels and oils in female A.SW mice. Clin Diagn Lab Immunol. 2000;7:366–70.
11. Heggers JP, Kossovsky N, Parsons RW, Robson MC, Pelley RP, Raine TJ. Biocompatibility of silicone implants. Ann Plast Surg. 1983;11:38–45.
12. Eltze E, Bettendorf O, Rody A, Jackisch C, Herchenröder F, Böcker W, Pfleiderer B. Influence of local complications on capsule formation around model implants in a rat model. J Biomed Mater Res A. 2003;64:12–9.
13. Naim JO, van Oss CJ, Ippolito KML, Zhang J-W, Jin L-P, Fortuna R, Buehner NA. In vitro activation of human monocytes by silicones. Colloids Surfaces B: Biointerfaces. 1998;11:79–86.

14. He B, Rhodes-Brower S, Miller MR, Munson AE, Germolec DR, Walker VR, Korach KS, Meade BJ. Octamethylcyclotetrasiloxane exhibits estrogenic activity in mice via ERalpha. Toxicol Appl Pharmacol. 2003;192:254–61.
15. Worsing RA Jr, Engber WD, Lange TA. Reactive synovitis from particulate silastic. J Bone Joint Surg Am. 1982;64:581–5.
16. McDonald AH, Weir K, Schneider M, Gudenkauf L, Sanger JR. Silicone gel enhances the development of autoimmune disease in New Zealand black mice but fails to induce it in BALB/cAnPt mice. Clin Immunol Immunopathol. 1998;87:248–55.
17. Naim JO, Lanzafame RJ, van Oss CJ. The adjuvant effect of silicone-gel on antibody formation in rats. Immunol Invest. 1993;22:151–61.
18. Schaefer CJ, Wooley PH. The influence of silicone implantation on murine lupus in MRL lpr/lpr mice. J Rheumatol. 1999;26:2215–21.
19. Maharaj SVM. Assessment of the FDA backgrounder on platinum in silicone breast implants: implications for public health policy. Int J Health Serv. 2008;38:95–102.
20. Hennekens CH, Lee IM, Cook NR, Hebert PR, Karlson EW, LaMotte F, Manson JE, Buring JE. Self-reported breast implants and connective-tissue diseases in female health professionals. A retrospective cohort study. JAMA. 1996;275:616–21.
21. Gabriel SE, O'Fallon WM, Kurland LT, Beard CM, Woods JE, Melton LJ 3rd. Risk of connective-tissue diseases and other disorders after breast implantation. N Engl J Med. 1994;330:1697–702.
22. Sánchez-Guerrero J, Colditz GA, Karlson EW, Hunter DJ, Speizer FE, Liang MH. Silicone breast implants and the risk of connective-tissue diseases and symptoms. N Engl J Med. 1995;332:1666–70.
23. Edworthy SM, Martin L, Barr SG, Birdsell DC, Brant RF, Fritzler MJ. A clinical study of the relationship between silicone breast implants and connective tissue disease. J Rheumatol. 1998;25:254–60.
24. Weisman MH, Vecchione TR, Albert D, Moore LT, Mueller MR. Connective-tissue disease following breast augmentation: a preliminary test of the human adjuvant disease hypothesis. Plast Reconstr Surg. 1988;82:626–30.
25. Park AJ, Black RJ, Sarhadi NS, Chetty U, Watson AC. Silicone gel-filled breast implants and connective tissue diseases. Plast Reconstr Surg. 1998;101:261–8.
26. Rose NR. The silicone breast implant controversy: the other courtroom. Arthritis Rheum. 1996;39:1615–8.
27. Bondurant S, Ernster V, Herdman R, editors. Safety of silicone breast implants. Washington, DC: National Academy Press; 2000.
28. Angell M. Evaluating the health risks of breast implants: the interplay of medical science, the law, and public opinion. N Engl J Med. 1996;334:1513–8.
29. Ferguson JH. Silicone breast implants and neurologic disorders. Report of the Practice Committee of the American Academy of Neurology. Neurology. 1997;48:1504–7.
30. Hochberg MC. Silicone breast implants and rheumatic disease. Br J Rheumatol. 1994;33:601–2.
31. Houpt KR, Sontheimer RD. Autoimmune connective tissue disease and connective tissue disease–like illnesses after silicone gel augmentation mammoplasty. J Am Acad Dermatol. 1994;31:626–42.
