# SILICONE TOXICITY

## The circle .....

## .... A new start .....

*Breast implants are improved but still gel bleed occurs in all of them and the shell (Textured) is not inert*

*Migration of silicone occurs throughout the body*

*Dosis Respons Curve is crucial*

*Explantation reduces symptoms and heals for >70%*

*Point of no return*

*Silicone is a wolf among sheep*

***Henry Dijkman RadboudUMC / HAN Applied Sciences*** *27-9-2019*

# Silicone ……. A wolf among sheep ……. Listen to your body!

## There is a Point of no return!

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# Gel Bleed and Rupture of Silicone Breast Implants Investigated by Light-, Electron Microscopy and Energy Dispersive X-ray Analysis of Internal Organs and Nervous Tissue

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## Abstract

**Objective:** We studied a patient who died in 2008 at the age of 56 and had been exposed to gel bleed from her silicone breast implants for 17 years. Tissue samples and nervous tissue could be obtained for analysis.

**Design:** During autopsy, a wide range of different tissue samples were collected, frozen and embedded in paraffin and plastic (Epon). The paraffin samples were stained with Hematoxylin and Eosin (HE) as well as with Modified Oil O Red (MORO). Tissues embedded in plastic (Epon) were sectioned and prepared for light microscopy using toluïdin blue staining for Transmission electron microscopy (TEM) and Energy Dispersive X-ray microanalysis (EDX) to measure elemental Silicon (Si).

**Results:** We found 2 types of silicone material in multiple tissue and brain samples of this patient. The first is a droplet-like form. EDX measurements demonstrated that the droplets are composed of elemental Si. The second is a plaque-like form; these structures are comprised of elemental Si and Ti (Titanium). Occasionally we found that these plaques were located inside the tissue without a lining and sometimes they were located inside the lumen of blood vessels.

**Conclusions:** The use of EDX analysis over light microscopic examination only, is now a contributing factor for the establishment of silicone bleeding and migration throughout the whole body in high amounts.

## Keywords

Silicone breast implants, Silicone gel bleed, PDMS, Si, TEM, EDX

## Introduction

Some women, who have received silicone breast implants either for breast augmentation or breast reconstruction, develop health problems in different gradations over the years and a thorough explanation for this has yet to be given [1-3] this is because this kind of research can only be performed on living humans. In addition, as the existence of associated complaints is still largely denied and neglected by the various medical disciplines, they are not recorded in medical histories of the involved women and thus do not appear in meta analyses [4] So, only combining various pieces of scientific information can give us insight. It is already known that explantation of the implants can up to a certain point and especially in the early stages cause an improvement of these complaints [5,6] With regard to the silicone issue, EDX analysis has been performed only once before, in excised lymph nodes [7]. In this study, with a novel approach, the light microscopic presence of silicone droplets and plaques in the various tissues (Table 1), are subjected to TEM and EDX analysis for measuring Si-counts. This adds a new element to the already existing knowledge with regard to silicone gel bleed from, and rupture of silicone breast implants.

## Materials and Methods

### Patient

During autopsy, tissue samples of multiple organs and different sections of brain and spinal cord areas were collected. The patient received the silicone breast implants in 1985. In her medical files her general practitioner reported in 1997 that she had developed "adverse reactions to her implants", without specifying what these reactions were. In 2001 they were replaced by new silicone breast implants together with a capsulectomy. At this operation the implants appeared to be ruptured, thus leaving a near empty elastomer shell. Still in 2001 she developed capsular contracture of the left breast and had a capsulectomy. At that time the medical health complaints she had enumerated, such as painful breasts, a burning sensation of the breasts, lymph packages in the left armpit, severe memory function disorder, walking function disorder, sleeping disturbances, complaints about bowel function and skin disorders. She described an overall feeling of chronic illness and complained of sudden numbness of the legs. In 2002 both her one-year-old implants were removed. In June 2003 she developed a subcutaneous swelling in her left armpit and subsequently axillary lymph nodes were removed for histological examination. The pathologist reported that he found extensive histiocytic reaction on small needle-like particles, in concurrence with a reaction on silicon. Two weeks later the patient developed enlarged lymph nodes in her left groin area. In 2004 she developed an invasive ductal carcinoma of the left breast; however, this might be coincidental and not linked to the silicone implants. Post mortem, the same ductal carcinoma has been histologically found in

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**Table 1:** A summary of positive silicone holding material of the patient. The plaques are comprised of elemental silicon and titanium. The vacuoles (droplets) are comprised of elemental silicon. Several techniques are included in this table, illustrating the amount of silicon in Frozen sections, paraffin sections and plastic sections.

| Body Material patient ↓ | MORO (Frozen) | HE (paraffine) | | MORO (paraffine) | | | ToluidinBlue (EPON) | | EDX (EPON) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | plaques | vacuoles | plaques | vacuoles | macrophages | plaques | vacuoles | Plaques | vacuoles |
| Colon | +++ | - | - | - | - | + | - | - | - | - |
| Small intestine | +++ | + | - | + | - | + | - | - | - | - |
| Kidney | + | - | - | - | - | + | + | - | + | - |
| Spleen | + | - | - | - | - | - | - | - | - | + |
| Thyroid | + | + | - | + | - | - | + | - | + | - |
| Epiglottis | ++ | - | - | + | + | - | - | - | + | + |
| Lung | + | + | - | + | - | + | - | - | - | + |
| Liver | - | - | - | + | - | + | - | - | - | - |
| Pancreas | +++ | + | - | + | - | + | - | - | - | - |
| Stomach | +++ | NE | NE | NE | NE | NE | - | - | - | - |
| Breast | +++ | NE | NE | NE | NE | NE | - | - | - | + |
| Fibro-adenoma breast | | - | - | + | + | + | NE | NE | | |
| (right) peri-prosthetic capsule | +++ | - | - | - | + | - | - | - | - | - |
| Rib tumor | | - | + | - | + | + | NE | NE | | |
| Ovary | + | + | - | + | - | - | + | - | + | - |
| Fallopian tubes | - | NE | NE | NE | NE | NE | + | - | + | - |
| Uterus | + | NE | NE | NE | NE | Ne | + | - | + | - |
| Urine bladder with cystitis | +++ | + | - | + | - | + | + | - | + | - |
| Diaphragm | | - | - | - | + | - | + | - | + | - |
| Gallbladder | +++ | - | - | - | - | - | + | - | + | - |
| Skin | ++ | NE | NE | NE | NE | NE | - | - | - | - |
| Lymph nodes of unknown origin | +++ | - | - | - | - | - | - | - | - | + |
| Psoas muscle | | + | - | + | - | - | NE | NE | | |
| Septum and ventricular wall | ++ | - | - | - | - | - | - | - | - | - |
| Pericardium | ++ | NE | NE | NE | NE | NE | - | - | - | + |
| Aorta | + | NE | NE | NE | NE | NE | - | - | - | - |

| Nerve / brain material patient ↓ | MORO (Frozen) | HE (paraffine) | | MORO (paraffine) | | | ToluidinBlue (EPON) | | EDX (EPON) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | plaques | vacuoles | plaques | vacuoles | macrophages | plaques | vacuoles | plaques | vacuoles |
| Nerve of unknown location | NE | - | - | - | - | - | NE | NE | NE | NE |
| Spinal cord | NE | + | - | + | - | - | + | + | + | + |
| Pons | NE | - | - | - | - | - | NE | NE | NE | NE |
| Medulla oblongata | NE | - | - | - | - | - | NE | NE | NE | NE |
| Mesencephalon | NE | - | - | - | - | - | NE | NE | NE | NE |
| Pituitary | NE | - | - | + | - | + | - | - | - | - |
| Thalamus | NE | - | - | - | - | - | NE | NE | NE | NE |
| Amygdala | NE | - | - | - | - | + | NE | NE | NE | NE |
| Hippocampus | NE | - | - | - | - | - | NE | NE | NE | NE |
| Frontal cingulum | NE | - | - | - | - | + | NE | NE | NE | NE |
| Striatum and lens core | NE | - | - | - | + | + | NE | NE | NE | NE |
| Occipital lobe | NE | - | - | - | - | - | NE | NE | NE | NE |
| Frontal cortex left (white substance) | NE | NE | NE | NE | Ne | NE | + | - | + | - |
| Frontal cortex right | NE | NE | NE | NE | Ne | NE | - | - | - | - |
| Temporal and parietal gyrus | NE | - | - | - | - | - | - | - | - | - |
| Tumoral lesion brain | NE | - | - | - | - | - | NE | NE | NE | NE |
| Cerebellum | NE | - | - | - | - | - | - | - | - | - |

-: Negative or no findings; **NE**: Not embedded; + to +++: High amounts of silicon

the liver, ribs, vertebrae and hypothalamus. In the end, this caused her death. For orientation purposes in this new type of study, a second case was introduced, acting as a 'positive control'. This patient had silicone implants for 14 years and upon removal both implants were ruptured. The peri-prosthetic capsule only could be harvested. Of both patients in this study the samples were processed (HE, MORO and Toluidine blue staining) and assessed by light microscopy. Subsequently, EDX measurements were performed to quantify the amounts of silicone as found in the TEM.

## Light microscopy

The modified Oil Red O (MORO) is a histological staining, used to visualize silicone. This was initially performed on frozen sections to maximize detection as paraffin preparation can dissolve some of the silicone. Paraffin sections were deparaffinized before staining with MORO. This was done with xylene for 15 minutes and 3 dips into absolute alcohol. Next, the slides were rinses in demineralized water. For the MORO staining an oversaturated colouring solution of Oil Red O (0.5 g In 100 ml 100% 1,2-propanediol) was used, which acts like a solvent. The silicone polymers, which likely have fatty rest groups, are stained by the oil red O, because the Oil Red O is better resolved in the silicone polymers than in the 1,2-propanediol. The oil Red O moves from the relatively polar solvent to the non-aquatic polymers of the silicone. The principle of this staining thus is the physical binding between the Oil Red O molecules and the silicone polymers. After 5 days, the slides were agitated and differentiated in 85% 1,2-propanediol. After rinsing in tap water, the slides were stained with Hematoxylin Mayer to counter stain the nuclei in the surrounding tissue. After 10 minutes of rinsing in tap water, the slides were dipped in a 1% acetous alcoholic solution for further differentiation. After this, the slides were rinsed for 4 minutes and dipped in saturated lithium carbonate solution (4 g lithium carbonate

in 100 ml demineralized water). In the next and final step the slides were rinsed for 4 minutes in tap water and covered with gelatine-glycerin, a water based cover medium. Positive staining is seen as bright and deep red staining.

### Electron microscopy

The plastic (Epon) embedded tissues were fixated in a 2% glutaraldehyde 0.1 M sodium cacodylate buffer solution with a pH of 7.4 for a minimum of 4 to a maximum of 24 hours [8]. Removal of free non-reacted aldehydes was done by a washing step in 0.1 M sodium-cacodylate buffer solution with pH range of 5.0 - 7.4. All tissues were dehydrated in an ethanol-propylene oxide series and manually imbedded in EPON, an epoxy resin. EPON polymerizes for 1 night at 45°C and for 2 days at 67°C in an incubator [9]. Semi- and ultra thin sections were obtained with a Reichert-Jung ultramicrotome by using a Histo diamond knife for 1 µm semi thin sections and an Ultra diamond knife for the 90-200 nm ultrathin sections. Semi thin 1 µm sections were stained with toluïdin blue. This staining gives a clear overview of the semi thin sections and can be used to visualize areas of interest to be viewed in the ultrathin TEM sections or measured with EDX. Ultra thin 90-200 nm sections were collected on membrane coated (polyvinyl formal in 1% ethylene dichloride) 3.05 mm 100 mesh copper grids. The 90 nm ultrathin cuts were additionally contrasted with 4% uranyl acetate solution for 30 minutes and lead citrate for 6 minutes so they obtained the desired contrast for morphological examination. The uncontrasted 200 nm ultrathin cuts were used for EDX measurements. Specimen were next studied with a Jeol (JEM-1200 EX II TEM/STEM) Transmission/ Scanning Electron Microscope operating at 64 kV with Energy Dispersive X-ray (EDX) equipment.

## Results

Droplets and plaques containing silicone were found in the random parts of the sampled tissues. They could be seen in the HE, MORO and Toluïdin blue through light microscopy. An overview of silicone containing organs and tissues of our patient and the findings in TEM/EDX analysis is presented in table 1. Table 1 is a summary of positive silicone containing material. The plaques are

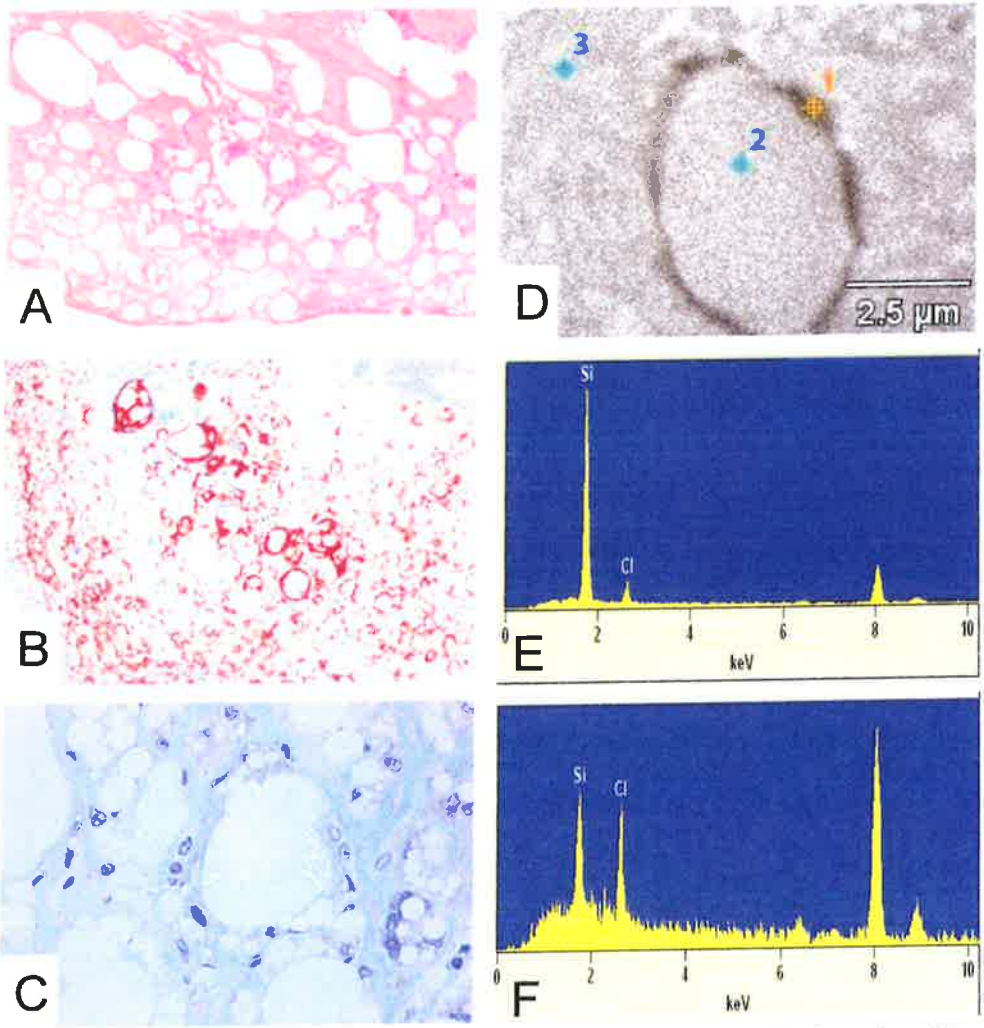


**Figure 1: (A)** A histological 4 µm paraffin cut of the capsule surrounding the silicone implants from patient 2 with bleeding and complete rupture of the implant. As can be seen there are numerous vacuoles which are, as viewed by a higher magnification, filled with threadlike structures of translucent amorphous refractile non-polarizing material suggestive of silicone deposition (HE staining); **(B)** A histological 4 µm paraffin cut from the capsule surrounding the silicone implant from patient 2 stained with the MORO to demonstrate if the translucent amorphous thread like structures are stained. As can be seen strong positive stained material is present, particularly located perivacuolar; **(C)** A higher magnification of the semi thin toluïdine blue stained cut from the capsule surrounding the silicone implants of patient 2. As can be seen clearly there is a vacuole partially filled with threadlike structures of translucent material. Also here the vacuoles are not completely filled with the material, suggesting there is material lost in the processing steps. The embedding of the tissue in epon makes it inappropriate to visualize (stain) the silicone with the MORO staining. EDX analysis is performed to conclude if high concentrations of silicone are measurable; **(D-F)** EDX spectra and EDX analysis of a non contrasted 200 nm EPON section from the capsule surrounding the implant from patient 2. Top right image shows three measuring points. Point 1 is on the electron dense perivacuolar material, point 2 and 3 are in and around the vacuole; As can be seen in spectra 1 there is a high peak of elemental silicon at 1.74 KeV **(E)**; In measuring points 2 and 3 there are considerable less amounts of elemental silicon found and stay under 500 silicon net counts **(F)**. With this in mind we have set a standard: net counts lower than 500 are negligible and counts over 1000 are of silicon stacking and of pathological interest. As can be seen in measure point 1 there are 6626 Si- counts and thus suggestive for silicone stacking. Chlorine peaks found at approximately 2.6 KeV are originating from the EPON, peaks at resp. 8 and 9 KeV are due to copper, used as material for the grid holder. Both peaks can be ignored. Picture E EDX on dense perivacuolar material (point 1). Si count 6.626, Inside the vacuole (point 2). Si count 302 and picture F EDX on the surrounding tissue (point 3). Si count 447. Original microscopic magnification A-B 50x, C 400x.

comprised of elemental silicon and titanium. The vacuoles (droplets) are comprised of elemental silicon. Thus we identified two variants of silicone containing material. These were also found in macrophages. Different stainings are the MORO silicone staining and Sudan Black/ Normal ORO fat stains which have been performed on a silicone positive paraffin control, consisting of a peri prosthetic capsule. Also electron microscopical investigation and EDX analysis was done on this positive control. Questions about the specificity of the MORO staining for silicone in freeze and paraffin cuts could thereby be established (figure 1).

The Modified Oil Red O (MORO) staining was initially performed on 4 µm freeze cuts from frozen material of our patient, acquired in body autopsy. This first staining was performed to check if any positive material is present and stainable. Results of this first MORO staining show large quantities of positive stained material in a large range of tissues. (Table 1 and Figure 2).

To ensure that the frozen material from patient 1 also contains the silicone after treatment with different fixatives we performed MORO staining on different samples. As can be seen in all panels there is a significant amount of positive material present (Figure 3).

Also different lymph nodes were excised for histological examination and showed extensive foreign body reaction in the presence of many epithelioid multinucleated giant histiocytes and the presence of translucent material, suggestive for silicone. MORO positive stained material is located inside vacuoles and histiocytes (Figure 4). Samples are cut approximately 100 and 200 nm thick for assessment in TEM and analysis by EDX. EDX analysis is performed on this lymph node material to see if large amounts of elemental silicon is measurable. (Figure 5).

EDX analysis reveals the true nature of the plaque like structures found in the toluïdin blue stain, elemental silicon and titanium were found in all the plaque like structures. The found component of elemental titanium represents the dens particles located inside the plaques. Also loose droplets of elemental silicon were found, situated partially in vacuoles, for instance in the thyroid gland, figure 6.

The plaque like structures found in the spinal cord of patient 1 are located inside the surrounding spinal cord tissue. The TEM micrographs demonstrate the plaque like structure and a higher magnification of a TEM micrograph show small particles inside the plaque, clearly visible around the asterisk. EDX analysis is performed

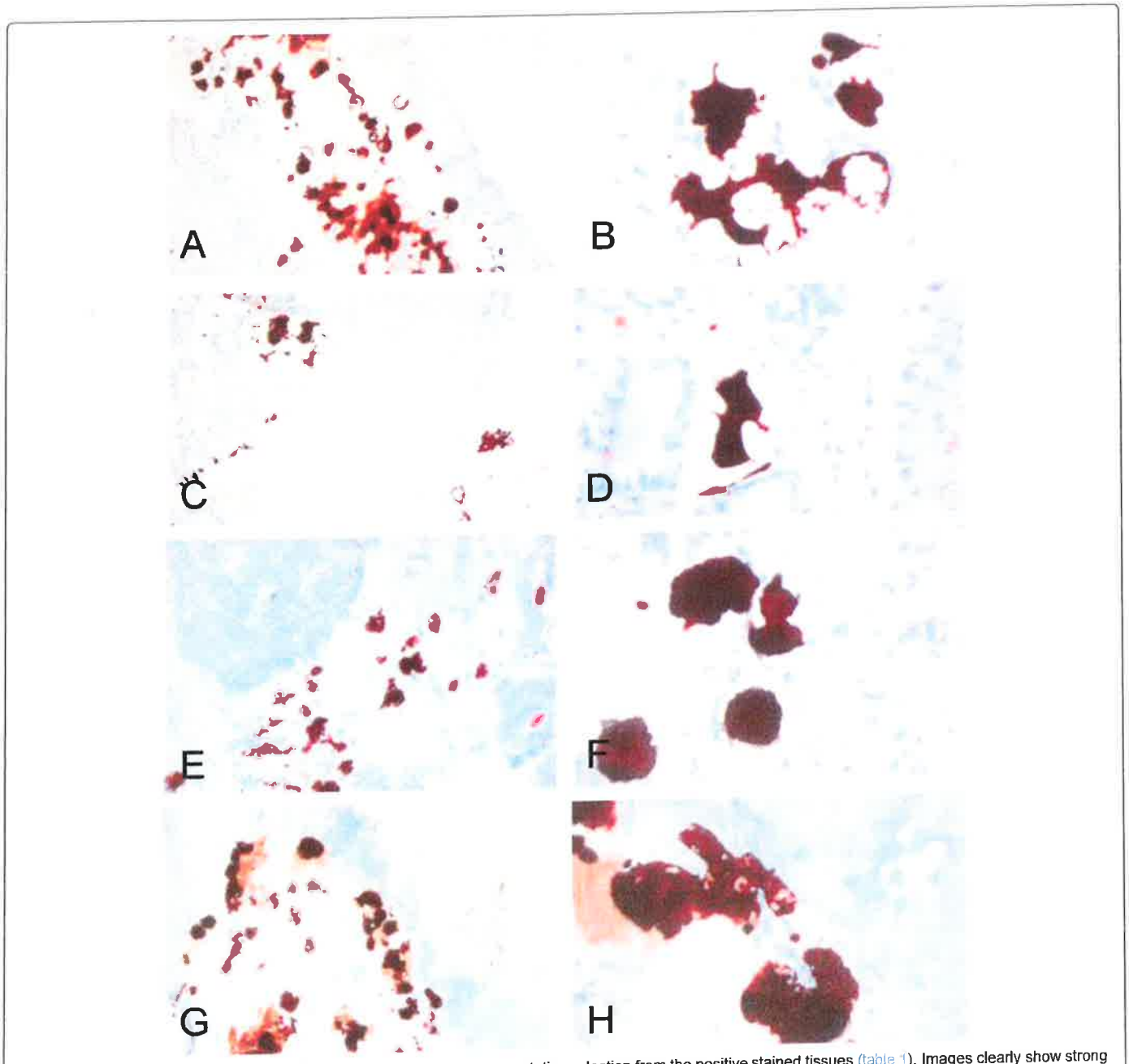


**Figure 2:** Pictures of the MORO stained 4 µm cryosections, are a representative selection from the positive stained tissues (table 1). Images clearly show strong positive stained material in; diaphragm (**A-B**); small intestine (**C-D**); pancreas (**E-F**) and colon (**G-H**), of patient 1. The positive material is often presented in vacuoles but often this material is not contained in the vacuoles and appears to be dragged or washed out. Original magnifications left 50x and right 200x.

