Close to 700 articles can be found in the medical literature relating illness to silicone gel implant mammoplasty. Most of these articles are case series or single case reports describing autoimmune disorders (e.g., rheumatoid arthritis, scleroderma, or lupus erythematosus) in women with silicone gel implants. An estimated one to two million women have these devices implanted. Several recent articles and abstracts have linked neurologic disorders to silicone breast implants, engendering inquiries to the American Academy of Neurology (AAN). AAN's Practice Committee was thus asked to search for and summarize relevant scientific evidence and to draw conclusions regarding the nature of the associations, if any, between breast implants and neurologic disorders. A review of some recently published epidemiologic studies concerning breast implants and autoimmune disorders, the most frequently alleged association, is included in this paper for comparison.

A Medlars search was performed, including Medline and Backfiles through 1975. Several search strategies were tried, but the search described here generated the greatest number of relevant articles. Both foreign language articles and case reports were included. The search terms all breast: was linked by and to all silicon: which was then linked by and to all adverse affects pre-exploded (AE&[px]), which resulted in 671 citations, the majority concerned with connective tissue disorders. This output was linked by and to nervous system diseases (px) (pre-exploded) or neurologic manifestations (px) (pre-exploded). This search led to 14 articles. Most of these 14 reports do not outline neurologic disorders per se but often describe case reports of painful syndromes of one kind or another as in the examples that follow.

Vasey\(^1\) indicated that some women who had silicone breast implants complain of chronic fatigue, muscle pain, peripheral neuritis, and bladder dysfunction. Collins et al.\(^2\) presented an MRI study of the brachial plexus suggesting that the brachial plexus can be compromised by ruptured silicone breast implants. Another report of 11 patients published by Lu et al.\(^3\) suggested that an atypical chest pain syndrome develops in some women with breast implants. All 11 women had their implants removed and eight had abnormal findings on pectoralis major muscle biopsy (neurogenic atrophy in six patients, myositis in one, and a neuroma in one). The authors concluded that the pain was secondary to local inflammatory reactions. Frey et al.\(^4\) described tarsal tunnel syndrome secondary to silicone injections, and Sanger et al.\(^5\) described silicone gel infiltration of the superficial radial nerve that produced painful paresthesias after migration of silicone from a ruptured implant.

For this report, we also sought information regarding neurologic disorders and breast implants by placing a “Call for Comments” in several issues of the AAN's newsletter, AANews. We received 10 responses, two of which had been submitted as abstracts to journals. Most were personal observations without controls or analysis except for one published abstract. The published abstract\(^6\) described 330 women participating in a class action law suit and compared these with 248 controls. The study compared ruptured versus unruptured implants and found GM1 antibodies in 3.3% of patients with ruptured and in 5.4% of patients with unruptured implants. Controlling for age, there was a difference of 19.1% for rupture versus 7.1% for the no-rupture group, which was not statistically significant. There was no difference in antinuclear antibodies (ANA) between controls and patients with implants. The authors suggested an increased prevalence of GM1 antibodies in the patients with ruptures because an increased chance of rupture with age increases risk for GM1 antibodies.

Shoaib et al.\(^7\) provided us with several published articles and unpublished manuscripts. In one study, they describe 100 consecutive patients referred for evaluation of problems related to their breast implants. Based on history and physical examination, the authors diagnosed a polyneuropathy syndrome in 83 of the 100 patients. Ninety-three patients had EMG and nerve conduction studies, of which 44 were normal and 49 abnormal. Of the 83 polyneuropathy syndrome patients had normal EMGs and nerve conduction studies is not noted. Ten patients were described as having a multiple sclerosis (MS) like syndrome (eight of these patients also had polyneuropathy syndrome). The authors do not state whether these eight are part of the group of 83 patients. Five patients had a motor neuron disease syndrome and two had myasthenia gravis. The authors report abnormal laboratory tests such
as MRI, lumbar puncture, EMG and nerve conduction studies, visual evoked responses, sural nerve and muscle biopsies, and immunoglobulin values in various patient groups.

In another paper, Shoaib and Patten describe 26 women with silicone breast implants who developed an MS-like syndrome. Symptoms started an average of 5.7 years after the implant. All patients were seen by other neurologists and then referred to the authors for further evaluation. These 26 patients had a variety of signs and symptoms such as ataxia, spastic paraparesis, optic neuritis, dysarthria, nystagmus, and hyperreflexia. Many also had signs and symptoms of peripheral nerve disorder. The course of the disorders was progressive, not remitting. MRI imaging was abnormal in 22 of 26 patients. Twenty-one studies showed white matter lesions. Spinal fluid revealed oligoclonal bands in 18 of 23 patients, visual evoked responses were delayed in 14 of 23 patients, and there were autodirected antibodies in 16 of 26. Sural nerve biopsy revealed demyelination in 15 of 15 patients. EMG and nerve conduction velocity studies were abnormal in nine of 19 patients. Seventeen of 24 patients had their implants removed and, in 12 of the 17, the implants had ruptured. The study does not state whether condition of any patients improved after implant removal. All 26 of the patients in the study had additional rheumatologic symptoms (e.g., myalgia, joint stiffness, sicca complex, Raynaud's phenomenon, etc.).