32. Whysner J. Epidemiology of silicone breast implants. Ann Intern Med. 1997;126:667.
33. McLaughlin JK, Lipworth L, Tarone RE. Suicide among women with cosmetic breast implants: a review of the epidemiologic evidence. J Long Term Eff Med Implants. 2003;13:445–50.
34. Stein ZA. Silicone breast implants: epidemiological evidence of sequelae. Am J Public Health. 1999;89:484–7.
35. Mann RD. Breast implants: the tyranny of the anecdote. J Clin Epidemiol. 1995;48:504–6.
36. Ferguson JH. Breast implants redux. This time with data. Neurology. 1998;50:849–52.
37. Brautbar N, Campbell A, Vojdani A. Silicone breast implants and autoimmunity: causation, association, or myth? J Biomater Sci Polym Ed. 1995;7:133–45.
38. Hill AB. The environment and disease: association or causation? Proc R Soc Med. 1965;58:295–300.
39. Claman HN, Robertson AD. Antinuclear antibodies and breast implants. West J Med. 1994;160:225–8.

40. Perkins LL, Clark BD, Klein PJ, Cook RR. A meta-analysis of breast implants and connective tissue disease. Ann Plast Surg. 1995;35:561–70.
41. Sanchez-Guerrero J. Autoantibody testing in patients with silicone implants. Clin Lab Med. 1997;17:341–53.
42. McLaughlin JK, Wise TN, Lipworth L. Increased risk of suicide among patients with breast implants: do the epidemiologic data support psychiatric consultation? Psychosomatics. 2004;45:277–80.
43. Claman HN. Autoimmunity after silicone breast implants. Ann Allergy Asthma Immunol. 1997;79:89–90.
44. PubMed. [database on the Internet]. Bethesda, MD: National Library of Medicine. c2011 [cited 2011 Mar 8]. Available from: http://www.ncbi.nlm.nih.gov/sites/entrez.
45. Capozzi A, Du Bou R, Pennisi VR. Distant migration of silicone gel from a ruptured breast implant. Case report. Plast Reconstr Surg. 1978;62:302–3.
46. Mason J, Apisarnthanarax P. Migratory silicone granuloma. Arch Dermatol. 1981;117:366–7.
47. Baldwin CM Jr, Kaplan EN. Silicone-induced human adjuvant disease? Ann Plast Surg. 1983;10:270–3.
48. Morgenstern L, Gleischman SH, Michel SL, Rosenberg JE, Knight I, Goodman D. Relation of free silicone to human breast carcinoma. Arch Surg. 1985;120:573–7.
49. Walsh FW, Solomon DA, Espinoza LR, Adams GD, Whitelocke HE. Human adjuvant disease. A new cause of chylous effusions. Arch Intern Med. 1989;149:1194–6.
50. Appleton BE, Lee P. The development of systemic sclerosis (scleroderma) following augmentation mammoplasty. J Rheumatol. 1993;20:1052–4.
51. Borenstein D. Siliconosis: a spectrum of illness. Semin Arthritis Rheum. 1994;24:(Suppl 1)1–7.
52. Fenske TK, Davis P, Aaron SL. Human adjuvant disease revisited: a review of eleven post-augmentation mammoplasty patients. Clin Exp Rheumatol. 1994;12:477–81.
53. Giltay EJ. Silicone breast prostheses and rheumatic symptoms: a retrospective follow-up study. Ann Rheum Dis. 1994;53:194–6.
54. Garrido L, Pfleiderer B, Jenkins BG, Hulka CA, Kopans DB. Migration and chemical modification of silicone in women with breast prostheses. Magn Reson Med. 1994;31:328–30.
55. Hirmand H, Hoffman LA, Smith JP. Silicone migration to the pleural space associated with silicone-gel augmentation mammaplasty. Ann Plast Surg. 1994;32:645–7.
56. Lu LB, Shoaib BO, Patten BM. Atypical chest pain syndrome in patients with breast implants. South Med J. 1994;87:978–84.
57. Shoaib BO, Patten BM, Calkins DS. Adjuvant breast disease: An evaluation of 100 symptomatic women with breast implants or silicone fluid injections. Keio J Med. 1994;43:79–87.
58. Bridges AJ. Rheumatic disorders in patients with silicone implants: a critical review. J Biomater Sci Polym Ed. 1995;7:147–57.
59. Cuellar ML, Gluck O, Molina JF, Gutierrez S, Garcia C, Espinoza R. Silicone breast implant–associated musculoskeletal manifestations. Clin Rheumatol. 1995;14:667–72.