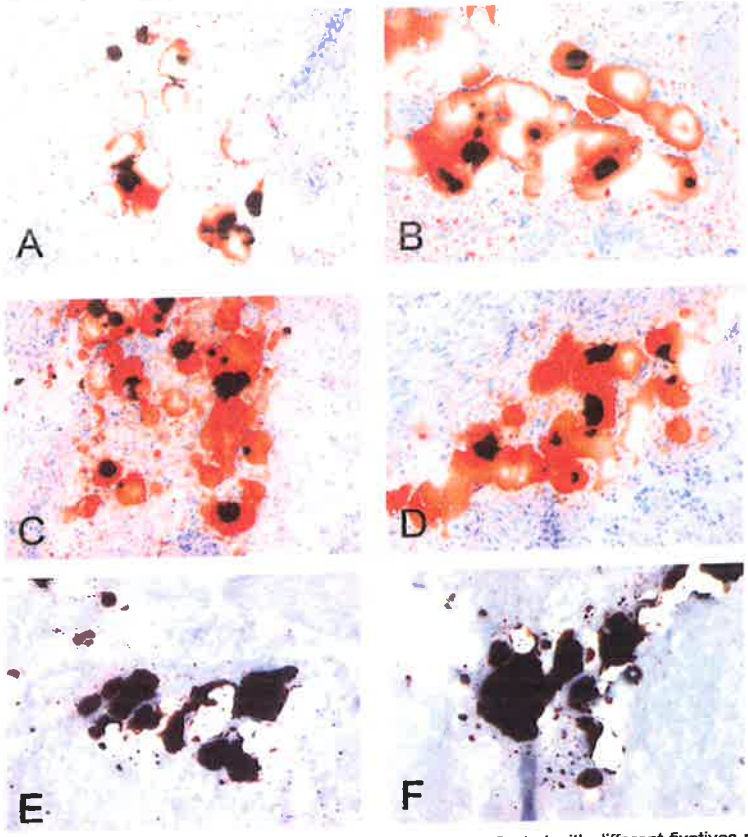


**Figure 3:** Pictures all show the same freeze cut of the frozen urinary bladder from patient 1 fixated with different fixatives previous to MORO staining. All left images are 4 µm thick, all right images are 9 µm thick. Panel A/B 15 minutes 4 % buffered formalin fixation. Panel C/D shows 15 minutes 2% glutaraldehyde fixation. Vacuoles are both in the 4 and 9 µm cuts completely filled with positive stained material. Panel E/F shows 15 minutes 2% glutaraldehyde + 15 minutes 2% osmium tetroxide fixation. As can be seen in all panels there is a significant amount of positive material present. Original magnification: all 100x.

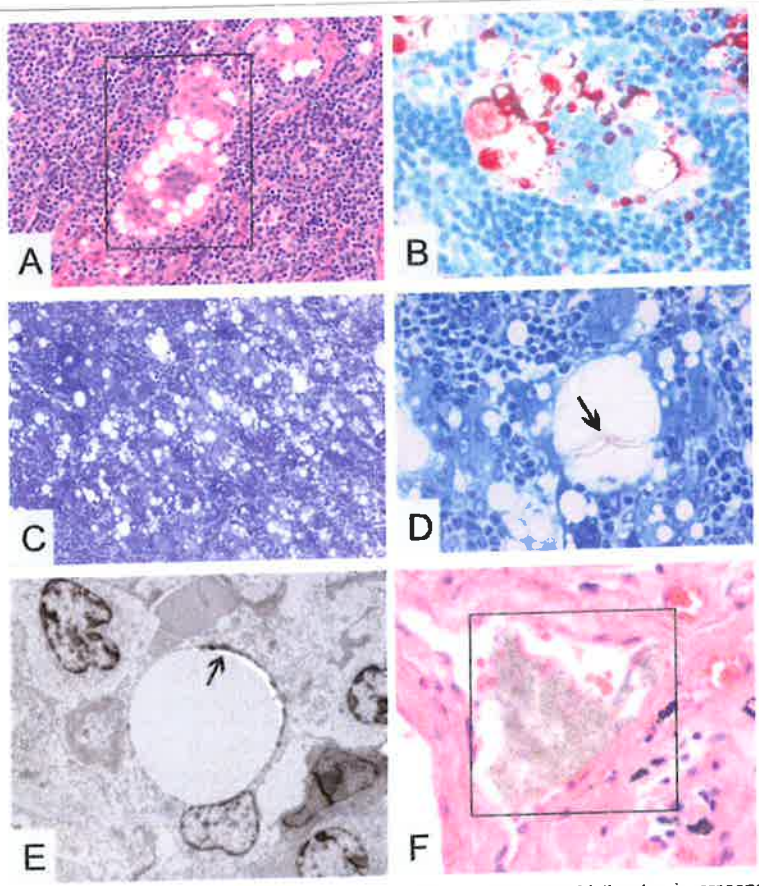


**Figure 4:** Multiple lymph nodes of patient 1 were filled with large quantities of multinucleated giant histiocytes in presence of possible exogenous material, suggestive of silicone A-E. (**A**) A 4 µm paraffin cut stained with Hematoxylin and Eosin in presence with a giant histiocyte and cytoplasmatic vacuoles filled with, when viewed with higher magnification, translucent amorphous material; (**B**) A 4 µm paraffin cut stained with the MORO, positive stained material is present inside the giant histiocytes; (**C**) A 1 µm toluïdin blue stain where multiple giant histiocytes are seen in presence of multiple vacuoles; (**D**) A higher magnification of the toluïdin blue stain were threadlike translucent material is present inside the vacuoles; (**E**) A TEM micrographs of a vacuole with dens perivacuolar material, on this dens material EDX analysis is performed, see details Figure 5 A-B. Often material is clearly located inside a bloodvessel, this event can be found throughout all tissues (**F**). Original microscopic magnification; A/B and D/F; 400x, figure C; 200x and figure E 5000x

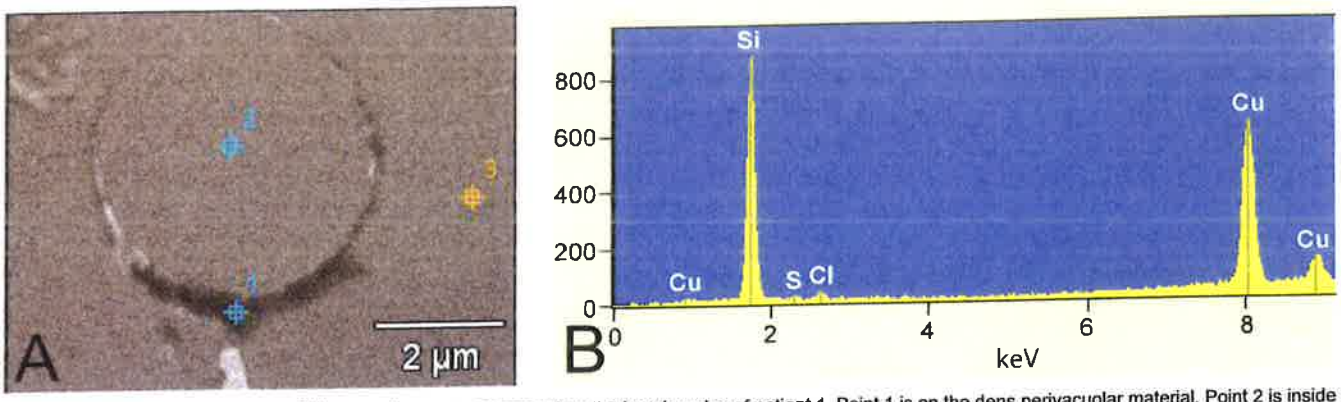


**Figure 5:** TEM micrograph of the EDX measuring points performed on the lymph nodes of patient 1. Point 1 is on the dens perivacuolar material. Point 2 is inside the vacuole and point 3 is on the surrounding tissue (**A**); EDX analysis of patient 1 lymph nodes from the subcutaneous swelling in the left armpit. Point 1 (spectra 1) = 10759 Si-counts (**B**). As can be seen in measuring point 1 there is a large peak of elemental silicon found which corresponds with the electron dens perivacuolar material.

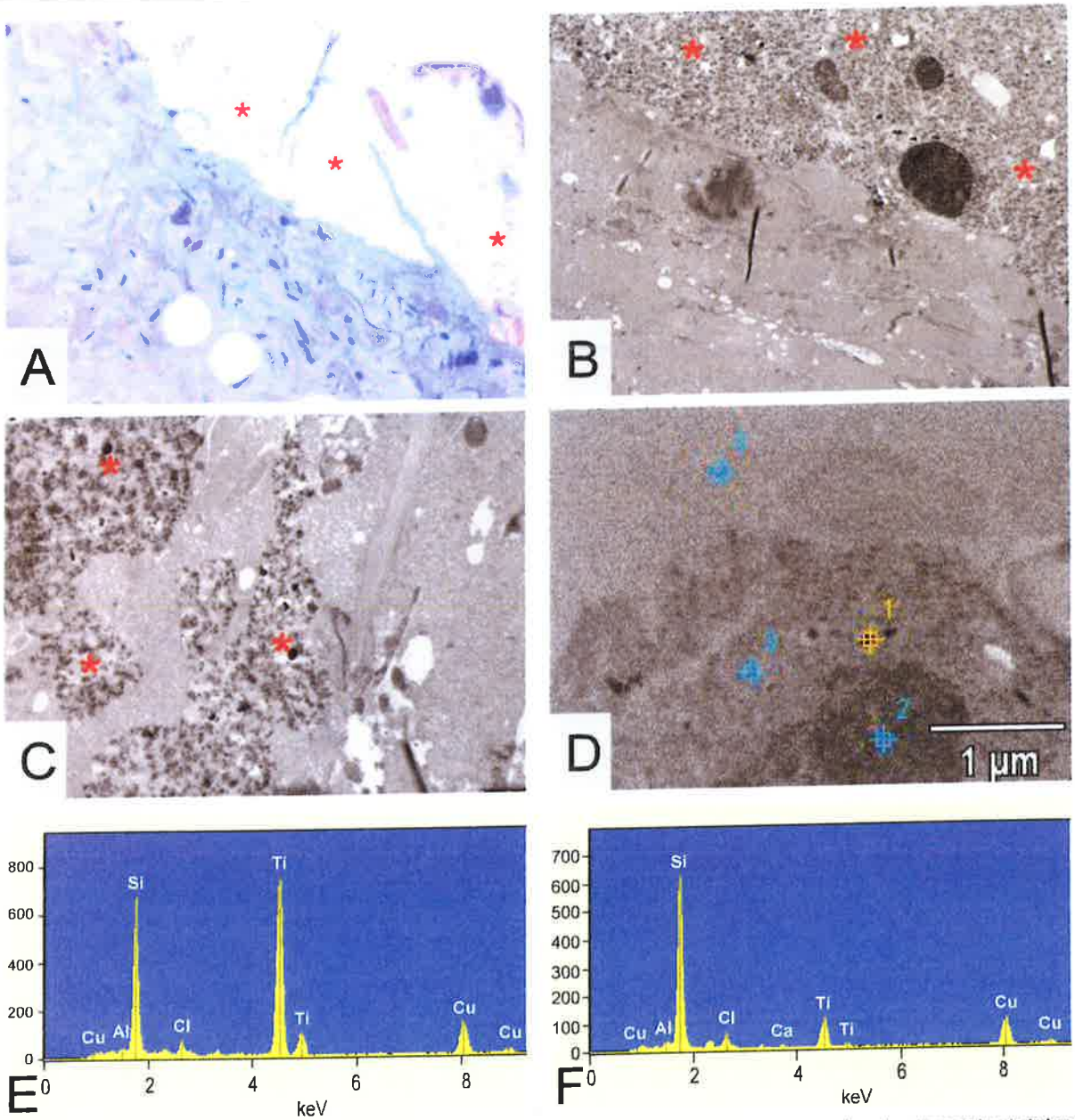


**Figure 6:** Figures show the plaque like structures * found in the thyroid of patient 1. **(A)** The toluïdin blue stained eponsection, the plaque is located alongside the tissue, suggesting that is has no connection with the tissue; **(B)** A TEM micrograph where it is nicely demonstrated that the plaque like structure is situated around collagen; **(C)** A higher magnification of a TEM micrograph were it is nicely demonstrated that the plaques are completely surrounded by thyroid tissue. Dens small particles inside the plaque are clearly visible. EDX analysis is performed on these structures; **(D)** The TEM micrograph of the EDX measuring points performed on the thyroid of patient 1; **(E)** Depicted EDX on a dens particle found inside the plaque (spectra 1) = 7200 Si-counts/11652 Ti-counts; **(F)** EDX on the plaque itself (spectra 2) = 7252 Si-counts/1579 Ti-counts and point 3 is on the surrounding tissue (spectra 3) = 545 Si-counts (not shown). Original microscopic magnifications figure A/B and C; resp. 400x, 3K and 7.5K.

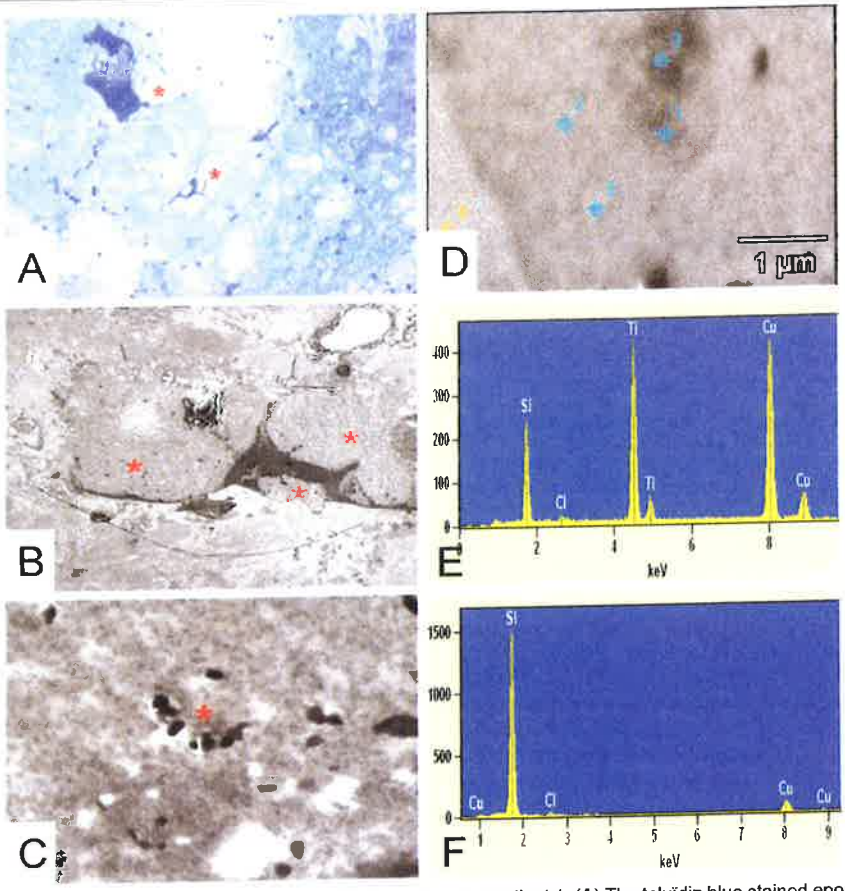


**Figure 7.** (**A**,**B** and **C**) The plaque like structures * found in the high cervical spinal cord of patient 1. (**A**) The toluïdin blue stained eponsection, the plaque is located inside the surrounding spinal cord tissue; (**B**) A TEM micrograph where it is nicely demonstrated that the plaque like structure is situated around collagen and in close proximity of nerve tissue; (**C**) A higher magnification of a TEM micrograph were small particles inside the plaque are clearly visible around the asterisk. EDX analysis is performed on these structures and detects Si and Ti, (**E**); (**D**) The TEM micrograph of the EDX measuring points performed on the high cervical spinal cord of patient 1 and demonstrates inside the plaque (spectra 1) = 16854 Si-counts (**F**). Original microscopic magnifications figure A/B and C; resp. 200 x, 1.5K and 12K.

**Table 2:** A summary of the EDX-measured Si counts in different samples. It gives an overview of the Si counts in the tissues examined with EDX. These numbers give an impression. Measurements are done with spot-analysis, surface in the range of 0.1 - 0.15 square um.

| | first measuring point | second measuring point | On (empty) vacuole | On surrounding tissue |
|---|---|---|---|---|
| pure silicone gel | 337559 | | | |
| tissue from patient without implants | < 500 | | 302 | 447 |
| Uncontrasted peri-prosthetic capsule with implant ruptur | 6626 | | | 288 |
| Contrasted peri-prosthetic capsule with implant rupture | 108200 | 73834 | 195 | 235 |
| Lymphnodes | 10759 | | | 545 |
| Thyroid | 7200 | 7252 | | 641 |
| Gallbladder | 4857 | 13186 | | 770 |
| Ovary | 5238 | 4990 | | 550 |
| Bladder | 4074 | 7168 | | 364 |
| Diaphragm | 2697 | 4311 | | 293 |
| Uterus | 3758 | 3365 | | 674 |
| High Cervical Spinal Cord | 16854 | 10967 | | |
| Thoracic Spinal Cord | 22211 | | 6082 | 195 |

on these structures (Figure 7 and Figure 8). Measurements are done using EDX-spot-analysis, measuring a surface in the range of 0.1-0.15 square microns. A summary of the EDX–measured Si counts is given in table 2.

## Discussion

Gel bleed is a phenomenon that is inherent to all types or models of silicone breast implants, regardless whether they are soft and round or cohesive anatomically shaped [10-14]. The bleed retardation layer in the late models, retards the bleeding, but does not abolish it. The bleeding silicone polymers behave like softeners and eventually weaken the silicone elastomeric shell of silicone breast implants, regardless of the brand [15]. This could be the reason why spontaneous ruptures occur. It goes without saying that implant rupture is an intensified form of gel bleed. Table 1 gives a good impression of the dissemination of the silicone polymers found throughout the body. This also gives an impression of the Si-presence, although the amount can be variable, depending on which part of the organ analysis had been performed. As a starting point, EDX-measurement was done on pure silicone gel. The average Si-net counts of 4 measurements was approximately 345,500 counts (data not shown). In contrast, EDX measurements in control tissues of patients without silicone breast implants, always levelled below 500 net counts. With that in mind we maintained a safe threshold of 1000 silicon net counts in the tissues examined. Counts below 1000 were considered negligible and can act as a negative control, whereas net counts beyond 1000 represent Silicon stacking and thus are of pathological interest. Epidemiological studies have not been able to show a statistical significant

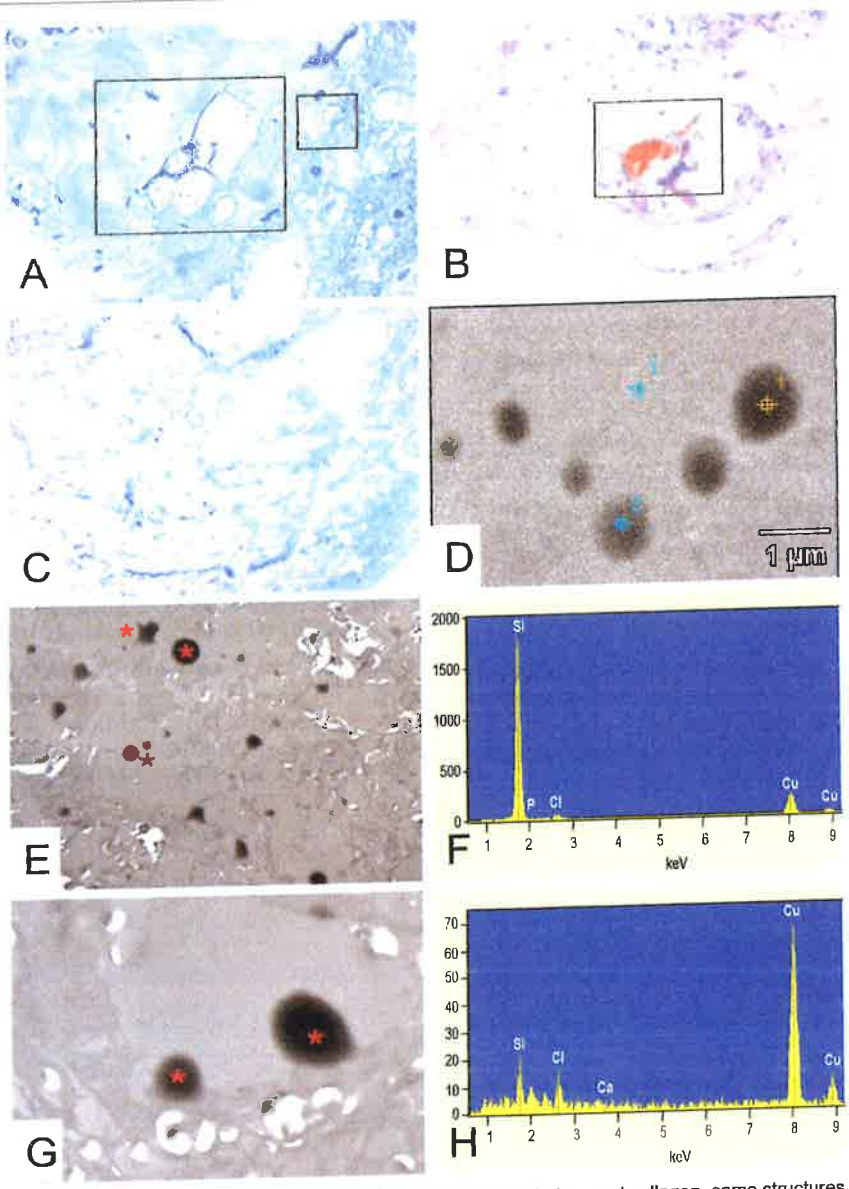


**Figure 8:** (**A**) Toluïdine blue of the spinal cord high cervical, clearly visible is a structure located around collagen, same structures often are positive with MORO staining, reddish plaque is visible (**B**); (**C**, **D** and **E**) The droplets * found in the thoracic spinal cord of patient 1; (**C**) The toluïdin blue stained epon section, no visible droplets are detectable; (**E**) A TEM micrograph where it is nicely demonstrated that there are actually droplets present located inside vacuoles which appear to be partially washed out; (**G**) A higher magnification of a TEM micrograph were it is clearly seen that the droplets actually are located inside a vacuole and are part of the tissue. EDX analysis is performed on these droplets, figure D shows a TEM micrograph of the EDX measuring points performed on the thoracic spinal cord of patient 1; (**F**) Demonstrates EDX analysis Point 1 on a droplet found inside vacuolated spaces (spectra 1) = 22211 Si-counts. Point 3 is on the surrounding tissue (spectra 3) = 195 Si-counts (H). Original microscopic magnifications figure A and B 400x, resp. 200x, C-E and G; resp. 50 x, 2.5K and 10K.

connection between silicone breast implants and "silicone Implant Incompatibility Syndrome" [3]. The common conception seems to be that if the connection cannot be demonstrated epidemiologically, it has to be absent. Studies to elucidate the silicone issue, should at least document the health complaints that surface in some women with silicone breast implants and follow them for many years. However, women with health complaints are present and when the transplants were explanted they often report an improvement of their condition. What is also remarkable, is that hours after explantation surgery, the pre-operative complaints can first increase tremendously for days to weeks, before they subside. These two experiences with this group of patients clearly suggest that such a link exists.