On the basis of these two studies, the authors concluded that these disorders represent a new disease, which they called human adjuvant disease. However, there are several reasons to doubt the conclusion. First, both case series are from one group and the findings have not been reported by anyone else. Second, although several clinical types of patients are described in the first paper, such as the polyneuropathy and MS groups, the symptoms and signs of patients are simply listed in a table, making it impossible to determine which groups of patients had which symptoms, signs, or laboratory test abnormalities. In the paper that focuses on the MS-like syndrome, the symptoms, signs, and laboratory tests are listed for each patient but only in tabular form. Only two patients are described in detail. There is virtually no analysis or discussion of the patient groups and no attempt to demonstrate causation in either paper. Third, and very importantly, a recently published review of the medical records of 131 of the patients examined by these authors casts doubt on the extent of neurologic involvement in these patients. This further weakens the alleged association between silicone implants and neurologic syndromes. The author of the review discloses that he was retained as a consultant for the implant manufacturers but that the review was not funded by them.

**Breast implants and connective tissue disorders.** In contrast to the literature on breast implants and neurologic disorders, the literature concerned with an alleged association of silicone breast implants with connective tissue disorders is immense. Although most of the literature consists of case reports and case series, recently, several observational (retrospective cohort or case control--Class II evidence) studies investigating this alleged association have been published. These studies, the best epidemiologic evidence to date, suggest only weak or inconsistent relationships between breast implants and the risk of connective tissue diseases. The study by Hennekens et al., a large retrospective cohort study of 395,543 female health professionals, did find a slight increase with a relative risk of 1.24 (95% confidence interval of 1.08 to 1.41, \( p = 0.0015 \)) of self-reported connective tissue disease in women with breast implants. The authors felt that the large sample size made chance an unlikely explanation of the results, but felt that there was clear bias due to differential over-reporting or selective participation by symptomatic women with breast implants. It can be concluded that the epidemiologic studies completed thus far have shown no clear association of silicone breast implants with a risk of connective tissue disorders.

**Discussion.** The published literature linking the risk of neurologic disease to silicone breast implants is meager and virtually all comes from one group of authors. These are case series and consist of highly selected referred patients who had both neurologic symptoms and breast implants. Case series are the poorest form of evidence for drawing causal inferences. No control populations were studied, thus these studies are Class III evidence. The extent of neurologic disease in many patients has been questioned, but it is likely that at least some had neurologic involvement.

What is missing, however, is epidemiologic evidence of any association or causal relationship of the neurologic disorders with silicone implants. Studies do not demonstrate that the disorders were in any way caused by the silicone breast implants. The proof of causality using epidemiologic studies has been outlined by Sir Austin Bradford Hill:

1. Temporality – the cause should precede the effect.
2. Strength – the relative risk should be high. Most epidemiologists feel that this should be at least 2 to 3 and that relative risks less than 2 are questionable.
3. Dose response – with greater or longer exposures to the risk factor, the risk of disease should be greater.

4. Reversibility – removal of the risk factor should decrease the risk of disease or symptoms.

5. Consistency – studies conducted at different times and in different settings should produce similar results.

6. Biologic plausibility – there should be understandable reasons biologically and physiologically why the offending substance could or should cause the disease in question.

7. Specificity – ideally, there should be one cause and one effect. However, it has become clear that many offending agents, such as cigarette smoking, can cause many different diseases, and lung cancer can be caused by several different offending agents. Even infectious agents can cause several different kinds of diseases.

8. Analogy – there are other examples of similar illnesses caused by similar offending agents.

None of these criteria can be satisfied to make a case for the occurrence of neurologic disease in women that is caused by silicone breast implants. One could argue that in the case series, authors describe anecdotally that the surgical implantation preceded the symptoms, but the time described is widely inconsistent. No relative risk and no dose-response information is provided in the literature. A few anecdotal reports suggest that removal of implants has led to improvement in symptoms. There has been no consistency except in the recent observational cohort and case control studies for connective tissue diseases, which have shown no clear relationship between these disorders and breast implants. Biologic plausibility might be inferred by the ability of some silicone products to act as adjuvants to produce illness similar to the animal models in experimental autoimmune encephalitis or polyneuritis. However, given that the same neurologic disorders occur in individuals who have never been exposed to silicone, that the disorders have not been described in patients who are exposed to silicone in other forms, and that not all women with breast implants who develop these illnesses have had rupture of the implants, this matter seems far from settled.

Most of the patients reported with neurologic symptoms also had symptoms compatible with connective tissue disorders. Well-known neurologic disorders are occasionally associated with some connective tissue diseases and it might be postulated that the neurologic syndromes were secondary to the connective tissue disorders. However, the best scientific evidence to date, namely the several large cohort or case control studies (Class II evidence), show no, or a weak, association of silicone breast implants with connective tissue disorders. No studies presently support any association with neurologic disorders. The National Institutes of Health is currently funding a number of studies of the antigenicity and carcinogenicity of silicone and the possibility of autoimmune disorders in patients with silicone reconstruction mammoplasty.

Conclusions. The best observational studies to date (some retrospective cohort and case control studies [Class II]) show no clear relationship of silicone breast implants to connective tissue disease. Research in this area is ongoing. Existing studies (some case series--Class III) do not support any association or causal relationship between silicone breast implants and neurologic disorders. If such a relationship exists, we must await proper observational studies, preferably prospective cohort studies, or less preferably, case control studies.

Acknowledgments
The Practice Committee expresses its gratitude to Therapeutics and Technology Assessment (TTA) Subcommittee, chaired by John H. Ferguson, MD, for their help in preparing this report. TTA Subcommittee would like to acknowledge the helpful critique of Douglas Weed, MD, PhD, Chief of Preventive Oncology, National Cancer Institute.

Note. This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

Definitions
Class I: Evidence provided by one or more well-designed randomized controlled clinical trials, including overviews (meta-analyses) of such trials.
**Class II:** Evidence provided by well-designed observational studies with concurrent controls (e.g., case control and cohort studies).

**Class III:** Evidence provided by expert opinion, case series, case reports, and studies with historical controls.

**References**


Published in *Neurology* 1997;48:1504-1507.

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