60. Pfleiderer B, Garrido L. Migration and accumulation of silicone in the liver of women with silicone gel-filled breast implants. Magn Reson Med. 1995;33:8–17.
61. Teuber SS, Ito LK, Anderson M, Gershwin ME. Silicone breast implant–associated scarring dystrophy of the arm. Arch Dermatol. 1995;131:54–6.
62. Shoaib BO, Patten BM. Human adjuvant disease: presentation as a multiple sclerosis–like syndrome. South Med J. 1996;89:179–88.
63. Katayama I, Umeda T, Nishioka K. Adult Still's-disease-like illness in a patient with silicone breast implants. Clin Rheumatol. 1998;17:81–2.
64. Abbondanzo SL, Young VL, Wei MQ, Miller FW. Silicone gel–filled breast and testicular implant capsules: a histologic and immunophenotypic study. Mod Pathol. 1999;12:706–13.
65. Malyon AD, Dunn R, Weiler-Mithoff EM. Expanding silicone granuloma. Br J Plast Surg. 2001;54:257–9.
66. Vermeulen RCW, Scholte HR. Rupture of silicone gel breast implants and symptoms of pain and fatigue. J Rheumatol. 2003;30:2263–7.

67. Błasiak A, Błachowicz A, Gietka A, Rell-Bakalarska M, Franek E. Still's disease in patient with silicone breast implants: case report. Pol Arch Med Wewn. 2008;118:65–7.
68. Sagi L, Baum S, Lyakhovitsky A, Barzilai A, Shpiro D, Trau H, Goldan O, Winkler E. Silicone breast implant rupture presenting as bilateral leg nodules. Clin Exp Dermatol. 2009;34:e99–e101.
69. Levy Y, Rotman-Pikielny P, Ehrenfeld M, Shoenfeld Y. Silicone breast implantation–induced scleroderma: description of four patients and a critical review of the literature. Lupus. 2009;18:1226–32.
70. Byron MA, Venning VA, Mowat AG. Post-mammoplasty human adjuvant disease. Br J Rheumatol. 1984;23:227–9.
71. Heredero FXS, Semper EM. Polyarthralgia after augmentation mammaplasty with saline-filled implants. Eur J Plast Surg. 1992;15:1–8.
72. Copeland M, Choi M, Bleiweiss IJ. Silicone breakdown and capsular synovial metaplasia in textured-wall saline breast prostheses. Plast Reconstr Surg. 1994;94:628–33.
73. Brunner CA, Feller AM, Gröner R, Dees E, Biefel K, Biemer E. Increase of immunologically relevant parameters in correlation with Baker classification in breast implant recipients. Ann Plast Surg. 1996;36:512–18.
74. Finegold I. Allergy to silicone: is it real? Compr Ther. 1996;22:393–8.
75. Sabbagh WH, Murphy RX Jr, Kucirka SJ, Okunski WJ. Idiosyncratic allergic reaction to textured saline implants. Plast Reconstr Surg. 1996;97:820–3.
76. Hsiao HT, Tung KY, Lin CS. Late hematoma after aesthetic breast augmentation with saline-filled, textured silicone prosthesis. Aesthetic Plast Surg. 2002;26:368–71.
77. Thompson PA, Lade S, Webster H, Ryan G, Prince HM. Effusion-associated anaplastic large cell lymphoma of the breast: time for it to be defined as a distinct clinico-pathological entity. Haematologica. 2010;95:1977–79.
78. de Camara DL, Sheridan JM, Kammer BA. Rupture and aging of silicone gel breast implants. Plast Reconstr Surg. 1993;91:828–34.
79. Melmed EP. A review of explantation in 240 symptomatic women: a description of explantation and capsulectomy with reconstruction using a periareolar technique. Plast Reconstr Surg. 1998;101:1364–73.
80. Cocke WM, Leathers HK, Lynch JB. Foreign body reactions to polyurethane covers of some breast prostheses. Plast Reconstr Surg. 1975;56, 527–30.
81. Jabaley ME, Das SK. Late breast pain following reconstruction with polyurethane-covered implants. Plast Reconstr Surg. 1986;78:390–5.
82. Raso DS, Greene WB. Synovial metaplasia of a periprosthetic capsule surrounding a polyurethane foam breast prosthesis. Ann Plast Surg. 1995;35:201–3.
83. Katzin WE, Centeno JA, Feng LJ, Kiley M, Mullick FG. Pathology of lymph nodes from patients with breast implants: a histologic and spectroscopic evaluation. Am J Surg Pathol. 2005;29:506–11.