In this study agglomerates of silicone in the form of plaques together with titanium or in the form of droplets are detected in several organs and nervous tissue. Titanium was frequently used in the sealing patches of the silicone breast implants and that could possibly be the source of the titanium in the plaques. In the lymph nodes there are signs of chronic inflammation, but this does not seem to be the case in the organs and nervous tissue, where the silicone material is either located within vessels or encapsulated in collagen. However, the presence of silicone embolism or more fibrosis within internal organs could interfere with proper functioning of its cell systems. In nervous tissue it could interfere with conduction of nerve impulses. Many of the patients with silicone related complaints demonstrate a more neurological form of the disease with ultimately loss of control of the lower extremities and walking difficulties. This phenomenon has sporadically been coined as pre-MS by neurologists. The patient in this study had those walking difficulties and became wheelchair bound. But other neurological phenomena also exist, like loss of clear thinking, tremors and psychological disturbances. This has to be investigated further.

Although strict Si-counts are not absolute in number, the samples that we have seen by electron microscopy, do reveal that the disseminated silicone material is everywhere in the body. The larger silicone polymer molecules can be detected in agglomerates. The smaller molecules of siloxane monomers and oligomers, may infiltrate on a cellular level and at random work their way through the multitude of biochemical intracellular pathways, stressing the cells and creating a variable syndrome of various health complaints.

In this way this syndrome may appear to be elusive and parade

over a long period of time as no more than the accelerated aging process, too subliminal for any epidemiological study to be detected, but which will in due course surface in susceptible women. This hypothesis can only be tested through further research.

## Conclusion

Our study using light microscopy and EDX-analysis, clearly demonstrates that silicone material is present in patients who have been exposed to gel bleed from silicone breast implants for longer time, in all organs and nervous tissue in great amounts.

## Acknowledgments

Our patient had silicone breast implants and health complaints. She decided to donate her body for collecting tissues samples and nervous tissue, to further investigate the science of the pathogenesis of "Silicone Implant Incompatibility Syndrome" (SIIS).

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SPECIAL ISSUE ON

# SILICONE TOXICITY

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# EDITORIAL

## SILICONE TOXICITY AS A RESULT OF SILICONE IMPLANTS

In this issue of the *International Journal of Occupational Medicine and Toxicology*, we are presenting the most current international scientific data on various silicone implants, toxicity, and immunologically mediated multisystem disease.

The studies published in this journal and other peer-reviewed literature clearly show: 1) silicone is not inert and is associated with immunogenic reaction; 2) various silicone implants (breast, joint, testicular, and penile) are associated with the migration of silicone into the lymphatic system and subsequent travel into distant locations (myocardium, lymph glands, liver, spleen, and brain); 3) the immune reaction elicited by silicone is an adjuvant reaction, which in turn causes the production of silicone-specific antibodies; 4) the immunological reaction causes a spectrum of clinical symptoms and diseases, and connective tissue diseases such as lupus or scleroderma account for only 11–15% of the patients (The rest of these patients have neurological, pulmonary, and gastrointestinal diseases.); 5) in order to diagnose this condition, the clinician, preferably a Board Certified physician with training in internal medicine and knowledge and experience in clinical patient care in toxicology, should evaluate the patient and, when necessary, perform an immunological, neurological, pulmonary, and gastrointestinal workup; 6) silicone has a direct effect on natural killer cell activity and has been shown to act as a carcinogen in experimental animals; 7) lymphocytes develop memory to silicone dioxide in some patients, and may further aid in the diagnostic workup; 8) the neurological disease induced by silicone toxicity is specific and is associated with neurocognitive and neuroimmunological findings; 9) as a multisystem disease, silicone immune disease reaction causes antibodies to multiple endocrine organs and is compatible with an immune-mediated endocrinopathy; 10) We have addressed medical causation and provided evidence showing that causation clearly and scientifically has been established; 11) We have stressed that in addition to silicone breast implants, other silicone implants, such as Norplant, orbital implants, chin implants, testicular, and penile implants, are all associated with immunological reaction and a spectrum of disease processes; and 12) We have addressed the "famous" Mayo study and Harvard study, and showed very clearly why these studies are flawed and irrelevant, and do not address issues of causation.

Finally, we feel a responsibility to discuss the issue of treatment, a subject which is in the hearts and minds of physicians and patients alike. Treatment should be performed based on sound scientific theory, with biological plausibility, medical sense, and data that have been published in peer-reviewed medical literature. It is very tempting to prescribe one treatment

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modality or another just because one believes that this has worked before, but as physicians we are given the responsibility of adhering to scientific principles. While being open-minded and willing to include some new, alternative modalities, we must evaluate the data with a scientific medical probe before applying such to our patients.

This issue combines work that is the fruit of academic and clinical minds with vast experience in the fields of toxicology, internal medicine, rheumatology, neurology, pathology, immunology, biomaterials, and NMR analysis. These papers underwent rigorous scientific peer review and meet the criteria of scientific evidence.

To those researchers and practitioners who are confronted with these problems on a daily basis, this issue of the Journal provides information from several disciplines of research and practice, which we hope will be helpful in the daily care of patients.

NACHMAN BRAUTBAR, M.D.
Editor-in-Chief

ANDREW CAMPBELL, M.D.
Associate Editor

# SILICONE IMPLANTS AND IMMUNE DYSFUNCTION: SCIENTIFIC EVIDENCE FOR CAUSATION

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*A bitter and much publicized debate on the immunological effects of silicone implants in patients has been waged between the opponents and proponents in the medical and legal communities. The issue of silicone implants and human immune disease is not only scientific but also has significant societal effects. Recently, we have reported potential major complications as a result of Norplant implants (Campbell and Brautbar, 1995), related to the silicone form of the drug. Because this drug has been used in socioeconomically low parts of the world, one must consider the potential societal and socioeconomic magnitude of the problem. The Norplant implants are only one example. Problems with silicone implants have been described with penile implants (Barrett et al., 1991), testicular implants (Elsahy, 1972), joint implants (Worsing et al., 1982), orbital implants (Brautbar and Campbell, submitted), and breast implants. Nevertheless, the manufacturers and defense attorneys, and their team of experts, claim "silicone is safe," and "there is no causation." We have summarized the scientific evidence showing that causation exists, and review the criteria to be utilized by physicians to establish causation.*

The purpose of this article is to:

1. Describe the available data from the peer-reviewed literature;

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2. Key Words: breast implants, causation, immune disease, silastic, silicone, silicone immune dysfunction.

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2. Examine the meaning of "causation" and what is required by the physician to conclude causation;
3. Review critically the few studies which claim that silicone is safe; and
4. Prove that scientific medical causation exists.

Silicone has been used for approximately 30 years for cosmetic procedures, as well as for reconstruction of breasts after mastectomies. Whereas silicone fluid injections have been known to be harmful, and descriptions of disfigurement, severe local tissue reaction, and systemic disease have been published in the peer-reviewed medical literature since the early 1970s (Myoshi et al., 1973), breast and other implants containing silicone have been considered relatively harmless.

Recently, several single-patient reports, experimental animal studies, and studies of groups of patients with silicone breast implants have shown immunological abnormalities associated with systemic diseases. These studies, coupled with major public pressure, led the Food and Drug Administration (FDA) to ban silicone breast implants for cosmetic purposes, effective 1992.

## EVIDENCE THAT SILICONE CAUSES DISEASE

*Evidence from Animal Experiments*

The potentially harmful effects of silicone droplets have been documented by Ben-Hur et al. (1967), and Rees et al. (1967), who demonstrated a widespread distribution of intraperitoneal injected silicone and a lymphocytic infiltration in response to deposits of silicone. Accumulated phagocytes containing ingested silicone fluid formed granuloma-like lesions, and were shown histologically to have occurred without an acute inflammatory infiltration. The injected silicone was engulfed by the wandering histiocytes, transported to a region of lymph nodes, and eventually distributed throughout the reticuloendothelial system. Conglomerations of cells filled with silicone liquid accumulated at the corticomedullary junction of the adrenal gland. Silicone injected into the peritoneum migrated to the liver, spleen, ovary, and kidney, and via the lymphatic system to other organs. These investigators concluded that subcutaneous administration of silicone in mice caused accumulations of silicone-containing cells in the regional lymph nodes, and that fat atrophy appeared as early as two weeks post-injection.

Brody and Fray (1968) injected silicone into the peritoneum of rats and, due to the significant cellular reaction, concluded that "liquid silicone should not be used intraperitoneally in humans" until "further long-term studies" were completed. It seems to us that any medical student would have easily concluded that: 1) silicone causes foreign body granulomas; 2) it is transferred from the site of injection to various different organs of the body; and 3) it is a biologically incompatible agent, especially for placement in the human body.

Dow Corning Research Laboratory has demonstrated that silicone acts as an adjuvant and is immunologic. Experimental animals were injected with silicone, and results showed a significant reduction of the reticuloendothelial system functions (Lake and Radonovich, 1975). These studies were conducted with the knowledge that silicone is immunogenic, and may act as an adjuvant in vaccines (Lake and Radonovich, 1975).

*Evidence from Human Studies*

Myoshi et al. (1964) described several autoimmune abnormalities as a result of silicone injections into the breasts of augmented women.

Although these abnormalities were initially attributed to impurities within silicone, it has become apparent that unadulterated medical-grade silicone causes inflammatory reactions. Liquid silicone, which is injected subcutaneously for cosmetic reasons, causes granulomatous reactions. This same reaction has been described in patients who experience rupture of silicone gel–filled breast prostheses (Barker et al., 1978; Thomsen et al., 1990). The reaction was inflammatory, with redness, swelling, and pain. Histologic examination showed clear spaces surrounded by a chronic inflammatory reaction. Often the silicone is not "fixed," and it leaves clefts or clear spaces in the tissue, with occasional foreign body giant cells.

That this is not unique to breast implants has been shown by Elsahy (1972), who reported that a testicular implant made of silicone was associated with chronic inflammation and giant cell reaction, which is the hallmark of silicone reaction. Barrett et al. (1991) have shown that silicone penile implants shed silicone and are associated with foreign body granulomas. Furthermore, examination of the implants very clearly showed shedding of silicates and silicones. The authors concluded that "genitourinary prosthesis (silicone), shed silicone particles that can be found in the fibrous capsule and lymph nodes." It seems to us that these data from various silicone implants clearly show shedding of silicone and, in time, creation of a pathological immunological reaction.

*Evidence That Implants "Bleed" (Leak)*

It was initially suggested, and many were led to believe, that silicone implants are inert, stable, and cannot cause any biological reaction. Many studies showed that after implantation, a fibrous capsule surrounds the prosthesis. This capsule may contract, become hard and deform, and feel uncomfortable. Capsular contraction may relate to the leakage of silicone from its envelope into the surrounding tissue. Several investigators have shown that the silicone envelope is semipermeable, and substances pass through it in either direction, even without a rupture (Barker et al., 1978; Housner et al., 1978; Thomsen et al., 1990). Borgan and Ruben (1975) have shown in histological studies that silicone is distributed from breast implants through the reticuloendothelial system to the kidney, lung, liver, brain, and serum. Vargas (1979) demonstrated that silicone breast implants are not inert. Patients with intact implants demonstrated bleeding of silicone material through the intact bags.

Recent studies (Pfleiderer et al., 1993) utilizing nuclear magnetic resonance (NMR) technology *in vivo* showed very clearly that *in vivo* spectroscopy of the livers of animals with long-term silicone implants (10 to 12 months) revealed the presence of silicone. *Ex vivo*, spectroscopy of the liver, spleen, and capsule, 9 to 12 months after implantation, clearly demonstrated and confirmed that a significant amount of free silicone migrates from silicone gel–filled implants. These investigators also showed that silicones are not metabolically inert, and their biodegradation in tissue is within the implant and can be monitored after 9 to 12 months of implantation. The animal findings were supported by findings obtained by atomic absorption spectroscopy. The three-dimensional structure of the gel disintegrates, increasing the molecular mobility of the polymer Measurements of the soluble fraction extracted with chloroform from silicone gel implants at various implantation sites, 12 months after the implantation, with no rupture and with intact implant membrane, were associated with a significant reduction of silicone gel contents, which further demonstrates that leakage can occur without rupture. These studies show very clearly that: 1) there is degradation of silicone gel; 2) this degradation is noticeable after 12 months of implantation and can be detected with NMR spectroscopy as well as atomic absorption; 3) the silicone which leaves the implants migrates from the implants to adjacent tissues and distant sites; and 4) silicone is not metabolically inert. Furthermore, these investigators, utilizing Silicone Nuclear Magnetic Resonance Spectroscopy *in vivo* in animals, showed that silicone migrates from implants to the liver, and new silicone-containing compounds form after the silicones are introduced into rats. The observation indicated that degradation samples are indicative of the presence of silica and silicone complexes. They concluded that: 1) silicone is not inert; 2) is biodegradable under normal conditions *in vivo*; and 3) is associated with production of silicon products such as silica and additional polymeric silicones (Garrido et al., 1993). Since silica is a widely known and accepted immunogenic and carcinogenic agent, the observation that silica from the elastomer is found in the silicone complex which left the implant is of extreme importance. This suggests an additional mechanism by which silica, leaving the elastomer (hard silicone), participates in the immunogenic reaction, and explains why silicone gel and elastomer are immunogenic.

These studies and those by Thomsen et al. (1990), who actually measured the amount of silicone which had leaked from the intact implant, showed very clearly that the amount of silicone in the implant was significantly reduced as a result of "leaking" into the breast tissue.

Based on these data from these several independent investigators, it is concluded that: 1) silicone implants are not inert; 2) silicone and silica leak out of the implants; and 3) silicone and silica in fact cause a pathological immunological reaction.

*Human Autoimmune Disease and Silicone*

In the 1980s, chronic arthropathy, after silicone augmentation mammoplasty, and autoimmune connective tissue disease were described in women who underwent silicone breast augmentation with implants (Spira, 1988; Sahn et al., 1990; Silver et al., 1993). Kaiser et al. (1990) described a patient who presented with immunological features of systemic lupus

erythematosus, 11 years after silicone augmentation. After explantation, antinuclear antibody titers decreased and the patient improved. The dramatic improvement upon removal of the silicone indicates that silicone is reactive, probably via an immunological reaction. Since then, several case studies have shown recovery from symptoms and immunological abnormalities in 50–60% of the patients who underwent explantation (Vasey et al., 1994).

Clinical findings in 18 patients and a review of 28 published Japanese patients were evaluated by Kumagai et al. (1984), who classified them into two major groups. Group 1 consisted of 24 patients with definite connective tissue disease: 12 had scleroderma, including 8 with progressive systemic sclerosis, 6 with rheumatoid arthritis, 5 with systemic lupus erythematosus, and 1 with polymyositis. Group 2 included 22 patients with human adjuvant disease, with some symptoms, signs, and laboratory abnormalities suggestive, but not diagnostic, of connective tissue disease. It was concluded that progressive systemic sclerosis is approximately three times more frequent in women with silicone injection implants. Progressive systemic sclerosis developed primarily in individuals injected with paraffin. Persistent injected substances may induce immunological disorders by acting as adjuvants.

Other investigators have described autoimmune disease in patients after mammoplasty. Van Nunen et al. (1982) described three patients in whom autoimmune connective tissue disease developed within two-and-a-half years after cosmetic mammary augmentation with a silicone gel–filled elastomer envelope–type prosthesis. Two of the patients studied had cryoglobulin and one had markedly elevated antinuclear antibodies. They concluded that "it seems reasonable to suggest that silicone gel–filled mammary implants could precipitate connective tissue disease in a susceptible host."

Additional case reports showing effects of silicone breast implants on other organ systems have been very impressive. Celli et al. (1978) described adult respiratory distress syndrome following mammary augmentation. This was associated with sudden digressive hypoxemia and diffuse pulmonary infiltrates following intramammary injection of silicone. The presence of birefringent particles in the alveolar macrophages implies entrance of this material into the vascular compartment, its embolization to the lung, and its migration across the damaged alveolar capillary membrane. It was concluded that silicone droplets gained access into the circulation through the lymphatic system, and from there, migrated into the pulmonary system, causing respiratory distress syndrome. Indeed, the patient displayed abnormalities of the pulmonary function tests. Furthermore, the particles were seen in alveolar macrophages, which was suggestive of migration of this material to the lungs.

*Evidence That Silicone Is Immunogenic*

Naim and Lanzafame (1993) compared the immune potentiation effects of silicone gel with that of Freund's adjuvant, using bovine serum albumin as the test antigen in rats. They found that silicone gel is a potent immunological adjuvant and concluded that it may mediate an autoimmune reaction. This observation, taken together with the 1975 studies by Dow Corning

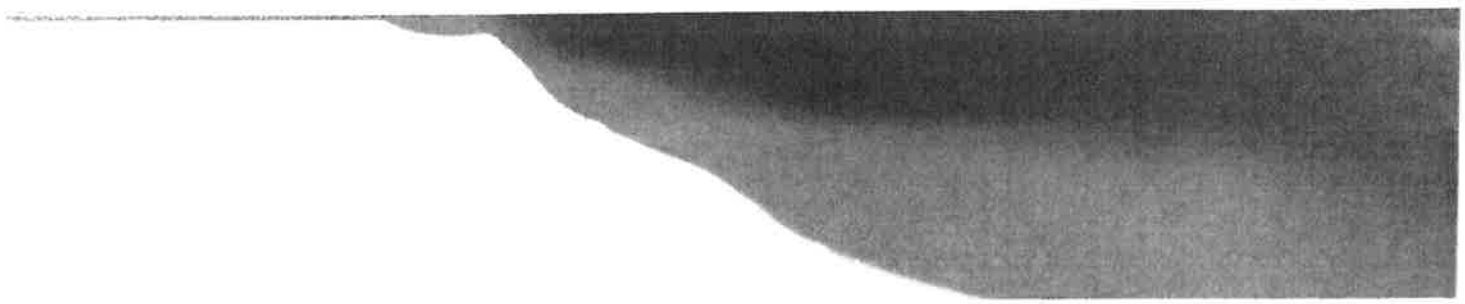
in experimental animals (Lake and Radonovich, 1975) lays the foundation for the clinical picture of silicone-mediated immune disease in humans.

*Evidence that Silicone Causes an Immune Disease in Humans*

Press et al. (1992) studied antinuclear antibodies (ANAs) in 24 women with breast implant history. Of 11 patients who had symptoms and signs of autoimmune disease, 7 had scleroderma or a subset of this disorder, and others had systemic lupus erythematosus, rheumatoid arthritis, or overlapping autoimmune disease. High ANA titers were present in 10 of these 11 patients, and the ANA specificities were similar to those found in idiopathic forms of the corresponding autoimmune disease. Traumatic rupture of implants accelerated the onset of symptoms in 13 other patients who had autoimmune disorder of a less clearly defined nature and a low titer of ANA. It was concluded that antinuclear antibodies are associated with the development of autoimmune complications in women with silicone breast implants.

Bridges et al. (1993) studied 156 women with silicone breast implants and rheumatic disease complaints. The controls for their serologic studies were asymptomatic women with silicone implants. The authors measured various immunoglobulins, complement C-reactive protein, rheumatoid factor, and autoantibodies, by indirect immunofluorescence, immune diffusion, and Western blot. Three subgroups of patients were defined based on clinical and laboratory findings. Joint and muscle pains were seen in 95 patients, joint swelling in 32 patients, and connective tissue disease in 29 patients. Most women had normal immunological studies. The patients with joint swelling had mild asymmetric rheumatoid factor–negative synovitis that did not meet American College of Rheumatology Criteria for rheumatoid arthritis. Fourteen patients had a scleroderma-like illness and had anticentromer and anti-PMSCI antibodies by Western blot. Ten patients had a positive Western blot for BB polypeptide (a small nuclear ribonucleoprotein), but did not meet criteria for systemic lupus erythematosus. In the control group, no antibodies to known disease-related polypeptides were detected on Western blot. The authors concluded that most women with silicone implants and rheumatic complaints had normal serologic tests and nonspecific symptoms, suggesting no serious connective tissue disease. However, a subset of women had clinical signs and serologic tests that were unusual, even for referral patients.

Vojdani et al. (1992) evaluated autoantibodies, including ANAs, as well as lymphocyte subset analysis and natural killer cell cytotoxic activity, which are markers for immune compatibility. Significant elevations of myelin basic protein, a marker of antibodies against the myelin sheath of the nervous system, occurred with significant T-helper/suppressor ratio abnormalities, with distributions toward the lower and upper ends, which were statistically and significantly different from control patients. Lymphocytic mitogenic response was also abnormal in silicone-exposed patients. These studies suggested that silicone triggers autoimmunity and lymphocyte subcellular responses via an adjuvancy mechanism. The lymphocytes and macrophages needed for an immune response are present in relatively high concentrations around the silicone and fibrous material of the breast implant; the protein antigen is absorbed into the silicone droplets, which are then phagocytized by the antigen-



presenting cells with an enhanced humoral immune response. This humoral immune response may end with production of an antibody to silicone, or a native macromolecule, or a combination of the two.

Goldblum et al. (1992) described two patients who had shown immunological reaction to silicone tubing used for ventricular peritoneal shunts. They concluded that elastomers of silicone elicit specific silicone antibodies. We recently (Vojdani et al., 1994) have shown that patients with silicone breast implants who have displayed the symptomatology of fatigue, diffuse joint pain, myalgias, and reduced cognitive functions have a 60% incidence of specific antibodies against silicone (IgG, IgH, IgA, or IgE). In a large study, Wolf et al. (1993) found specific antisilicone IgG antibodies in those patients who had implants. The highest antisilicone antibody levels were in patients with rupture or leakage of the implants, demonstrating very clearly a dose-response relationship. They demonstrated a correlation between silicone-specific IgG antibody levels and patients' history vis-a-vis breast implants. Statistical analysis confirmed that sufficiently high antisilicone antibody levels indicated systemic exposure to silicone.

Teuber et al. (1993) reported that 35% of women with silicone breast implants had measurable levels of anticollagen antibodies — higher levels than observed in any other autoimmune disease and similar to levels found in chronic rheumatoid arthritis. They concluded that silicone breast implants make immunopathology probable.

These studies clearly show that silicone implants are associated with immunological abnormality. Furthermore, these studies show that this abnormality is specific to silicone, with specific antibodies, and displays a dose-response relationship.

## DEFINITION OF SILICONE-MEDIATED IMMUNE DYSFUNCTION (SILICONE-MEDIATED ADJUVANT DISEASE)

Based on the available literature, and the thousands of symptomatic patients examined by various independent physicians, it is now well established that this is a multisystem disease with immunological abnormalities, and a spectrum of signs and symptoms ranging anywhere from fatigue and joint pain (Borenstein, 1994) to neuropathy (Ostermeyer Shoaib and Patten, 1992) and organic brain syndrome (Solomon, 1994), from interstitial or obstructive lung disease to full-blown scleroderma and lupus. Therefore, it would be a mistake to classify it as a rheumatic disease only. Rather, it is a multiorgan disease with a variable spectrum of clinical and laboratory presentations.

*Evidence That Silicone Implants Are Associated with a Multisystem Disease*

While the reaction to silicone originally was described as a "rheumatic phenomenon," we, and others, have said repeatedly that this is a multisystem disease, mediated via an immunological mechanism. Indeed, recent studies by Solomon (1994) and Ostermeyer Shoaib and Patten (1992), and our own recent studies (Brautbar et al., 1995), have shown clearly that this is a

multisystem disease associated with central and peripheral nervous system, pulmonary, gastrointestinal, and cardiovascular damage, while rheumatic diseases account for only 20% of the symptoms, the systemic accounting for 80%. It is therefore very clear that any study attempting to assess these patients must address all organs, and not just look into rheumatic diseases. We feel that the erroneous belief that this is only a rheumatic disease is the source of confusion. This confusion at times serves as a "smoke screen" for the manufacturers, who say "there is no connection" to disease. However, they cite studies that examine only rheumatic diseases, which account at best for only 15–20% of the symptomatic patients but miss the majority of the patients who have a multisystem disease.

## MEDICAL CAUSATION

What is required to establish cause and effect? This issue has been a source of confusion due to lack of basic knowledge in the medical community. From a system of causation describing infectious and parasitic diseases to a system of viruses, and finally to a system of toxic exposures, it is very clear that to establish causation, the physician need not wait for epidemiological studies, which require large population studies and many years of follow-up, and are designed to address prevalence or risk assessment but not causation in a specific given patient. The physician requires simple scientific logic, and sound medical, scientific criteria.

These criteria were set forth by Sir Bradford Hill in 1965 and have been relied on since then. In establishing causation between silicone and immune-mediated disease, they are:

1. Strength of association: Has the disease been reported from several independent laboratories or medical centers?
2. Consistency of association: Has the association been reported from multiple independent centers utilizing the same methodology?
3. Specificity: Is the association specific? (Indeed, all investigators report foreign body granulomas, inflammatory response, and silicone-specific antibodies.)
4. Is there a temporal relationship? and Can the disease be reversed upon removal of the cause? [Indeed, many of the studies (Kaiser et al., 1990; Vasey et al., 1994) have shown that 60–70% of the patients improved upon removal of the implants.]
5. Biological plausibility: Can the disease be reproduced in experimental animals? [Indeed, the studies by Ben-Hur et al. (1967), Brody and Fray (1968), Naim and Lanzafame (1993), and Dow Corning (Lake and Radonovich, 1975) have shown very clearly that silicone is immunogenic in animals.]

The following studies and case reports confirm the fulfillment of the Hill criteria for causation:

1. Multiple case reports and population studies show the strength of association (Myoshi et al., 1973; Van Nunen et al., 1982; Vojdani et al., 1992).

2. The association is consistent (Borgan and Ruben, 1975; Barker et al., 1978; Kaiser et al., 1990; Press et al., 1992; Naim and Lanzafame, 1993; Vasey et al., 1994).
3. The association is specific for silicone and is reversible upon removal of the silicone, and the antibodies to silicone are specific (Press et al., 1992; Vojdani et al., 1992; Bridges et al., 1993; Naim and Lanzafame, 1993; Vasey et al., 1994).
4. Recovery of patients upon removal of the implants clearly shows a temporal relationship (Kaiser et al., 1990; Press et al., 1992; Naim and Lanzafame, 1993; Vasey et al., 1994).
5. It is shown to be plausible in the *in vivo* and *in vitro* studies that silicone is immunogenic (Goldblum et al., 1992; Press et al., 1992; Vojdani et al., 1992; Bridges et al., 1993; Vojdani et al., 1994).

It is very clear that causation has been established. One naturally then asks the question, "If causation has been established, why is the scientific medical community divided?" To answer this question, one must look at the studies published by those who claim that "there is no causation," and that "silicone implants are safe."

1. Mayo Clinic study by Gabriel et al. (1994): This study is severely flawed, and one wonders how it came to be published. Not even one patient was examined. The study did not evaluate even one sick patient, and examined only connective tissue disease in nonsymptomatic patients. This is like trying to answer "What causes diarrhea?" in a group of patients who do not have diarrhea. Furthermore, this study did not address a multisystem disease (which afflicts 80% of the patients), but limited the record review to only 20% of the silicone-symptomatic patients.
2. Recent "Harvard" study: In this study, not one patient was examined; only charts were reviewed. No charts were examined for lung disease, nervous system disease, or abnormalities of T- and B-cells. Unfortunately, the medical doctors who examined the charts did not understand that this is a multisystem disease, and did not understand that to establish causation they need probability, meaning, more likely than not, a 51% probability, not a 95% probability.

For the doctor who sees patients with a certain pattern of exposure and disease presentation, all that is needed is medical probability. To claim that "we need large-scale studies" is to let the bodies fall and patients die in the name of statistics, not in the name of medicine.

If the Hill criteria, described above, are fulfilled, one can conclude that causation has been established. And indeed, the data clearly document that these criteria have been fulfilled.

In summary, the data show that:

1. Silicone leaks from breast implants;
2. The leaked silicone causes a local and systemic immunological reaction;
3. This reaction presents in a clinical spectrum of diseases;

4. Based on animal studies, patient case reports, and population case studies, causation has been established; and
5. The practicing clinician must not overlook organs that are not joints.

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# SPECIAL EDITORIAL

# IS THERE TREATMENT FOR SILICONE TOXICITY?

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Due to a recent flurry of "special" treatments for silicone toxicity, we felt that a review of this issue would be helpful to those of us who treat these patients and are faced with the daily problems of caring for a sick and symptomatic patient. We have not addressed the treatment of scleroderma, systemic lupus erythematosus, or mixed connective tissue disease since that information is readily available in a recent review in Rheumatic Diseases Clinics of North America (Cash and Brody, 1995).

Is there any specific treatment modality available? When analyzing the answer to this question, which will be the goal of this paper, one needs to address the following questions:

1) Does the patient require treatment?
2) Is the treatment specific and has it been scientifically tested?
3) Is the treatment beneficial and does it outweigh the risk of any potential side effects?
4) Is the treatment cost effective and does it change the quality of life or prognosis of the patient?

If the treatment is experimental, the doctor must be part of a study group which has had an experimental protocol approved by a human use committee, and has gone through the appropriate channels. The patient must know that this is an experimental treatment, and must sign a consent form stating that she or he understands that they are participating in a study which is experimental, and which may or may not benefit them. Finally, patients *should not be charged* for any services or studies rendered in relation to an *experimental protocol.*

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There is an inherent risk involved when the treating physician attempts to use "something new" which sounds like it may help the patient. By sympathizing with and wanting to help the patient, the doctor may use experimental treatment without going through the proper channels. In medicine, we attempt to treat the underlying offending agent causing the disease; for instance, in the case of pneumonia, we treat the bacteria which cause the pneumonia, and we may at the same time treat any shortness of breath which results from the pneumonia. However, treating the shortness of breath without trying to get rid of the bacteria will not resolve the problem, and the treatment will be a failure. The same is true for silicone-related immune diseases. Since such diseases are caused directly by silicone, the first treatment modality must be to remove the breast implants. To be more specific: in patients who are symptomatic, who have any of the entities described above, and who have been diagnosed with silicone-related immune disease, the treatment of choice would be a removal of the breast implants. It is known that 50–60% of patients improve, while 30–35% do not improve, and 10–15% may experience actual deterioration (Bridges et al., 1993). Generally speaking, a more than 50% chance of improvement justifies a surgical approach by removal of the implants. What happens to those patients who do not improve after explantation? One must always consider the possibility that an amount of capsule and silicone was left behind, or that an amount of silicone still remains in the anterior chest wall or axilla. This should be re-assessed by Magnetic Resonance Imaging (MRI) of the chest, breast, and axilla, and, if possible, the silicone should be removed by a well-experienced surgeon. Patients who do not improve, and who have had negative MRI findings, will then be divided into groups as described below:

## THE CLASSICAL TRADITIONAL TREATMENT

The classical traditional treatment of autoimmune diseases is to administer immunosuppressive drugs, since such diseases are caused by an activation of the immune system against the body's own organs as a result of exposure to an invader, in this case, silicone. Therefore, many physicians have been using steroids or immunosuppressives such as Cyclophosphamide or Imuran. Commonly, one should try *to avoid these drugs* since they are associated with severe side effects, including devastating effects on the immune system. Again, according to the attending physician's assessment in each particular case, the decision musts be made whether these drugs should be used.

## PLASMAPHERESIS

Plasmapheresis has been used successfully in the treatment of several autoimmune conditions. For instance, it is administered on a daily basis to patients with AIDS-related peripheral nervous system disease and demyelinating diseases, and hyperviscosity syndrome. Plasmapheresis is a good treatment modality, but does not always lead to permanent recovery. Based on observations made in each individual case, the attending physician must decide whether some patients with demyelinating neuropathy or evidence of disease associated with active circulating immune complexes may benefit from plasmapheresis.

## INSULIN GROWTH FACTOR I (IGF-1)

Insulin growth factor I is a hormone which has been found in reduced amounts in patients with conditions such as myalgia and fatigue. It has been suggested that the administration of this material my help in such conditions. Such treatment is still experimental, and if physicians would like to try it, they must go through the appropriate channels to obtain a permission for experimental use. Moreover, the patient must be informed and *should not be charged.*

## IMMUNOGLOBULINS

It has been demonstrated that the administration of immunoglobulins is extremely effective in autoimmune conditions such as autoimmune thrombocytopenic purpura and demyelinating neuropathy. While the administration of immunoglobulins has led to permanent relief from thrombocytopenic purpura, it appears, however, that only a temporary relief can be obtained from demyelinating neuropathies. Nevertheless, depending on the circumstances of each case, the treatment may be judged necessary by the attending physician, despite the fact that it is expensive and may provide only temporary relief.

## INTERFERON

Recently, interferon has been released by the Food and Drug Administration (FDA) for the treatment of demyelinating neuropathies, particularly multiple sclerosis. I believe that there is a reasonable probability that this drug will be helpful in treating some patients (again, the physician's decision to do so should be based on the findings and history of each specific case) with demyelination neuropathy. I want to emphasize that at this point the use of this medication should be limited to the treatment of demyelination neuropathy, and that it would be inappropriate to use it for other diseases, unless an experimental protocol has been approved.

## ALTERNATIVE MEDICINE

Recently, alternative medicine has received much attention by the Federal Government and other bodies. Thirty years ago, such a treatment modality would not have been accepted. Today, however, it has become very clear that some aspects of alternative medicine may be beneficial. An example of the increasing attention given to alternative medicine is the recent study by Greenberg et al. (1994) in the New England Journal of Medicine entitled "A Critical Trial of Antioxidant Vitamins to Prevent Colorectal Adenoma." One must bear in mind, however, that scientific studies *have yet to be published.* It still needs to be demonstrated that the administration of megadoses of vitamins, antioxidants, or metals such as zinc or manganese. I believe an informed consent must be obtained from patients who are treated with these modalities; it must be explained to them that the basis for the treatment is *empirical* and *not scientific*, and that scientific studies are awaited. One must bear in mind

also that megadoses of some vitamins can lead to *toxification of the body.* Therefore, the careful judgment of the attending physician in each specific case is a must before one can address alternative medicine methodology. (We have recently heard of a physician promoting "care and detoxification" by the administration of intravenous Vitamin C.) *I would caution against such practices unless they are based upon scientific findings, and unless an informed consent has been obtained.* I personally believe that some aspects of alternative medicine will be effective in the future. *Scientific studies, however, conducted with controlled groups, are mandatory prior to their acceptance as a mode of treatment.*

## CHELATION THERAPY

Chelation therapy is a most controversial issue. The treatment consists of the infusion into the patient's blood of a material which binds some heavy metals or ions in exchange for the infused material. Chelation has been used for many years to treat toxicity from lead and other heavy metals. *There is no reason to believe that chelation therapy will work in patients with silicone toxicity.* From a chemical point of view, this does not make sense because silicone is not ionized. Just a few months ago, I saw a patient who asked me about chelation therapy; I answered that "this does not make scientific sense," and that I would oppose it. It turned out that this patient (a high school teacher) had written to Dr. Linus Pauling (Noble Prize recipient in chemistry) and had asked him (eight years ago), whether chelation therapy could help her. I still have the original letter which the patient gave to me as a courtesy. Dr. Pauling's letter states very clearly that "chelation therapy does not make any scientific sense because silicone is not ionized and would not bind." Therefore, I would caution anyone who has considered chelation therapy to discuss carefully with their physician where this treatment for silicone toxicity was devised; they should ask for scientific studies that support some physicians' claims that chelation therapy works for silicone toxicity.

## HYPERBARIC OXYGEN

During the past two years, patients have been prescribed hyperbaric oxygen to treat certain symptoms. During my career in medicine, I have observed that hyperbaric oxygen works in patients who have developed diver's disease, gangrene, or carbon monoxide poisoning. Although it does make scientific sense to claim that hyperbaric oxygen may work on the blood vessels in the brain, I still believe that a plausible mode of treatment has not yet been established for silicone patients. We are looking forward to seeing such studies published in *peer-reviewed* journals.

## ORAL TOLERIZATION

This treatment seeks to turn off the patients' rejection of their own tissues by feeding them some amounts of the protein which is directly or indirectly involved in the attack by their own

immune system on their own organs. This approach apparently is not new. As a matter of fact, the Chinese did something similar about four thousand years ago. For example, if a patient had problems with a pancreas, she or he was fed pancreas; and if the problem was related to the liver, the patient was fed with liver [see article citing Dr. Mayer from Harvard Medical Center (Brody, 1994)]. In oral tolerization, we take advantage of the fact that the intestine is a lymphatic system in which the first contact of an ingested antigen of foreign material with the patient's immune system takes place. Indeed, in laboratory studies of animals with autoimmune disease, feeding the animals a specific protein has been shown to result in tolerance to the protein causing the disease. Furthermore, in some experiments with animals, this modality was successful in either curing or delaying the onset of autoimmune diseases such as experimental animal autoimmune multiple sclerosis. Currently, studies testing the effect of oral tolerization on patients with multiple sclerosis are in progress in twelve medical centers. Some patients are fed with myelin derived from cows, while others receive a control drug placebo. We believe that this modality makes a lot of scientific sense; once the experimental studies are completed and some preliminary scientific studies are published, we believe that this will probably be the future in immunology and in the treatment of autoimmune diseases.

## TREATMENT FOR ARTHRITIS WITH ANTIBIOTICS

The January 1995 issue of the Annals of Internal Medicine published a study on the use of minocycline in the treatment of rheumatoid arthritis (Tilley et al., 1995). This study concluded that minocycline (antibiotic) was safe and effective for patients with mild to moderate rheumatoid arthritis. Tetracyclines have some nonantibiotic effects that appear to be beneficial in patients with rheumatoid arthritis. Minocycline, which is a semisynthetic tetracycline, inhibits the collagenase activity of fibroblasts. Moreover, tetracycline analogues inhibit protein synthesis, and have an anti-inflammatory effect. The logic behind the study was that the effects on the collagen, as well as the anti-inflammatory effects, are helpful in some patients with rheumatoid arthritis. Adverse effects are modest. So far, two independent randomized placebo-controlled clinical trials with substantial sample sizes showed a modest, but *significant clinical benefit* in patients who had had rheumatoid arthritis for an average of 8–14 years. These studies also showed a highly significant improvement with minimal adverse effects in acute phase reaction and IgM rheumatoid factor titers. Furthermore, minocycline and doxycycline inhibit and decrease the motion of leukocytes and lymphocyte proliferative responses, and have anti-inflammatory effects. These studies support the use of tetracyclines in cases where the clinician feels that arthritis seems to be inflammatory and can benefit from the activity of tetracyclines such as minocycline, and where there are no contraindications. Since many of our patients with silicone adjuvant disease have inflammatory arthritis with definite evidence of inflammation of the joints, and increased collagenase activity as well as increased rheumatoid factor, it seems reasonable to believe that a trial with minocycline could be beneficial, if other nonsteroidal anti-inflammatory medications have failed to work.

## MYALGIA SYNDROME

Many patients with silicone adjuvant disease display symptomatology of myalgia. We specifically indicate myalgia which stands for "muscle pain," rather than fibromyalgia which is a condition that is not currently believed to be immunologically mediated and requires specific pressure point positivity for diagnosis. While myalgia, *an immunologically mediated disease*, is a silicone adjuvant condition, fibromyalgia is not. Myalgia can be significantly disabling and, at times, resistant to treatment. One needs to develop a reasonable medical approach to treatment of the myalgia syndrome. Myalgia usually is not part of a systemic disease such as lupus or mixed connective tissue disease, and if it is not part of an arthritic condition one must rule out fibromyalgia. Fibromyalgia is a diagnosis that is best entertained over time and is typical in patients who have positive pressure points above and below the waist in at least 11 out of 18 of the known and described pressure points. If fibromyalgia has been ruled out, the treating physician has to contend with myalgia, which requires specific attention.

Flexeril is a tricyclic agent with a chemical structure similar to that of amitriptyline, but its antidepressant effects are very minimal. It is used as a muscle relaxant for musculoskeletal disorders with a maximum duration of therapy of three weeks. Its muscle relaxant activity is a result of its ability to modulate muscle tension at a supraspinal level. Several studies have shown a great deal of effect from Flexeril, and it is also my personal experience that Flexeril can be helpful in the treatment of the myalgia syndrome. Studies in patients with fibromyalgia clearly showed significant improvement with Flexeril and, although fibromyalgia differs from myalgia, which is mediated via immunological conditions, it seems reasonable to use Flexeril in patients who show no contraindications. The most bothersome side effects are dry mouth and drowsiness. In patients who do not respond to Flexeril, one could consider treatment with amitriptyline. Low-dose amitriptyline is recommended and seems beneficial in cases where Flexeril and nonsteroidal anti-inflammatory medications have failed. It is interesting that in more than 40% of patients, both myalgia and fatigue seem to improve with the administration of amitriptyline It is my experience that in patients with no contraindications, amitriptyline is an important adjunct in the treatment of silicone mediated adjuvant disease, fatigue, and myalgia.