84. Cantisani C, Cigna E, Grieco T, Miller DM, De Gado F, Calvieri S, Scuderi N. Allergic contact dermatitis to synthetic rubber following breast augmentation. Eur Ann Allergy Clin Immunol. 2007;39:185–8.
85. Bassetto F, Scarpa C, Caccialanza E, Montesco MC, Magnani P. Histological features of periprosthetic mammary capsules: silicone vs. polyurethane. Aesthetic Plast Surg. 2010;34:481–5.
86. Hodgkinson DJ. Buckled upper pole breast style 410 implant presenting as a manifestation of capsular contraction. Aesthetic Plast Surg. 1999;23:279–81.
87. Shaaban H, Jmor S, Alvi R. Leakage and silicone lymphadenopathy with cohesive breast implant. Br J Plast Surg. 2003;56:518–9.
88. Cantisani C, De Gado F, Grieco T, Faina P, Calvieri S, Scuderi N. Patch test reactions and breast implants. J Plast Reconstr Aesthet Surg. 2008;61:1540–1.
89. Goldblum RM, Pelley RP, O'Donell AA, Pyron D, Heggers JP. Antibodies to silicone elastomers and reactions to ventriculoperitoneal shunts. Lancet. 1992;340:510–3.
90. Fenske NA, Vasey FB. Silicone-associated connective-tissue disease. The debate rages. Arch Dermatol. 1993;129:97–8.

91. Brautbar N, Vojdani A, Campbell A. Silicone breast implants and autoimmunity: causation or myth? Arch Environ Health. 1994;49:151–3.
92. Lazar AP, Lazar P. Localized morphea after silicone gel breast implantation: more evidence for a cause-and-effect relationship. Arch Dermatol. 1991;127:263.
93. Selva-O'Callaghan A, Tura JM, Grau-Junyent JM, Labrador-Horrillo M, Solans-Laque R, Vilardell-Tarrés M. Silicone gel filled breast implants and dermatomyositis. Clin Exp Rheumatol. 2004;22:376.
94. American College of Rheumatology. Abstracts of Scientific Presentations. Annual Scientific Meeting of the American College of Rheumatology. Arthritis Rheum. 1992;35:(9 Suppl 1).
95. Sánchez-Guerrero J, Schur PH, Sergent JS, Liang MH. Silicone breast implants and rheumatic disease. Clinical, immunologic, and epidemiologic studies. Arthritis Rheum. 1994;37:158–68.
96. Brinton LA, Buckley LM, Dvorkina O, Lubin JH, Colton T, Murray MC, Hoover R. Risk of connective tissue disorders among breast implant patients. Am J Epidemiol. 2004;160:619–27.
97. Brown SL, Parmentier CM, Woo EK, Vishnuvajjala RL, Headrick ML. Silicone gel breast implant adverse event reports to the Food and Drug Administration, 1984–1995. Public Health Rep. 1998;113:535–43.
98. Deapen DM, Brody GS. Augmentation mammaplasty and breast cancer: a five year update of the Los Angeles study. J Clin Epidemiol. 1995;48:551–6.
99. Brinton LA, Lubin JH, Burich MC, Colton T, Brown SL, Hoover RN. Cancer risk at sites other than the breast following augmentation mammoplasty. Ann Epidemiol. 2001;11:248–56.
100. Jakub JW, Ebert MD, Cantor A, Gardner M, Reintgen DS, Dupont EL, Cox CE, Shons AR. Breast cancer in patients with prior augmentation: presentation, stage, and lymphatic mapping. Plast Reconst Surg. 2004;114:1737–42.
101. Le GM, O'Malley CD, Glaser SL, Lynch CF, Stanford JL, Keegan TH, West DW. Breast implants following mastectomy in women with early-stage breast cancer: prevalence and impact on survival. Breast Cancer Res. 2005;7:R184–93.
102. Brisson J, Holowaty EJ, Villeneuve PJ, Xie L, Ugnat AM, Latulippe L, Mao Y. Cancer incidence in a cohort of Ontario and Quebec women having bilateral breast augmentation. Int J Cancer. 2006;118:2854–62.
103. Lipworth L, Nyren O, Ye W, Fryzek JP, Tarone RE, McLaughlin JK. Excess mortality from suicide and other external causes of death among women with cosmetic breast implants. Ann Plast Surg. 2007;59:119–23.
104. Koot VCM, Peeters PH, Granath F, Grobbee DE, Nyren O. Total and cause specific mortality among Swedish women with cosmetic breast implants: prospective study. BMJ. 2003;326:527–8.