## TREATMENT OF FATIGUE

Silicone adjuvant disease is commonly associated with fatigue (90% of patients) and one should look at treatment modalities which will alleviate this symptom. It is not surprising that fatigue is a common clinical problem, since the majority of immunological disorders are associated with fatigue. It appears that fatigue is linked to the immune system and to the chemical transmitters from the brain in immunological diseases. It has been shown that treatment with both tricyclics and Flexeril has improved symptoms of fatigue in some patients. It is important to remember, however, that fatigue is only the symptom of an underlying immunological disease and that one must address the immune disorder before the

fatigue can be treated. It seems that patients who have received immunoglobulins for demyelinating neuropathies have shown some decrease in their fatigue. But this improvement has only been temporary. Indeed, while the use of immunoglobulins are indicated for a specific condition — in this case demyelinating neuropathy — they are also effective in the treatment of fatigue *per se*. Moreover, recent treatments with Zoloft and Prozac have shown some promise of improvement of fatigue in patients.

Fatigue continues to be one of the most disabling features of silicone-mediated adjuvant disease. No specific treatment is currently available, but should be decided upon from case to case. Commonly, the fatigue issue will require a multidisciplinary approach which, after ruling out any other conditions, may require both recreational and physical therapy. In some cases, where patients have developed psychiatric ailments as a result of a disabling fatigue, psychotherapy is advisable, in addition to any medical approach to the specific underlying immunological condition.

It is our experience that patients with disabling fatigue and myalgia have experienced some improvement with recreational, occupational, and physical therapy — for instance, aerobics and swimming — and that, in some cases, psychotherapy and engagement in group therapy can be beneficial in conjunction with specific medical protocols.

## ALTERNATIVE MEDICINE AND RHEUMATOLOGY

Additionally, the most recent study in the Journal of Rheumatology addressed the effect of alternative medicine upon rheumatology patients in a universal healthcare setting (Boisset and Fitzcharles, 1994). The study was triggered by the increased awareness in both the medical and public communities of the use of alternative treatments. The researchers reported that, according to a nationwide population survey conducted in 1992 in the United States, 34% of adults had used at least one form of unconventional therapy in the preceding year. They examined the extent, pattern, and cost of the use of alternative therapies by rheumatology patients and showed the correlation between alternative medicine use and such factors as socioeconomic status and cultural background. They studied 235 unselected consecutive patients who were attending a rheumatology clinic. *Sixty-six percent of these patients* had used alternative medicine intervention in the preceding twelve months, *fifty-four percent had used over-the-counter* products, thirty-nine percent had used spiritual aids, including prayer, relaxation and meditation, and thirteen percent had visited an alternative practitioner or used dietary interventions.

The annual cost for the patients of alternative medical therapies was $100. The investigators concluded that the use of alternative medicine by rheumatology patients was moderate, mostly involving inexpensive products and no-cost spiritual aids.

According to this study, the most commonly used alternative mode of treatment was that of nonprescribed over-the-counter herbs, vitamins, minerals, and topical remedies. The study

further indicated that the high prevalence of the use of over-the-counter products among patients was in accordance with the literature and that patients frequently purchase these products *following word-of-mouth recommendation or commercial advertising.* It also stated that "it is understandable that patients suffering from chronic diseases, in particular musculoskeletal diseases for which there is no cure, will attempt to seek any additional health or treatment modality which might give them some symptomatic relief."

We agree with these investigators that there must be an openness between the doctor and the patient regarding compliance with traditional treatment, as well as an awareness of alternative treatment. In discussing with our patients the overall question of the use of alternative medicine in our practices, *however, it is, our responsibility to address the issue of known side effects and potential toxicity of such treatments.* Both the risks and benefits should be systematically evaluated and reported. It is clear *that scientific data are not available* to assess further the long-term role of alternative medicine *in any of the populations* and that future studies and reports with *objective* evaluations of *risks and benefits* are necessary, before one can recommend such approaches to patients. We, as physicians, must remember that the medical community has been given the responsibility of utilizing scientific and medical data and reason in prescribing *any treatment modality*; it is our responsibility to follow this mandate rather than to regress to the not-so-distant era of snake oil practitioners who caused more harm than good.

In summary, as physicians, we are entrusted to keep an open mind and utilize scientific data; therefore, one needs to be critical of treatment modalities *which do not make scientific sense*, do not follow scientific medical protocol, and do not weigh the risks against the benefits, if any. *We are given the responsibility of guarding the well-being of our patients*, despite the fact that, at times, patients may want to convince the treating physician to utilize new alternative treatment modalities in order to *"do something" when "everything else is not working."* These are the times when medical science and medical sense must withstand such temptations, while, at the same time, open-mindedness and analysis of risks and benefits should direct our future.

We have tried to cover the issue of medical treatment, but there is not enough time or space to cover all the treatment modalities for specific and nonspecific diseases. One must understand that each patient is unique and must be evaluated by the attending physician before any decision about treatment is made. At times, treatment may not be available and *one must be very careful not to be tempted to utilize unproven, expensive, and perhaps risky* treatment modalities in order to "do something, treat something, help me with something."

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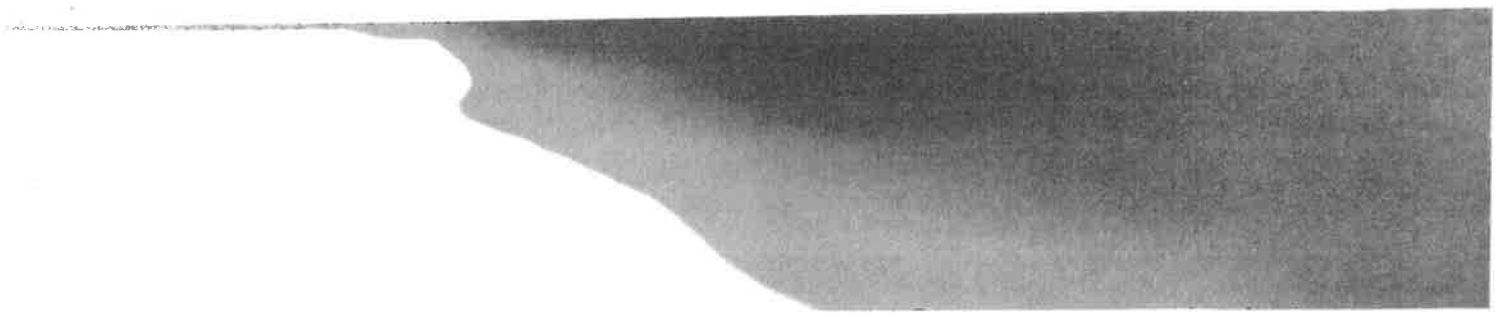

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# NEUROIMMUNOLOGIC EVALUATION OF PATIENTS WITH SILICONE IMPLANTS

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*Silicone can cause neuroimmunologic disorders with a variety of symptoms, probably due to global activation of the immune system. Immunological evaluations were conducted on the blood samples of two hundred symptomatic patients with silicone breast implants and compared with one hundred symptomatic patients with chronic fatigue and one hundred normal controls. These tests were classified under three different categories:*

*A. Neurologic antibodies, which included myelin-associated glycoprotein, ganglioside $GM_1$, and sulfatide IgG, IgM, and IgA antibodies. These antibodies were found to be elevated in up to 69.5% of the silicone*

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2. Abbreviations: ANA, antinuclear antibody; MAG, myelin-associated glycoprotein; MBP, myelin basic protein; RF, rheumatoid factor.

3. Key Words: antibody, connective tissue disease, immune function, neurological disorder, silicone.

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*patients while 37% of the group with chronic fatigue had elevated levels of these antibodies, as did 12% of the normal controls.*

B. *Immune functional abnormalities, which included T-helper/suppressor ratio, percent B-cell, lymphocyte immune function testing, and NK cytotoxic activity. T-helper/suppressor ratios were elevated in 37–38.5% of both symptomatic groups, compared to only 8% of controls. All other immunological testings were statistically significantly higher in the silicone group than in the chronic fatigue group or control group.*

C. *Tests for connective tissue disease, which consisted of rheumatoid factor, $C_1Q$ immune complexes, C3, C4 complement, ANA, thyroid antibodies, and phospholipid antibodies. Similar to the studies of neurologic antibodies and immune function, these tests were very abnormal in the silicone implant group, when compared to controls or even to the symptomatic group without silicone.*

*The results of this study indicate once more the need for proper laboratory testing for the diagnosis of atypical neurologic and connective tissue diseases exhibited in symptomatic patients with silicone breast implants.*

## INTRODUCTION

Silicones and related products, which have been used for mammary and other prostheses for approximately 30 years, are not natural substances. Similar to any foreign substance or nonself material, silicone is successfully attacked by the body's defense mechanisms immediately after its placement in the body. In fact, an acute inflammatory reaction occurs adjacent to silicone implants shortly after surgical placement (Fisher, 1990; Ganott et al., 1992; Silver et al., 1993; Smahel et al., 1993). Histopathological studies of these tissues and others far from the implants have yielded results which are indicative of both local inflammation and severe immunological and systemic reaction (Faga and Merlino, 1985; Shanklin, 1991, 1993). Similar to any other foreign-body reaction, the major cells involved in this immunological reaction are macrophage/histiocytes, lymphocytes, and plasmacytes which are found in the reticuloendothelial system. Intensity and immunological reaction correlate with the amount of silicone in the tissue (Baker et al., 1982; Shanklin 1991). Unlike many other systems, the immunological system is dispersed throughout the body. Therefore, silicone migrating from the mammary or other implants will find its way first to the regional or other lymphoid organs (thymus, tonsils, lymphoid structure in the lung, spleen, bone marrow) and thereafter to the circulation, and hence throughout the body's system. This spread of silicone to other parts of the body is clearly shown by migratory nodules found under the skin in the back and the detection of silicone in lymph nodes beyond the axilla. In fact, histopathological examination of tissues from mammary implant patients has demonstrated silicone and silica in nonmammary tissues (Baker et al., 1982; Shanklin, 1991). These tissues include, but are not limited to, the lymph nodes, spleen, thyroid, lungs, liver, ovary, bone marrow, capillaries, brain, and peripheral nerve preparation. In some cases,

silicone is not found in the tissues but severe immunological and pathological reactions are observed (for example, interstitial cystitis in the bladder and glomerular nephritis in the kidney) (Karjoo and Vojdani, 1995).

It is well documented that all silicone prostheses bleed or leak some material into the surrounding tissue. Because of the physicochemical properties of this material, tissue proteins may bind to it, be absorbed, or penetrate inside the silicone spheres to form liposome-like particles containing tissue antigens. These silicone-containing particles are then taken up by macrophages and histiocytes. Since these are wandering cells, silicone will pass to other sites in the body and thus, because of the adjuvant effect of silicone, a severe immunological reaction may occur (Kossovsky et al., 1987; Naim and Lanzafame, 1993). This cellular and humoral immune reaction to silicone, and its complex with tissue antigens, may end with numerous systemic reactions. The most common immunologic reactions are atypical connective tissue disease and atypical neuroimmunologic disorders (Vojdani et al., 1994). In this regard immunological tests, which were found to be abnormal in patients with silicone implants, are discussed under the following three categories: A) tests for diagnosis of neurological disorder; B) tests for connective tissue disease; and C) tests for immune functional abnormalities.

## PATIENTS AND METHODS

Test results of two hundred symptomatic patients with silicone breast implants, whose blood specimens were received in our laboratory for immunological evaluation, were reviewed and compared to the results of another group of one hundred patients who had no implants but had similar symptoms to patients with silicone. These results were then compared with one hundred blood samples from healthy blood donors. The ages of the patients ranged from 28 to 64, with a mean age of 46 years. The average duration from the time of initial implantation to blood-drawing was 8.5 years, with a range of 1 to 18 years. Per request of the physician, all patients underwent cellular and humoral immunity measurements including: myelin basic protein antibodies with ganglioside and sulfatide; ANA by Hep-2 cell line and Western Blot assay; DNA, thyroid, cardiolipin, striated muscle, smooth muscle, silicone-specific antibodies and quantitative measurements of complement C3 and C4, rheumatoid factor, and total immune complexes by ELISA and nephelometry. Enumeration of lymphocyte subset by flow cytometry and natural killer cytotoxic activity by $^{51}Cr$ assay also was performed on the blood of all patients and compared to the nonsilicone patient controls. Data are presented based on the frequency of positive results.

## LABORATORY TESTS FOR THE DIAGNOSIS OF NEUROLOGIC DISORDERS

*Myelin Basic Protein, Myelin-Associated Glycoprotein, Asialoganglioside $GM_1$, and Sulfatide Antibodies*

There is currently a strong interest in the relation between immunological disorders and neuropsychiatric manifestations. There is also much interest in how psychosocial factors

affect autoimmune processes. Several studies have suggested, for example, that autoimmune phenomena may lead to events precipitating Alzheimer's disease (Forster et al., 1988), parkinsonism (Populard et al., 1979), and AIDS dementia (Kumar et al., 1989). A recent study (Maag and Hoffman, 1993) clearly demonstrated the association between autoimmune processes, central nervous system functioning, and psychological processes in systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Sera drawn from 14 RA patients at biweekly intervals over three months showed the presence of antibodies against transmembrane proteins, which correlated positively with rheumatoid factor and joint swelling. There was a trend toward a correlation between depression and daily mood scores and the number of antibodies reactive with the brain. In addition, a correlation between cognitive coping styles in RA patients and autoantibodies was found. There was also evidence of a subpopulation of pathogenic antibodies. All these findings demonstrate that antibrain antibodies correlate with disease activity.

These antibodies are mainly produced in response to myelin basic protein, including myelin-associated glycoprotein (MAG), asialoganglioside $GM_1$, and sulfatide, which are present in multiple sclerosis (Populard et al., 1979; Forster et al., 1988; Kumar et al., 1989; Maag and Hoffman, 1993). Myelin is a multilamellar membrane surrounding nerve fibers in both the central and peripheral nervous systems. It is derived from the plasma membrane of the oligodendrocyte in the central nervous system and the Schwann cell in the peripheral nervous system. Myelin consists of approximately 70% lipid and 30% protein by weight. The proteins, the proteolipids, and basic proteins constitute 85% of the total protein of the membrane, of which myelin basic proteins (MBPs) are the most completely characterized. Antibodies of the human brain and peripheral nerves (IgG, IgM, IgA) against MBP and gangliosides, including $GM_1$, $GD_{1a}$, $GD_{1b}$, $GT_{1b}$, and $LM_1$, and other acidic glycolipids, including $LK_1$ and sulfatide, have been observed in a high percentage of patients with the following neurological conditions: multiple sclerosis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, motor neuron disease or peripheral neuropathies, peripheral neuropathy associated with monoclonal IgM antibody (IgM gammopathy), vascular multi-infarct dementia, Alzheimer's disease, RA, toxic chemical exposure, and silicone adjuvant disease (Koski et al., 1985; Vojdani et al., 1992, 1993, 1994; Maag and Hoffman 1993). Chronic inflammatory demyelinating polyradiculoneuropathy, motor neuron disease or peripheral neuropathies, and peripheral neuropathy are associated with monoclonal IgM antibody.

After receiving silicone gel implants, a certain percentage of women develop serious rheumatologic and neurologic symptoms (Vojdani et al., 1993, 1994; Ostermeyer Shoaib et al., 1994). When sural nerve biopsies are performed, neurogenic atrophy, myositis, vasculitis, and demyelination are detected (Ostermeyer Shoaib et al., 1994). Therefore, the demonstration of high levels of anti-MBP antibodies in more than 50% of patients with silicone breast implants, as reported two years ago by our laboratory, further corroborates the autoimmune phenomenon with possible involvement of the central and peripheral nervous systems (Vojdani et al., 1993, 1994). By extending these measurements to MAG,

asialoganglioside $GM_1$, sulfatide, and chondroitin sulfate, we have shown, first, that only patients with IgM or IgA anti-MBP demonstrated antibodies against all or some of the above antigens. Secondly, levels of these antibodies are correlated with neurologic abnormalities, including abnormal SPECT scans and other neurophysiologic tests. The mechanism by which these antibodies are produced is not yet clear. One proposed possibility is that the silicone breast implant oozes or bleeds small silicone particles, which are then absorbed by or bind to macromolecules surrounding the silicone bag. The combination of tissue antigen with silicone spheres is then presented to the macrophages. After cooperation between T-helper cells and B-cells, specific antibodies are produced which may react specifically to silicone and tissues from which antigens originate (Vojdani et al., 1994). Secondly, since silicone is a synthetic polymer containing a silicon-dioxide backbone and is an essential constituent of glycosaminoglycans such as chondroitin sulfate and sulfatides (components of connective tissues), antibodies produced against silicon dioxide may cross-react with connective tissue antigens (Teuber et al., 1993). Since histological staining for antibodies results in a high degree of false positivity with either result, antibodies against MBP, MAG, ganglioside, and sulfatides should be measured quantitatively by ELISA, as is done in our laboratory, and not by histological staining and microscopical examination. Moreover, a patient's simple "yes" or "no" result may not enable clinicians to follow improvements in the condition of these patients, due to certain treatments which presently are considered experimental.

*ELISA Method for Measurements of Myelin Basic Protein, Ganglioside, and Sulfatide Antibodies*

*Measurement of anti–myelin basic protein antibodies.* Human myelin basic protein (HMBP) was prepared and checked for purity by polyacrylamide gel electrophoresis (Heggers et al., 1983). Antisera to HMBP was induced in rabbits by repeated injection of HMBP in complete Freund's adjuvant. Antibody activity in rabbit sera and patients' samples was detected by adding different dilutions (1:10–1:1280) of sera to wells of a microtiter plate previously coated with HMBP (HMBP 250 µg/ml was dissolved in carbonate buffer, pH 9.6) Two hundred µl of either diluted rabbit or human serum were added to the wells. Incubation was repeated for one hour at 25°C and the sera was shaken out of the wells, which were then washed five times with wash solution. 200 µl of peroxidase-conjugated goat antirabbit or goat antihuman IgG, IgM, or IgA (optimal dilution) were added to the appropriate well. After incubation and repeated washing, 200 µl of ABTS substrate were added to each well. Plates were incubated for one hour at room temperature and read in a microtiter reader at 405 wavelength. Using rabbit antisera, a titration curve was plotted and patients' sera were compared to this standard curve. Results were expressed by the ELISA values.

*Measurement of myelin-associated glycoprotein antibodies.* The myelin-associated glycoprotein (MAG) is a neuronal recognition molecule involved in heterophilic interactions between myelin-forming cells and neurons. To characterize the molecular mechanisms underlying post-translational modifications which may be instrumental in signal transduction following the recognition event, measurement of MAG antibody is necessary.

Myelin-associated glycoprotein was purified from isolated myelin by lectin affinity chromatography using a sepharose-4B–concanavalin-A column. Glycoproteins were recovered by a very gentle elution procedure which involved a competing sugar such as L-methyl mannoside. After dialysis and measurement of protein concentration, wells of microtiter plates were coated with a solution of purified MAG concentration of 20 μg/ml and used in the ELISA assay, with all steps being similar to the above MBP antibody assay.

Analysis of this antigen, purified from myelin basic protein by lectin affinity chromatography, showed 80% glycoprotein or myelin-associated glycoprotein and 20% other proteins or glycolipids or contaminants.

*Asialoganglioside $GM_1$, antibody by ELISA.* Gangliosides are highly concentrated constituents of the cell membrane and overall active participants in cell metabolism and function. Asialoganglioside $GM_1$ is an acidic sphingoglycolipid and a principal target in patients with multifocal motor neuropathy. Human brain and peripheral nerve gangliosides were isolated by the procedure of Ledeen et al. (1973) and antiganglioside antibodies were characterized using one microgram of glycolipid per well. All other steps of this ELISA were similar to the MPB assay.

*Sulfatide and chondroitin sulfate antibodies by ELISA.* Sulfatide is the major acidic glycosphingolipid in myelin and is also present at the surface of oligodendroglia and Schwann cells. Sulfatide is involved in the $Na^+/K^+$-ATPase transport reaction, and in maintaining the integrity of myelin through electrostatic interaction with myelin basic protein. One microgram of sulfatide or chondroitin sulfate in 100 μl of methanol was added to the wells of microtiter plates and incubated overnight at 4°C. In both cases, 200 μl of 1% bovine serum albumin in PBS was used to block the remaining binding sites. All sera were tested in duplicate and the average absorbance values, read at 490 nm, were corrected by subtracting optical densities obtained in wells without antigen. Serum was considered positive if its absorbance value was 2 SD above the mean absorbance value for normal sera. The serum titer is defined as the highest dilution that exhibited reactivity. Reactivity was visualized using peroxidase-conjugated goat antihuman IgG or IgM (Capel, Durham, North Carolina) diluted 1:1000.

*Results and Discussion*

The results for myelin-associated glycoprotein ganglioside and sulfatide antibodies are presented in Table 1 and Figure 1. Compared to the controls, and even to patients with no implants, the percentage of patients with silicone implants who demonstrated antineuronal antibodies was significantly higher, with P-values less than 0.0001. The percentage of elevated antibodies was three- to five-fold when silicone implant patients were compared to asymptotic controls, and two-fold when compared to symptomatic but nonimplanted patients (Table 1). When these numbers were combined, the percentage with positive neuronal antibodies was 69.5% for the silicone patients group, 37% for nonsilicone patients, and 12% for the control group (Figure 1). In the majority of cases, gangliosides and sulfatide antibodies were positive only when patients had elevated IgM anti-MAG (data not shown). This was not

the case when patients demonstrated IgG anti-MAG. These results indicate that IgM antibodies against neuronal antigen are more significant than IgG antibodies for the diagnosis of motor neuron disease. Detection of these antibodies in about 70% of symptomatic patients with silicone implants is the best indication for presentation of atypical neurologic disorder in these patients.

TABLE 1. **Myelin-Associated Glycoprotein (MAG) Antibodies, Asialoganglioside $GM_1$, and Sulfatide Antibodies in Patients and Controls**

| | % Positive antineuronal antibodies in different groups | | |
|---|---|---|---|
| Antigen | Silicone implant patients | Nonimplant patients | Normal controls |
| MAG | 50 | 24 | 8 |
| Ganglioside $GM_1$ | 47.5 | 21 | 6 |
| Sulfatide | 29.5 | 14 | 9 |

## LABORATORY TESTS FOR IMMUNE FUNCTIONAL ABNORMALITIES

In the first chapter it was demonstrated that up to 70% of patients with silicone implant exhibited high levels of myelin-associated glycoprotein, ganglioside $GM_1$, and sulfatide antibodies. The clinical and diagnostic role of these antibodies in the development of motor neuron disease also was discussed (Populard et al., 1979; Koski et al., 1985; Forster et al., 1988; Kumar et al., 1989; Maag and Hoffman, 1993; Vojdani et al., 1993, 1994; Ostermeyer Shoaib et al., 1994). Since the central nervous system itself can be involved in immune reactions triggered by the brain or in response to peripheral immune stimuli (Epstein, 1993), immune functional studies were a further logical step as a follow-up to the above-documented abnormalities. With this in mind, lymphocyte subset, NK cytotoxic activity, and lymphocyte blastogenic responses which were found to be the most abnormal are presented.

*Flow Cytometry Analysis of Lymphocyte Subset*

The number and functional capacity of circulating peripheral blood leukocytes reflects the overall state of immune competence of an individual. In a variety of clinical situations, tests for granulocyte, lymphocyte, and monocyte number and function have become routine in the diagnosis of disease and in monitoring immunosuppressive and immunorestorative treatments. In recent years, flow cytometric tests for lymphocyte subsets have begun to be recognized as useful diagnostic prognostic indicators in several clinical situations, including bone marrow and organ transplantation, diagnosis of leukemias and lymphomas, and evaluation of immune deficiency disorders. Flow cytometric measurements allow the enumeration of different types of lymphocytes which are known to have distinctive functional activities (Reinherz et al., 1981, 1983).

*Helper/suppressor ratio and percentage of B-cells.* Disease-related changes in $T4^+$ (helper) and $T8^+$ (suppressor) lymphocyte levels may alter T4/T8 helper-inducer/suppressor-cytotoxic

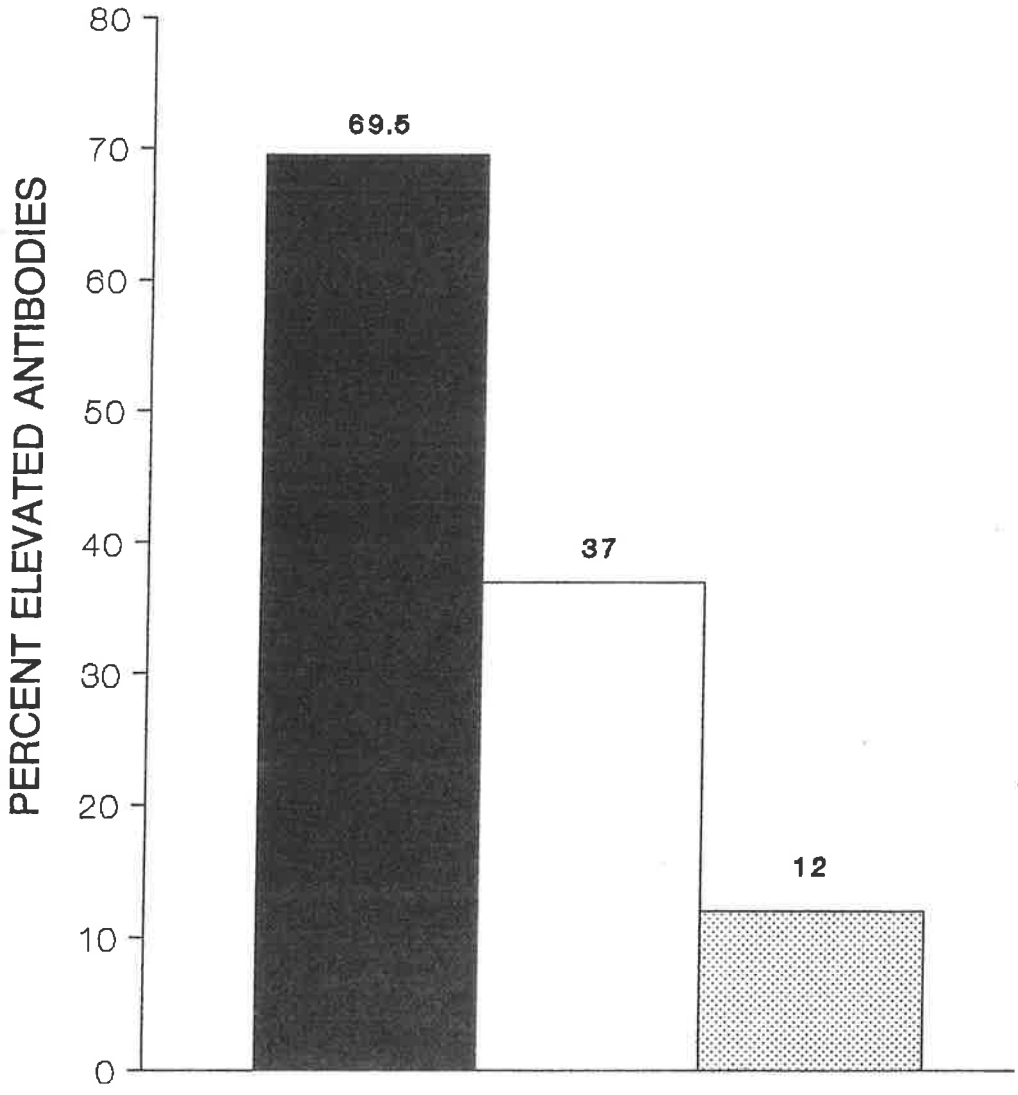


**FIGURE 1.** Myelin-associated glycoprotein and ganglioside and sulfatide antibodies in symptomatic patients with silicone breast implants ■, symptomatic patients without implants □, and normal donors ▨.

cell ratios. As a result, T4/T8 ratios may also be useful as diagnostic and/or prognostic indicators of immune competence.

T4/T8 ratios in conjunction with $T4^+$ lymphocyte cell numbers have been the most widely used laboratory parameters for the evaluation of AIDS-related complex and AIDS. T4/T8 ratios fall toward zero in advanced-AIDS patients, with no detectable levels of $T4^+$ lymphocytes. In such cases, $T8^+$ lymphocyte levels may be normal, increased, or decreased (Reinherz et al., 1983). Modulations in T4/T8 ratios and $T4^+$ and $T8^+$ lymphocyte levels may also occur in autoimmune diseases, such as multiple sclerosis (MS) and systemic lupus erythematosus (SLE). Increased T4/T8 ratios and decreased numbers of $T4^+$ and $T8^+$ lymphocytes have been observed in patients with progressive (active) MS. The lymphocyte response pattern in SLE, however, appears to reflect clinical disease activity and the level of organ involvement in the SLE disease process. To illustrate, high T4/T8 ratios and elevated $T4^+$ lymphocyte percentages have been found in active/inactive SLE patients with multisystem disease, including lymphadenopathy, although little or no renal disease has been detected. High T4/T8 ratios, but decreased percentages of $T8^+$ lymphocytes have also been documented in similarly active SLE patients (Smolen et al., 1985; Sato et al., 1987; Raziuddin et al., 1989). Additionally, high $T4^+$ and low $T8^+$ lymphocyte percentages have been measured in active SLE patients with central nervous system disease but no renal disease. In contrast, low T4/T8 ratios and decreased $T4^+$ lymphocyte percentages have been noted in active/inactive patients with SLE manifested by severe renal disease and/or thrombocytopenia. In other active/inactive SLE patients, both low $T4^+$ and high $T8^+$ lymphocyte percentages have been recorded.

B-lymphocytes are carried by a specific antigen and therefore are stained by CD19 monoclonal antibodies. This antibody is useful in defining the cellular lineage of non-T-cells. Acute lymphocytic leukemia (ALL) cells and chronic myelogenous leukemia (CML) cells are reactive with this antibody. This antibody also is useful in defining B-cells in immunoactivation and the study of immunodeficiency diseases.

*Method for lymphocyte subset enumeration.* A single-laser flow cytometer (Facs Scan Beckton Dickinson, San Jose, California) with discriminators forward and right-angle light scatter, as well as two colors, was used with a software package. Mononuclear cell populations were determined by two-color direct immunofluorescence using a whole-blood staining technique with the appropriate monoclonal antibody and flow cytometry (Hafler et al., 1985). The following pairs of fluorescein isothiocyanate (FITC), or phycoerythrin-conjugated monoclonal antibodies were selected for determination of T-cell/B-cell, T-helper/T-suppressor, $NKHT3^+/NKHT3^-$, and alternate pathways of lymphocyte activation, respectively: T11-RD/B4-FITC, T4-RD/T8FITC, T3-FITC/NKH-1-RD, and T11-FITC/Tal-PE. To monitor lymphocyte markers, bit maps were set on the lymphocyte population of positively stained cells for each marker pair, and the percentage of doubly stained cells was also determined. Estimates of absolute numbers of lymphocytes positive for the respective surface markers were determined by multiplying peripheral lymphocyte cell counts by the percentage of positive cells for each surface marker.

*Lymphocyte Immune Function Test*

It is very important to perform the lymphocyte immune function test with more than one mitogen since phytohemagglutinin (PHA) measures helper-cell-dependent T-cell function, concanavalin A (CONA) measures suppressor-cell-dependent T-cell function, pokeweed measures lipopolysaccharide, and Staphylococcus aureus measures B-cell function. These B-cell mitogens are particularly helpful in the stimulation of T-cells for B-cell help to yield immunoglobulin synthesis and secretion (Oppenheim et al., 1975; Dean et al., 1977; Farrant et al., 1980; Gratzner, 1982).

*Method for lymphocyte blastogenic assay.* Lymphocytes were isolated and tested for mitogenic activation as previously described (Wojdani and Alfred, 1984). Briefly, 5 x $10^5$ lymphocytes per 0.1 ml CM were cultured in quadruplicate in flat-bottom microtiter plate wells, without and with optimal concentration of PHA (Grand Island Biological Company, Grand Island, New York) (25 µg ml). After 48 hrs of incubation at 37°C in a water-saturated atmosphere of 95% air and 5% $CO_2$, cells were pulsed with tritiated thymidine (New England Nuclear) (2 µCI well) for 16 to 18 hrs. Incorporation of ($^3$H)-thymidine into cellular DNA was determined by harvesting the cultures in a Mash II unit. Radioactivity was measured by liquid scintillation counting.

Proliferative response to T-cell mitogen was calculated as follows:

$$\text{Stimulation index} = \frac{\text{Counts / min/ } 10^6 \text{ cells from mitogen - treated}}{\text{Counts / min / } 10^6 \text{ cells in complete medium}}$$

The mean counts/min (±S.D.) was determined from quadruplicate wells. The variability in this assay was less than 20%.

*Natural Killer (NK) Cell Activity*

Natural killer (NK) cells appear to play a role in a variety of human diseases (Herberman and Ortaldo, 1981). Compromised or absent natural immunity, as measured *in vitro* by decreased NK-cell activity and/or depressed absolute numbers of circulating NK cells, has been linked to: the development and progression of cancer; chronic and acute viral infections, including acquired immunodeficiency syndrome (AIDS); chronic fatigue syndrome; psychological dysfunction; various immunodeficiencies; and certain autoimmune diseases. Recent evidence indicates that NK cells may be involved in multiple effector, regulatory, and developmental activities of the immune system and that deficiencies or abnormalities in NK-cell function may contribute to, or be a biological marker for, disease. For the above reasons, it is important to reliably detect abnormalities in NK-cell function. Furthermore, recent evidence indicates that there is a relationship between an individual's reaction to emotional stress and NK-cell activity. Attempts are being made to define the mechanism responsible for low NK-cell activity in individuals who have difficulties in handling stress and those suffering from behavioral disorders (Whiteside and Herberman, 1989). The role of NK cells in viral disease

has been recognized for many years. The correlation between low NK-cell activity and serious viral infections in immuno-compromised hosts, e.g., in AIDS, after transplantation, and in certain congenital immunodeficiencies, has been well documented (Ljunggren et al., 1989). Abnormalities in NK-cell function have been described in a variety of autoimmune diseases and, since these diseases are frequently associated with serious viral infections and malignancy, low levels of NK-cell activity may be biologically important in individuals with autoimmune disorders. Finally, chronic fatigue immune dysfunction syndrome (CFIDS) is characterized by a number of immunologic abnormalities, the most consistent being a significant depression of NK-cell activity (Klimas et al., 1990).

*Method for determination of NK cell cytotoxity assay.* A modified $^{51}$Cr-release assay, as described by Whiteside and Herberman (1989) previously, was employed. Briefly, 1 x $10^4$ $^{51}$Cr-labeled K562 target cells (New England Nuclear Corporation, Boston, Massachusetts) in 0.1 ml CM were added per well in microtiter plates. Effector cells were pipetted into quadruplicate wells to give effector:target cell ratios of 100:1, 50:1, 25:1, and 12:1. These cells were allowed to interact at 37°C for four hours in an atmosphere of 5% $CO_2$ and 95% air. $^{51}$Cr-release was determined by centrifuging the plates at 1000 x g for five minutes and harvesting 0.1 ml of the culture supernatant for counting in a gamma counter. Total release was determined by adding 100 µl of 1.0% Triton X-100, and spontaneous release by adding labeled target cells alone in CM. The percent $^{51}$Cr-release was determined by the following formula:

$$^{51}\text{Cr - release} = \frac{\text{Experimental release} - \text{spontaneous release}}{\text{Total release} - \text{spontaneous release}} \times 100$$

*Lytic units.* Lytic units (LU) were calculated from effector titration curves, and 1 LU was defined as the number of effector cells required to achieve 20% lysis. LU/$10^6$ is the number of LU in $10^6$ effector cells. For assay reproducibility, criteria recommended by Whiteside and Herberman (1989) were employed.

*Results and Discussion*

Laboratory immunology test results of two hundred symptomatic patients with silicone breast implants were reviewed and compared to those of one hundred symptomatic patients with chronic fatigue but no silicone implants and of one hundred asymptomatic controls. The most significant test results are presented. These include enumeration of T-helper/T-suppressor ratio and B-lymphocytes, T- and B-cell function, and NK cytotoxic activity. Results shown in Figure 2 indicate that symptomatic patients present elevation in T-helper cells which results in a high T-helper/suppressor ratio.

In the control group, only 8% had a T4/T8 ratio greater than 2.2, while 38% of symptomatic patients of both the silicone and fatigue groups exhibited helper/suppressor ratios of greater than 2.2. Similar differences between symptomatic and control subjects were detected when monoclonal antibody CD19 was used for determination of percentage of B-cells: 40% of the

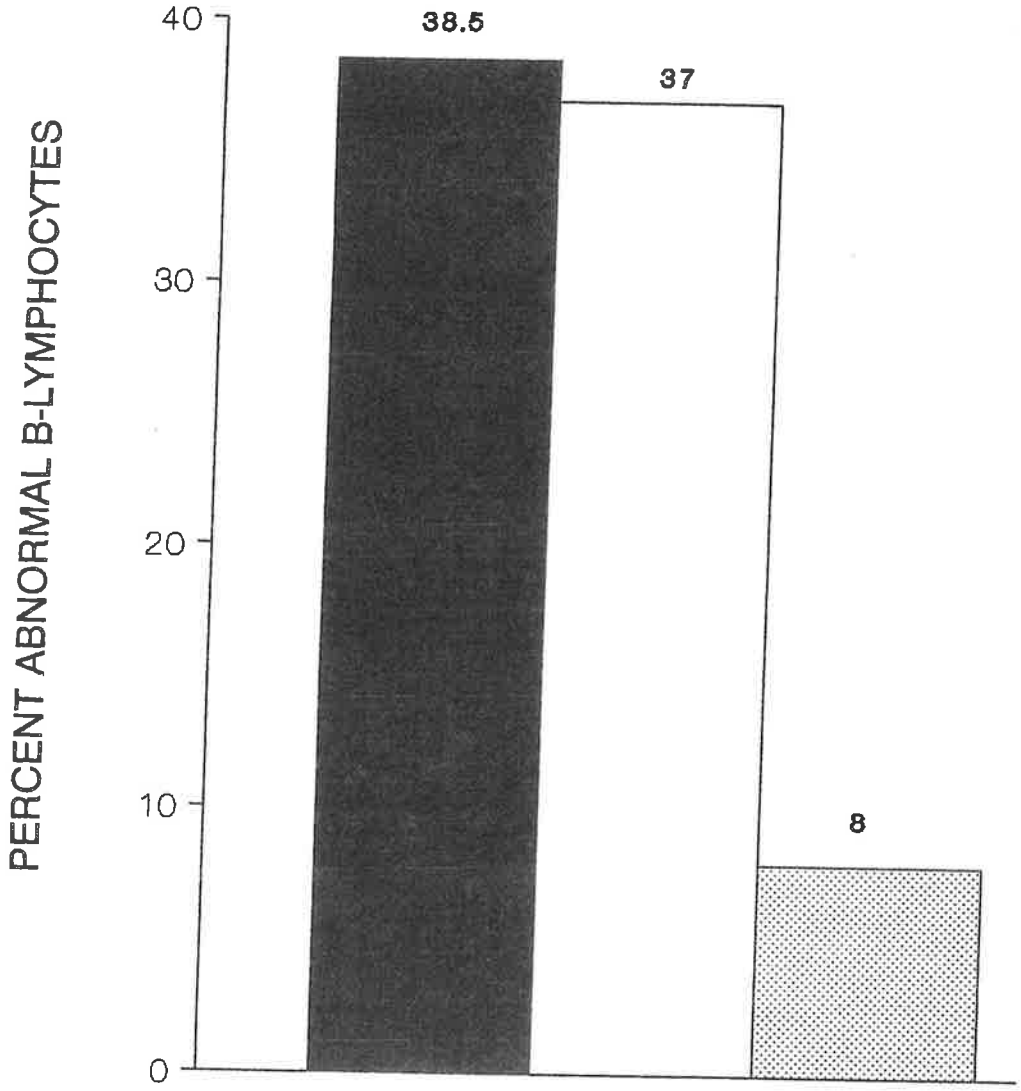


**FIGURE 2.** Abnormal T-helper/suppressor ratio in symptomatic patients with silicone breast implants ■, symptomatic patients without implants □, and normal donors ⊠.

silicone group and 16% of the fatigue group, but only 4% of normal controls, had a B-cell percentage higher than 15, which is the cutoff point in our laboratory (Figure 4). Interestingly, when lymphocyte mitogenic responses was performed on these samples using similar T- and B-cell mitogens, group differences were detected, with the highest level of abnormalities in the silicone group, followed by the group with fatigue (Figure 3). In contrast to the abnormal T4/T8 ratios, which were similar in the silicone (38.5%) and fatigue (37%) groups, both

B-cell count and activity were very abnormal in the silicone group (40% compared to 16%, and 38% compared to 29%, respectively).

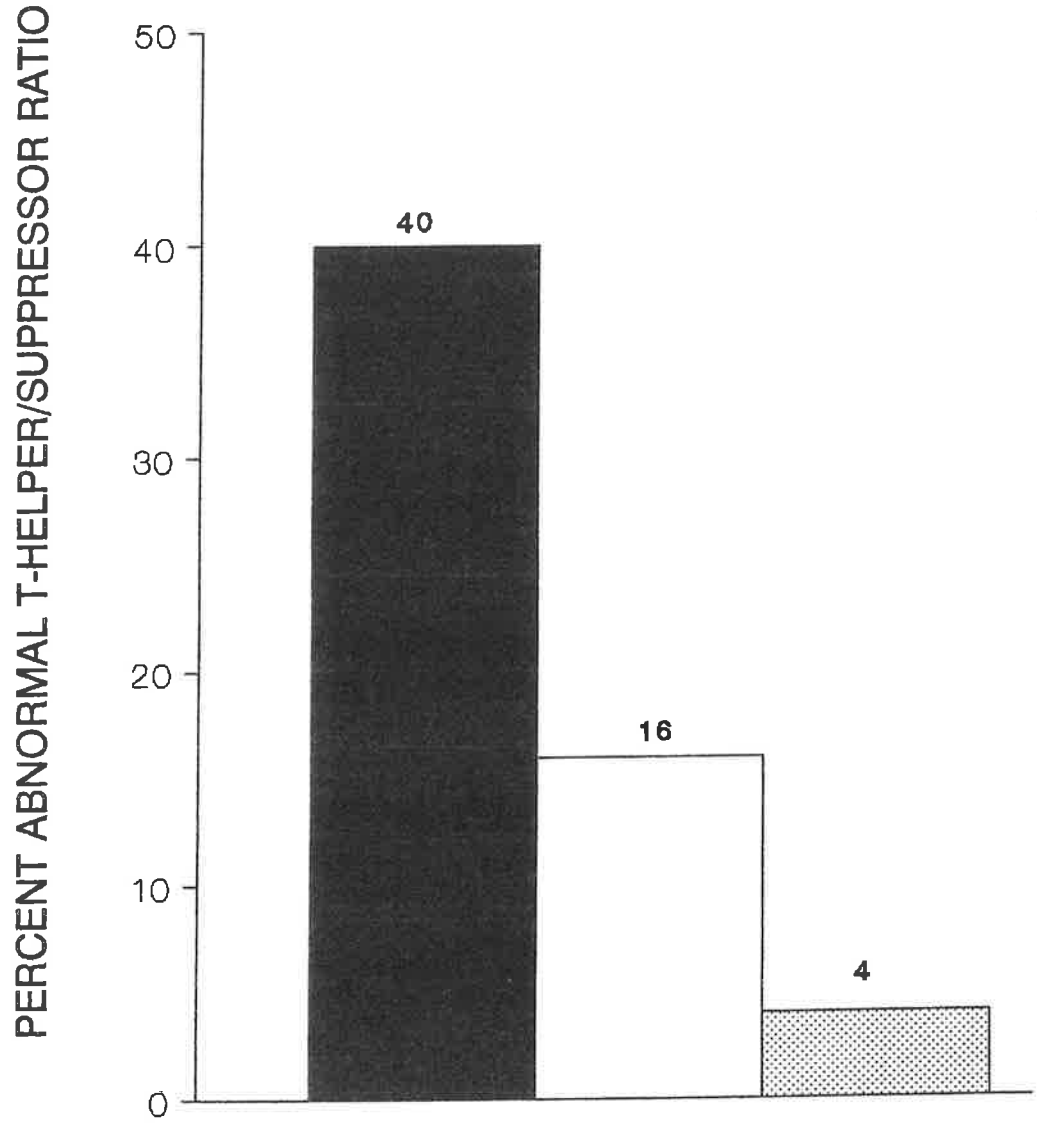


**FIGURE 3.** Abnormal percentage of B-cells in symptomatic patients with silicone breast implants ■, symptomatic patients without implants □, and normal donors ⊡.