105. Pukkala E, Kulmala I, Hovi SL, Hemminki E, Keskimäki I, Pakkanen M, Lipworth L, Boice JD Jr, McLaughlin JK. Causes of death among Finnish women with cosmetic breast implants, 1971–2001. Ann Plast Surg. 2003;51:339–42.
106. Shanklin DR, Smalley DL. Dynamics of wound healing after silicone device implantation. Exp Mol Pathol. 1999;67:26–39.
107. Rishpon A, Wohl Y, Barnea Y, Ehrenfeld M, Weiss J, Klaz I, Brenner S. Silicone implants and connective tissue disease: 5 cases. Skinmed. 2007;6:30–4.
108. Sergott TJ, Limoli JP, Baldwin CM Jr, Laub DR. Human adjuvant disease, possible autoimmune disease after silicone implantation: a review of the literature, case studies, and speculation for the future. Plast Reconstr Surg. 1986;78:104–14.
109. Spiera H. Scleroderma after silicone augmentation mammoplasty. JAMA. 1988;260:236–8.
110. Press RI, Peebles CL, Kumagai Y, Ochs RL, Tan EM. Antinuclear autoantibodies in women with silicone breast implants. Lancet. 1992;340:1304–7.
111. Genovese MC. Fever, rash, and arthritis in a woman with silicone gel breast implants. West J Med. 1997;167:149–58.
112. Campbell A, Brautbar N, Vojdani A. Suppressed natural killer cell activity in patients with silicone breast implants: reversal upon explantation. Toxicol Ind Health. 1994;10:149–54.
113. Fritzsche FR, Pahl S, Petersen I, Burkhardt M, Dankof A, Dietel M, Kristiansen G. Anaplastic large-cell non-Hodgkin's lymphoma of the breast in

periprosthetic localisation 32 years after treatment for primary breast cancer—a case report. Virchows Arch. 2006;449:561–4.

114. Alobeid B, Sevilla DW, El-Tamer MB, Murty VV, Savage DG, Bhagat G. Aggressive presentation of breast implant–associated ALK-1 negative anaplastic large cell lymphoma with bilateral axillary lymph node involvement. Leuk Lymphoma. 2009;50:831–3.
115. Teuber SS, Yoshida SH, Gershwin ME. Immunopathologic effects of silicone breast implants. West J Med. 1995;162:418–25.
116. Lappe MA. Silicone-reactive disorder: a new autoimmune disease caused by immunostimulation and superantigens. Med Hypotheses. 1993;41:348–52.
117. Freundlich B, Altman C, Snadorfi N, Greenberg M, Tomaszewski J. A profile of symptomatic patients with silicone breast implants: a Sjögrens-like syndrome. Semin Arthritis Rheum. 1994;24(1 Suppl 1):44–53.
118. Ericsson AD. Syndromes associated with silicone breast implants: a clinical study and review. J Nutr Environ Med. 1998;8:35–51.
119. Contant CM, Swaak AJ, Obdeijn AI, van der Holt B, Tjong Joe Wai R, van Geel AN, Eggermont AM. A prospective study on silicone breast implants and the silicone-related symptom complex. Clin Rheumatol. 2002;21:215–9.
120. Sergent JS. The Hirmand/Latrenta/Hoffman article reviewed. Oncology (Williston Park). 1993;7:24.
121. Hirmand H, Latrenta GS, Hoffman LA. Autoimmune disease and silicone breast implants. Oncology (Williston Park). 1993;7:17–24.
122. Fock KM, Feng PH, Tey BH. Autoimmune disease developing after augmentation mammoplasty: report of 3 cases. J Rheumatol. 1984;11:98–100.
123. Young VL, Mohanakumar T, Schorr MW. Invited discussion. Increase of immunologically relevant parameters in correlation with Baker classification in breast implant recipients. Ann Plast Surg. 1996;36:518–21.
124. Brozena SJ, Fenske NA, Cruse CW, Espinoza CG, Vasey FB, Germain BF, Espinoza LR. Human adjuvant disease following augmentation mammoplasty. Arch Dermatol. 1988;124:1383–6.
125. Spiera RF, Gibofsky A, Spiera H. Silicone gel filled breast implants and connective tissue disease: an overview. J Rheumatol. 1994;21:239–45.
126. Elberg JJ, Kjøller KH, Krag C. Silicone mammary implants and connective tissue disease. Scand J Plast Reconstr Surg Hand Surg. 1993;27:243–8