Furthermore, when natural killer cytotoxic activity was performed on separated lymphocytes, 67% of silicone implanted patients showed low NK activity, as depicted in Figure 5.

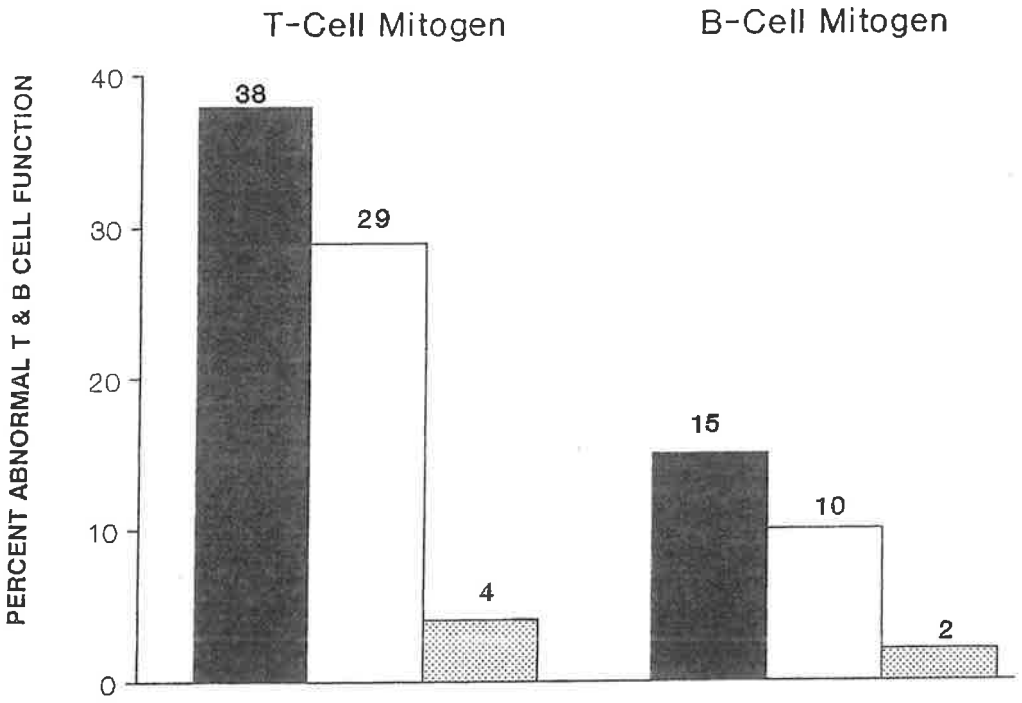


**FIGURE 4.** Abnormal T- and B-cell function in symptomatic patients with silicone breast implants ■, symptomatic patients without implants □, and normal donors ▨.

A similar phenomenon (low NK-cell cytotoxic activity) in patients who have a history of toxic chemical exposure and silicone breast implants (Vojdani et al., 1992, 1993) was reported earlier by our laboratory and others. In the latter group, 65% showed low NK-cell activity (below 20 lytic units), while this low level was found in only about 17% of controls. In individuals who chose to have their implants removed, when this assay was repeated one year following explantation, reversal to a normal NK-cell activity was observed in 60% of explanted patients (Campbell et al., 1994). This improvement in NK-cell activity after explantation is evidence for causation and effect.

These results were further confirmed in animals who were injected with silicone. In this report (Smith et al., 1994), it was indicated that NK-cell activity was suppressed in female $B6C3F_1$ mice exposed to silicone gel. Silicone gel was also found to suppress NK-cell activity in female Fischer 344 rats. Very recently, this study was further extended to NK-cell function of the spleen and peripheral blood vessels. It was found that NK-cell activity was suppressed by 38–61% as early as 14 days after implantation. There was a biphasic dose response to silicone gel at doses of between 50 and 100 ml/kg. NK suppression was reversed after silicone gel removal (Smith et al., 1994). In this study, the following was concluded: (1) spontaneous NK-cell activity was suppressed following exposure to silicone gel; (2) suppression was reversed following removal of the implants; and (3) low NK cells from

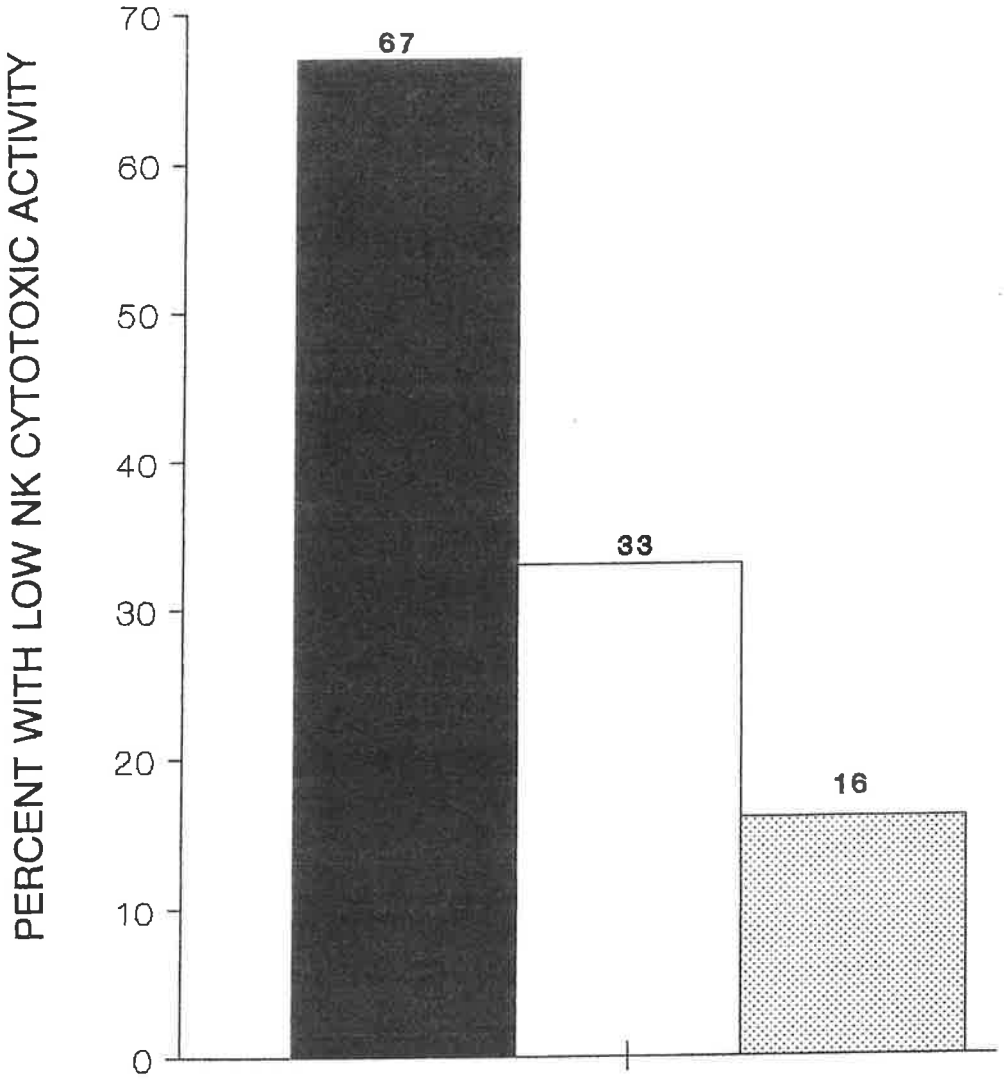


**FIGURE 5.** Low NK cytotoxic activity in symptomatic patients with silicone breast implants ■, symptomatic patients without implants □, and normal donors ⊡.

silicone-gel-implanted rats were capable of exhibiting augmented lytic activity in response to Poly I:C, which is a stimulator of interferon (Smith et al., 1994).

This pattern of immunological abnormalities, including immune dysfunctions and dysregulations shown in symptomatic silicone-implant patients and patients with chronic fatigue, has been detected previously following exposure to pentachlorophenol, chlordane, benzene, formaldehyde, polycyclic aromatic hydrocarbons, and solvents, and could extend to other chemicals. In fact, the nature of the humoral and cellular immune responses in immunological disorders associated with breast augmentation has recently been assessed, and

abnormalities at the level of T-cell, B-cell, helper cell, suppressor cell, and NK-cell activity were reported (Vojdani et al., 1993; Raso, 1994). Elevated T-helper/suppressor ratios in about 50% of silicone-implant patients and decreased T-helper/suppressor ratios in about 10% of these patients may have been the impetus for the induction of autoantibodies and autoimmune condition in some individuals (Vojdani et al., 1993).

## LABORATORY TESTS FOR CONNECTIVE TISSUE DISEASE

Many humoral factors which can be detected in the blood help in diagnosis of connective tissue disease. As an immunoserological marker for silicone, humoral immunity deals with different materials that are present in plasma or serum. These factors play an important role in natural body defense and their concentrations may increase or decrease during an inflammatory response. Examples of such humoral factors, the concentrations of which vary in patients with implants, are: C3, C4 complement, rheumatoid factor, and immune complexes.

Other humoral factors which are produced by lymphocytes and secreted into circulation are antibodies. These antibodies (IgG and IgM) may be directed specifically or nonspecifically against nuclear material and/or tissue antigens such as striated muscle, smooth muscle, the thyroid, immunoglobulins, and the brain, or directly against silicone after it is bound to these tissue antigens. During additional immunostimulation, antibodies are produced at a high concentration, which then form immune complexes and bind to complements. Immune complexes formed by binding to complements are activated, which directly or indirectly may cause membrane damage to the cells of the target organ. The end result of this autoimmune reaction is partial or complete loss of functional capacity of that target organ. Therefore, measurements of some or all these blood factors are important for the diagnosis of connective tissue disorders.

### *Rheumatoid Factors*

Autoantibodies of the IgG, IgA, or IgM isotype which are reactive with the FC portion of IgG are called rheumatoid factors (RF). Measurement of RF is done either by latex agglutination (a semiquantitative assay) or by quantitative assays (nephelometry, ELISA) the results of which are reported in IU/ML based on the W.H.O. reference standard.

IgM RF are found in approximately 2–10% of apparently healthy Caucasian adults (Hawkins et al., 1979; Del Puente et al., 1988; Koopman and Schrohenloher, 1990) and in about 50–70% of adults with classical RA as defined by accepted criteria (Ropes et al., 1958; Masi and Medsger, 1979). Over time, there is an inverse relation between functional capacity in RA and titer of IgM RF. The best available data indicate that positive titers of IgM RF in apparently healthy adults are risk factors for development of RA in proportion to the height of the IgM RF titer. These data suggest that IgM RF may be an early marker of the pathogenetic process of RA. During the first two years of disease due to RA, IgM and IgA RF (but not IgG RF)

concentrations decrease and do not correlate with disease activity, whereas after two years, IgG RF correlates with erosive joint damage (Aho et al., 1985; McKenna, 1988).

IgA RF are particularly common in IgA nephropathy (and in polyarticular onset RA) but, like IgM RF in RA, their role in pathogenesis is unclear. IgA RF and IgA-containing circulating immune complexes (CIC) are said to correlate with cartilage loss and bone erosion in RA (Walker et al., 1986; Eberhardt et al., 1990). IgG RF are reported in a variety of conditions, including vasculitis, but the clinical utility of the assay has yet to be determined (Miyata and Milgrom, 1988). IgM antihuman IgG was measured with the SIA Rheumatoid Factor Kit purchased from Sigma Diagnostics, St. Louis, Missouri. Results were expressed in international units.

*Detection of Immune Complexes*

Immune complexes are formed as the result of antibodies binding to antigens. Immune complexes have been detected in patients with many diseases, including SLE, RA, glomerulonephritis, malignancies, and certain infectious diseases. They also have been demonstrated in unexpected associations, e.g., with migraine headaches or psoriasis. The most accurate and clinically valuable results are obtained by utilizing $C_1Q$ for the measurement of immune complexes since this method measures the pathogenic complex of the immune complexes in the form of IgG, IgM, or IgA complexes. Assays employing interaction with $C_1Q$ or RF are among the most widely used to detect immune complexes in pathologic fluids. These methods have been greatly refined and now exhibit excellent sensitivity and reproducibility. The $C_1Q$ molecule is a part of the first component of complement. In response to a conformational change that occurs with antigen binding, it binds selectively to the FC region of immunoglobulin $G_1$ ($IgG_1$), $IgG_2$, $IgG_3$, and IgM. Because SLE is considered the prototype of human immune complex disease, studies of SLE with almost every type of immune complex assay have been conducted. A high incidence of positive tests and disease activity has been uniformly reported. There is considerable evidence that DNA–anti-DNA complexes are involved in the pathogenesis of SLE. Currently, immune complex determinations, coupled with the detection of serum antibodies to native DNA and the measurement of levels of hemolytic complement ($CH_{50}$) in serum, are useful diagnostic tests. Most studies have found a correlation between positive immune complex assays and antibodies to native DNA and low serum levels of hemolytic complement. With rare exceptions, immune complexes present in patients with active disease do not involve detectable DNA–anti-DNA complexes. Several serial studies have indicated that the $C_1Q$ solid-phase assay, which is performed in our laboratory, correlates better with disease activity than do other immune complex tests. However, the advantage over native DNA antibody and $CH_{50}$ assays is not clear. The $C_1Q$ binding and solid-phase assays have been shown to be useful in evaluating the effectiveness of plasmapheresis as a therapeutic approach to SLE (Gabriel and Agnello, 1977; Williams, 1980; Nydegger and Svehag, 1984), and may be useful in follow-up treatments for patients with silicone implants. Immune complexes have been detected in both synovial fluid and sera from patients with RA. Ultracentrifuge studies of

serum demonstrated IgG-RF complexes (9 to 17S) and complexes containing IgM RF and IgG (22S). During active rheumatoid synovitis, immune complexes are present in synovial fluid in association with depressed levels of complement. These high-molecular-weight immune complexes mainly contain self-associating IgG RF. These immune complexes consist of 19S and larger complexes of unknown origin and intermediate-size complexes composed of self-associating IgG RF (Agnello, 1983). In Lyme arthritis, almost all patients have abnormally elevated results in the $C_1Q$ binding test. In patients presenting with skin lesions only, the assay positivity disappears along with the rash. Persistent $C_1Q$ positivity is associated with neurologic or cardiac complications, and persistent synovitis is associated with high titers of $C_1Q$ reactant in the synovial fluid. The association of persistent positivity in the $C_1Q$ assay with neurologic and cardiac complications is a clinically useful indicator. Since patients with silicone breast implants exhibit atypical connective tissue disease and neurological disorder, measurements of $C_1Q$ immune complex assay are additional markers for silicone.

IgG, IgM, and IgA immune complexes were measured by using microtiter plates coated with anti-$C_1Q$ and antihuman IgG, IgM, or IgA antibodies.

*Complement*

Complement is a humoral factor which participates in the inflammatory process. Although the complement system consists of 11 distinct serum proteins which react with each other to produce a variety of biological effects, only the C3 and C4 components are discussed here.

*Complement C3*

C3 complement is a 180kD β-2 protein that is cleaved by C3 convertase to give the pharmacologically active fragment, C3a, and a larger fragment, C3b. C3b reacts with Factor B to produce more C3 convertase, and activates C5. As a person ages, C3 in serum and plasma is rapidly cleaved enzymically to inactive C3c (which is not susceptible to further degradation), plus other small fragments. Elevated serum levels of C3 are associated with acute inflammatory reactions; decreased serum levels are associated with Factor 1 deficiency, recurrent infections, systemic lupus erythematosus, glomerulonephritis, and a number of other conditions (Ward, 1965; Roitt et al., 1985). Both low and high levels of C3 complement have been observed in patients with silicone implants (Vojdani et al., 1993; Ostermeyer Shoaib et al., 1994).

*Complement C4*

C4 complement is a 210kD β-1 protein which is cleaved by activated C1s to produce C4a and C4b. C4b interacts with C2b to form classical pathway C3 convertase. Decreased serum levels, which are demonstrated here in silicone-implant patients, are associated with systemic lupus erythematosus, hereditary angioedema, glomerulonephritis, and repeated infections (Ward, 1965; Roitt et al., 1985).

Immunoassays for individual components, e.g., C4 and C3, are most useful in monitoring patients with immunologic diseases. Complement components assay is performed by nephelometry, which is highly sensitive and reproducible.

*Antinuclear Antibody (ANA)*

ANA is another nonspecific factor which was found to be elevated in 25–64% of patients with silicone breast implants (Press et al., 1992; Bridges et al., 1993; Teuber et al., 1993; Vojdani et al., 1993). Using this test, it is possible to examine the relationship between breast implants and autoimmunity. For example, in a highly refined study (Claman and Robertson, 1994), a cross-sectional survey was recently conducted which included 150 women, 131 of whom had implants. Group one was comprised of healthy women without implants and group two was made up of women with breast implants who felt healthy. Women with implants who had various symptoms, including fatigue, were placed in group three, and group four included women with implants who had autoimmune disease. With respect to these groups, 0%, 18%, 26%, and 64%, were found to have positive ANA antibodies. The authors concluded that women with breast implants may be at risk for development of ANA and autoimmunities (Claman and Robertson, 1994). Therefore, the detection of circulating antibodies to nuclear antigens is an important tool in the investigation of systemic rheumatic diseases in patients with implants. ANAs may be classified biochemically according to whether they bind nucleic acid *per se*, a chromatic component such as a histone, a ribonucleoprotein (RNP), or some other nuclear constituent. Antibodies within each class can be detected readily in assays based on immunofluorescence using HEP-2 cell line, enzyme immunoassay, and Western Blot assays which use biochemically purified antigens (Bridges et al., 1993; Claman and Robertson, 1994). Detection of an antibody to extractable nuclear antigens (ENA) or nonhistone nuclear antigens is helpful in the evaluation of patients with SLE mixed connective tissue disease (MCTD), scleroderma, Sjögren's syndrome (SS), dermatopolymyositis, and rheumatoid arthritis (RA).

Such antibodies include: Sm and n-RNP; SS-A/Ro and SS-B/La; Scl-70; Pm-1 and Jo-1; PCNA; RANA; and MA. Their detection is possible by taking the ANA test one step further, using biochemically purified antigens and ELISA or Western Blot assays. If the ELISA-ANA (EANA) is positive for ANA, it is important to determine the immunologic specificity of the ANA. For instance, detection of an antibody specificity to Sm antigen would be considered an important diagnostic criterion for SLE. Antibody to Scl-70 antigen detected in a patient with idiopathic Raynaud's phenomenon would strongly suggest that this patient might progress to the full clinical picture of scleroderma (Yamagata et al., 1984; Tan et al., 1986). There have been many reports that breast augmentation procedures have led to clinical syndromes resembling scleroderma, RA, SLE, and other rheumatic diseases (Baldwin and Kaplan, 1983; Endo et al., 1987; Spiera, 1988; Weisman et al., 1988; Varga et al., 1989; Gutierrez and Espinoza, 1990; Sann et al., 1990; Varga and Jimenez, 1990; Press et al., 1992; Bridges et al., 1993). Other patients have clinical syndromes that are less clearly defined, for which the term "human adjuvant disease" has been used. Idiopathic systemic autoimmune diseases are characterized by a high prevalence of autoantibodies, especially ANAs. These diseases can be

distinguished by the various specificities of ANAs, described above. In many cases, when the implants were removed, the ANA titers were reduced significantly and the symptomatology either improved or disappeared. The improvement in the laboratory markers and symptomatologies strongly suggests a relationship between silicone, its adverse effect, and causation. Another phenomenon which was described recently relates to nonspecific clinical features or atypical autoimmune illness in patients with silicone breast implants. For example, in a large group of patients with asymmetric arthritis, only 12 out of 97 had a positive RF but a high proportion of patients demonstrated scleroderma-like illness (Bridges et al., 1993).

A high proportion of patients with a scleroderma-like illness showed symptoms consistent with connective tissue disease, which has been associated with silicone implants (Baldwin and Kaplan, 1983; Spiera, 1988; Weisman et al., 1988; Gutierrez and Espinoza, 1990; Sann et al., 1990; Varga and Jimenez, 1990). These observations support a hypothesis that silicone may, like other occupational and environmental exposures, "trigger" scleroderma-like illness (Bridges et al., 1993). These atypical clinical and serologic features of the patients with a scleroderma-like illness also support an association between silicone implants and scleroderma. The clinical and serologic features of patients with both this scleroderma-like illness and silicone implants differ from classical scleroderma as reported in the scientific literature. Such features may indicate a unique difference in the autoantibodies of patients with silicone breast implants. An additional atypical marker which was found to be abnormal is BB polypeptide (Bridges et al., 1993). BB polypeptide is a member of the small nuclear ribonucleoproteins (SmRNP); autoantibodies to this polypeptide are found characteristically in SLE associated with Sm antigen, but also may be found in MCTD or scleroderma associated with RNP antigen reactivity. Of patients with silicone breast implants, 25–30% with nonspecific clinical features have a negative or low-titer ANA test, and do not have defined criteria for lupus MCTD or scleroderma. However, they do demonstrate an antibody to BB polypeptide with reaction with Sm, which is highly unusual. Whether these patients have an early SLE or they represent a new subgroup of patients with connective tissue disease is unclear. However, finding this marker is very important because these women did not have laboratory evidence of connective tissue disease until autoantibodies were assessed by Western Blot assay. The authors concluded that sensitive testing by Western Blot assay is necessary to detect atypical tissue autoantibodies suggestive of atypical connective tissue disease in patients with silicone implants (Bridges et al., 1993). For the detection of ANA and atypical antibodies, a combination of three different techniques is recommended: immunohistochemistry, ELISA, and Western Blot should be applied to the samples from silicone implant patients.

*Thyroid Antibodies*

Autoimmune thyroid gland disorders are characterized by the presence of antithyroid antibodies, primarily against thyroglobulin and microsomal thyroid antigens. Recently it has been shown that thyroid peroxidase (TPO) is the protein responsible for microsomal antigenicity. Thyroid microsomal autoantibodies occur in the sera of most autoimmune thyroid disease patients, with levels correlating with the degree of lymphoid infiltration of the thyroid gland. Thyroid antibodies (TA) are a characteristic finding in patients with

distinguished by the various specificities of ANAs, described above. In many cases, when the implants were removed, the ANA titers were reduced significantly and the symptomatology either improved or disappeared. The improvement in the laboratory markers and symptomatologies strongly suggests a relationship between silicone, its adverse effect, and causation. Another phenomenon which was described recently relates to nonspecific clinical features or atypical autoimmune illness in patients with silicone breast implants. For example, in a large group of patients with asymmetric arthritis, only 12 out of 97 had a positive RF but a high proportion of patients demonstrated scleroderma-like illness (Bridges et al., 1993).

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Hashimoto's and Graves' diseases. The presence of TA in the sera of 80% of patients with these two diseases led to the recommendation that some type of TA testing be a feature of the workup of any patient with a goiter. Although TA are predominantly associated with Hashimoto's or Graves' diseases, they may be found in the sera of patients with other diseases such as myxedema, granulomatous thyroiditis, nontoxic modular goiter, thyroid carcinoma, and silicone implants (Yoshida et al., 1978; Cowchock et al., 1984; Salvi et al., 1988; Vojdani et al., 1993). TA are also found in most cases of lymphocytic thyroiditis in children and rarely in patients with pernicious anemia. Most TA are of the IgG class. However, IgA- and IgM-type TA have been observed. As described below, there are three recognized thyroid organ-specific and antigen antibody systems: thyroglobulin antibodies directed against the thyroglobulin present in the lumen of thyroid tissue follicles; microsomal antibodies found in the cytoplasm of the columnar epithelium lining the follicles; and second colloid antigen antibodies localized in some, but not all, follicles.

The presence of thyroglobulin and/or microsomal antibodies in patients' sera at titers greater than 1:10 is significant in patients with thyroid disease. Titers greater than 1:1000 are frequently found in patients with Hashimoto's and Graves' diseases, but are rarely detected in those with other diseases. The clinical significance of antibodies for the second colloid antigen is unknown. Although the incidence of Hashimoto's disease is not precisely known, the disease is four times as common in white as in black persons, and is four times as common in women as in men (Yoshida et al., 1978; Cowchock et al., 1984; Salvi et al., 1988). Tests for thyroglobulin and microsomal antibodies are performed by a very sensitive ELISA assay using TPO and microsomal-coated plates.

*Antitissue Antibodies*

Immunoglobulin reacting to, or deposited in, muscle and other tissues can be demonstrated in numerous rheumatic disorders. The sarcolemmal basement membrane, fibers, and vessels may all be involved, individually or in combination. Overall anti–striated muscle antibody is helpful in the diagnosis of myopathic disorders. Anti–smooth muscle antibodies are found mainly in chronic active hepatitis, primary biliary cirrhosis, infectious mononucleosis, asthma, and neoplasm (Oxenhandler and Hart, 1983). Anti–parietal cell antibodies are detected in gastrointestinal disorders, including celiac disease, detected by ELISA as well as Western Blot assays.

*Antiphospholipid or Cardiolipin Antibodies*

Antiphospholipid autoantibodies (APLA), and more particularly antibodies to cardiolipin, are associated with a spectrum of clinical features which together have been termed antiphospholipid syndrome. The first antiphospholipid syndrome to be described was a biological false positive reaction for syphilis which appeared to have no clinical associations. The lupus anticoagulant appears to have specificity for a range of phospholipids, including cardiolipin. When identified by any of a number of different methods, it is associated with a subgroup of patients with an increased prevalence of thromboembolism, thrombocytopenia,

and recurrent fetal death *in utero*, irrespective of whether the patient has overt systemic lupus erythematosus (Kolke et al., 1984; Asherson and Harris, 1987; Soloninka et al., 1991).

Anticardiolipin antibodies were measured by ELISA and coating microtiter plate wells with alcohol-soluble phospholipid.

*Results and Discussion*

When humoral factors were measured in the blood of patients with silicone implants and compared either to patients with fatigue or normal controls, silicone-implant patients presented high levels of antibodies or factors. For example, 29.5% of silicone-implant patients had abnormal levels of RF, while only 6% of controls presented with mild elevation of RF (Figure 6). Similarly, immune complexes, C3, C4 complement, and antinuclear antibodies were elevated in 16%, 39%, and 27.5% of silicone-implant patients in comparison to controls of 3%, 4%, and 5%, respectively (Figures 6, 7, and 8). Thyroid antibodies were elevated in 18% of silicone-implant patients, but in only 2% of controls (Figure 9). Tissue antibodies, including striated muscle, smooth muscle, and parietal cell antibodies, were highly abnormal (62%) in silicone-implant patients, while only 7% of controls had elevated levels of tissue antibodies (Figure 10). In all the above cases, the differences between silicone-implant patients and controls statistically were highly significant, with P-values less than 0.0001. Even when this statistical analysis was made by comparing patients with silicone implants to the patients without implants but with fatigue, P-values of between 0.001 and 0.0001 were obtained. In the case of antiphospholipid antibodies (Figure 11), although a very low percentage showed elevated antibodies, statistical analysis showed similarity to other humoral factors. These results clearly indicate that patients with silicone implants produce autoreactive antibodies in a very high percentage, even when they are compared to another group of symptomatic patients who suffer from chronic fatigue syndrome but do not have silicone implants. This demonstrates again the importance of the measurement of humoral factors for the diagnosis of silicone-induced immune dysfunction syndrome.

*Silicone Antibody*

Evidence for the antigenicity and adjuvant effect of silicone has been presented in several recent studies (Goldblum et al., 1992; Kossovsky et al., 1993; Naim and Lanzafame, 1993; Wolf et al., 1993; Ostermeyer Shoaib et al., 1994; Vojdani et al., 1994). The detection of silicone-specific antibodies, which are very important serological factors, confirms immunological reaction and, if accompanied by symptomatology and pathology, may suggest an association between symptomatologies and the exposure. Since 1992, we have been testing silicone-specific IgG, IgM, IgA, and IgE antibodies. We found that up to 60% of symptomatic patients produce antisilicone antibodies, some may produce IgG antibodies, while still others may produce IgM, IgA, or IgE antibodies to silicone. The pathological meaning of these antibodies is not yet clear, but certainly it means a specific immunological response to silicone and possibly different tissue antigens (Vojdani et al., 1994). Recently, detection of a silicone antibody (IgG) was confirmed by two different investigators. Goldblum et al. (1992) described two patients who exhibited immunological reaction to silicone ventricular

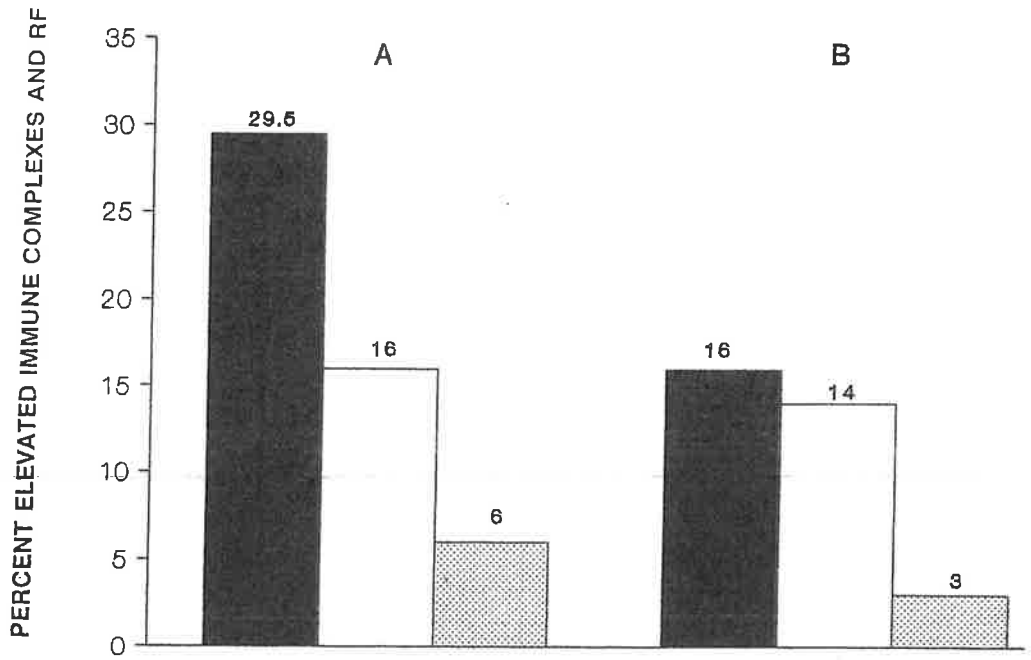



**FIGURE 6.** Levels of rheumatoid factor (A) and immune complex (B) in symptomatic patients with silicone breast implants ■, symptomatic patients without implants □, and normal donors ⊠.

peritoneal shunts. They concluded that their findings show specific immune reactivity to elastomers of silicone, which causes the development of specific silicone antibodies. Wolf et al. (1993) studied 111 patients with and without breast implants. The highest antisilicone antibody levels were measured in implanted women with either evident implant ruptures or leakage of their implants. They concluded: 1) that antisilicone antibody levels may prove useful to physicians and surgeons who wish to assess the integrity of an implant where rupture is suspected; and, 2) the high specificity of the test suggests that continuous monitoring of silicone antibody levels in implant patients on a regular schedule could be used as a screening procedure for suspected implant failure. Data obtained in our laboratory are in complete disagreement with the above findings since we detected antibodies in individuals with perfect implants and no antibodies in some patients with ruptured implants (Vojdani et al., 1994).

In a different study, Kossovsky et al. (1993) described a surface-dependent antigen, identified by high binding avidity of serum antibodies, in a subpopulation of patients with breast prostheses. Significant IgG activities were found against silicone surfaces treated with fibronectin-laminin, phospholipids, and fibrinogen, when compared with sera obtained from healthy, age-matched, nonimplanted women and a population of nonimplanted women with

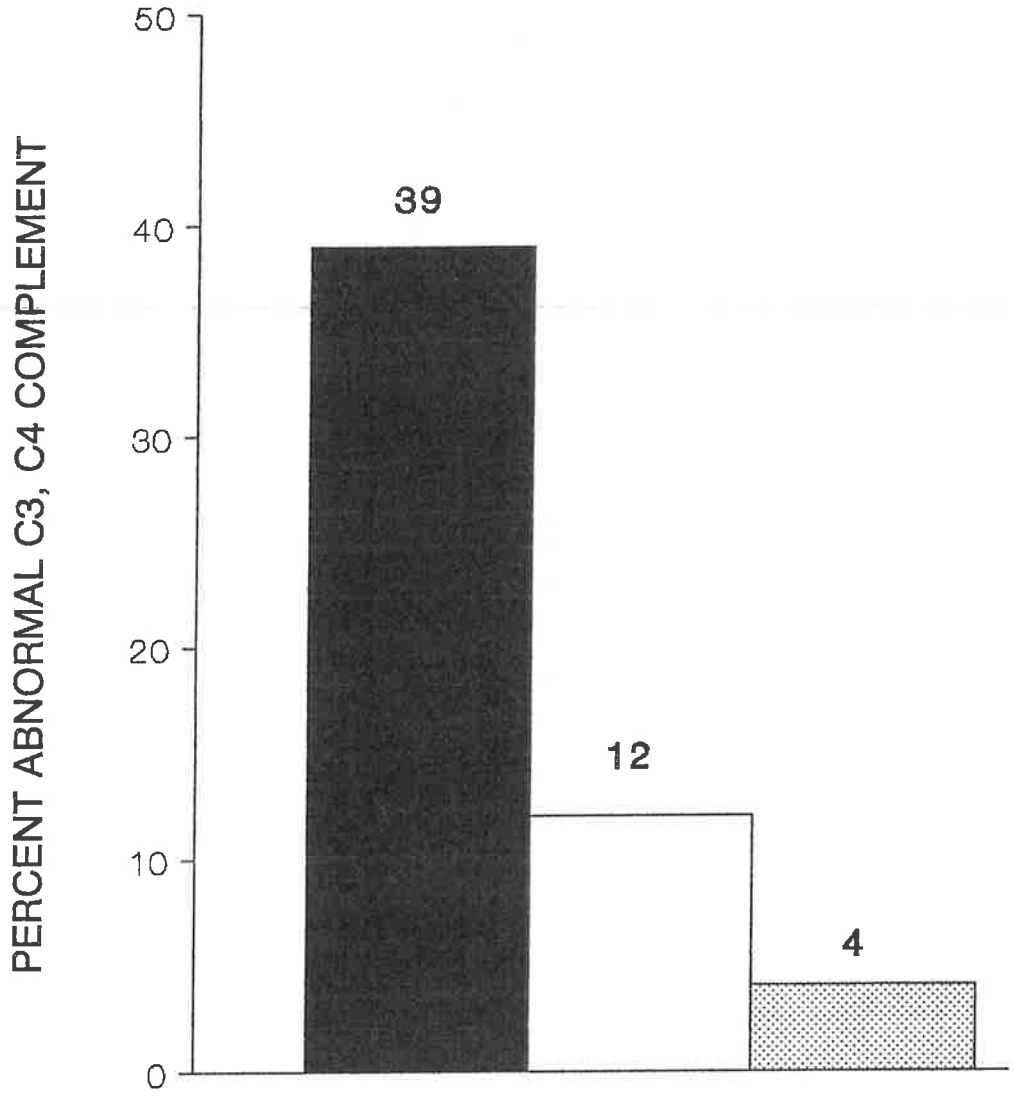



**FIGURE 7.** Abnormal C3 and C4 complement in symptomatic patients with silicone breast implants ■, symptomatic patients without implants □, and normal donors ▨.

previously diagnosed autoimmune diseases. Moreover, the sera from approximately 15% of the positive responders were found to react to matrix proteins independently of the siloxane polymer. From these data, they concluded that human antibody production to native macromolecules with antibody avidity was related to molecular conformation. Silicone may function as an adjuvant by inducing changes in the conformation of native molecules. Our data indicate that antibodies are produced against silicone and body macromolecules, and a combination of silicone plus the macromolecules (Vojdani et al., 1994). However, in contrast

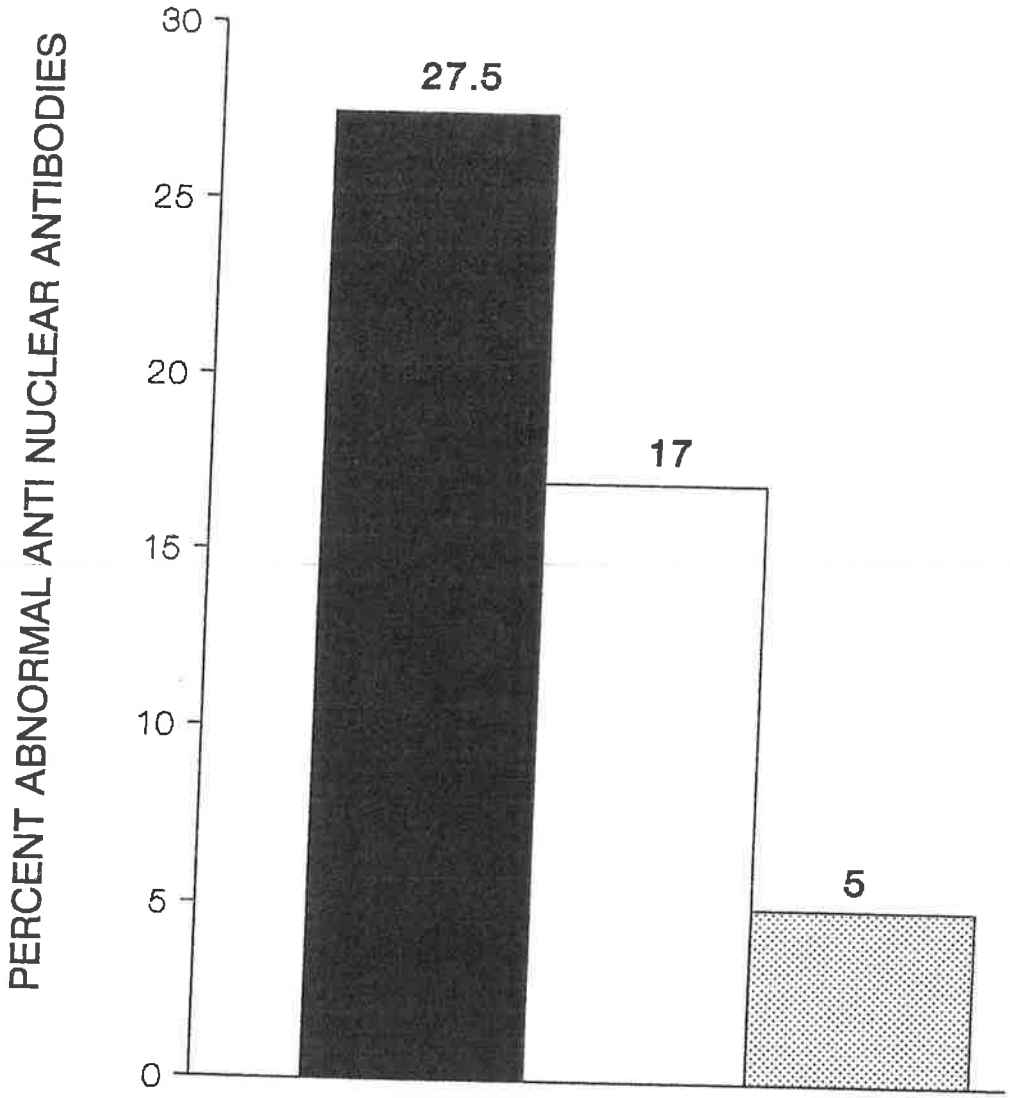
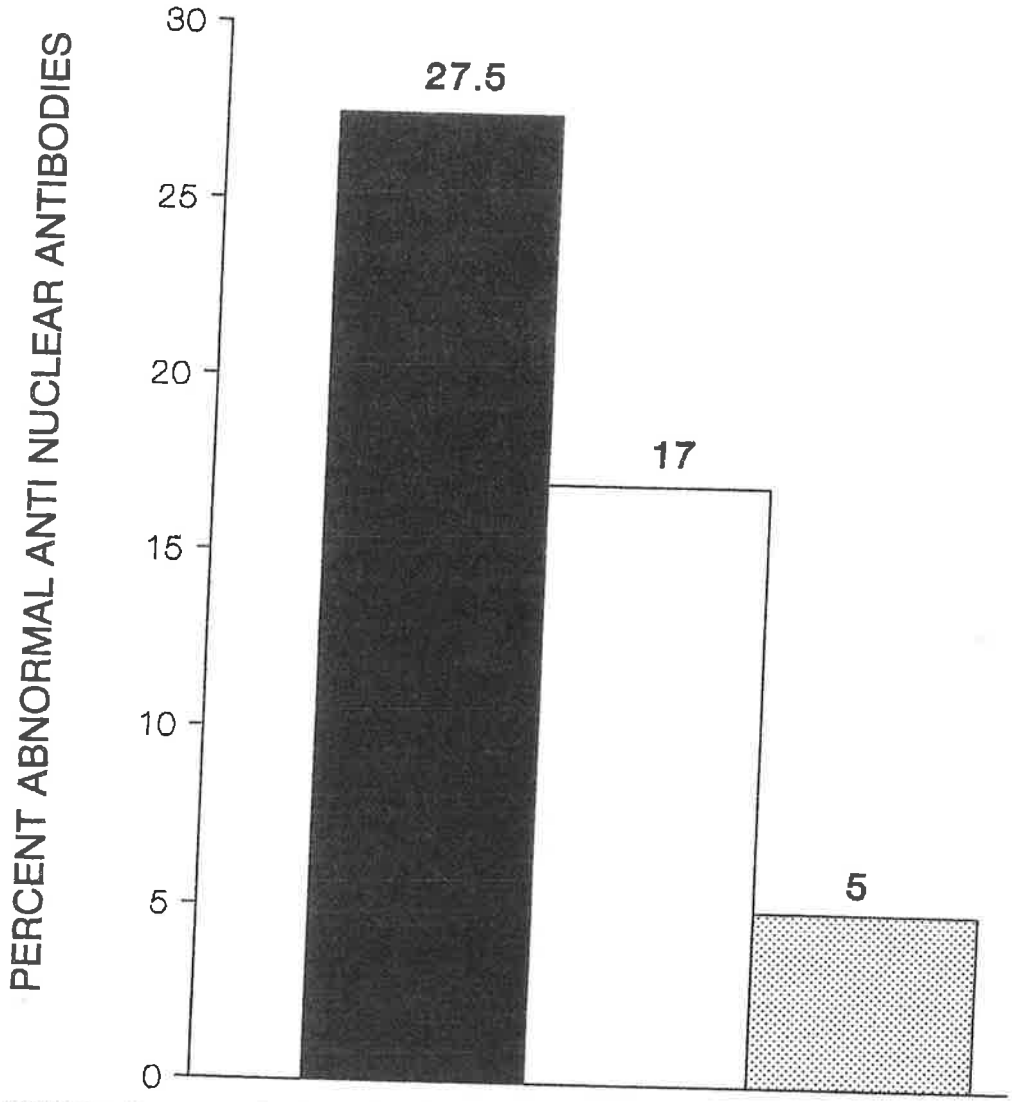



**FIGURE 8.** Abnormal antinuclear antibodies in symptomatic patients with silicone breast implants ■, symptomatic patients without implants □, and normal donors ▨.

to the Wolf et al. (1993) study, our investigation revealed no correlation between the levels of antibodies and ruptured implants. In fact, we had many cases with ruptured implants but nondetected levels of antibodies; in contrast, high levels of antibodies were detected in individuals who had perfect implants. Therefore, as mentioned in this chapter, the results of silicone antibody tests should be interpreted together with many other laboratory examinations including: neurological antibodies; tests for immune function; and assessment of humoral immunity for connective tissue disease. Results presented in Figure 12 showed

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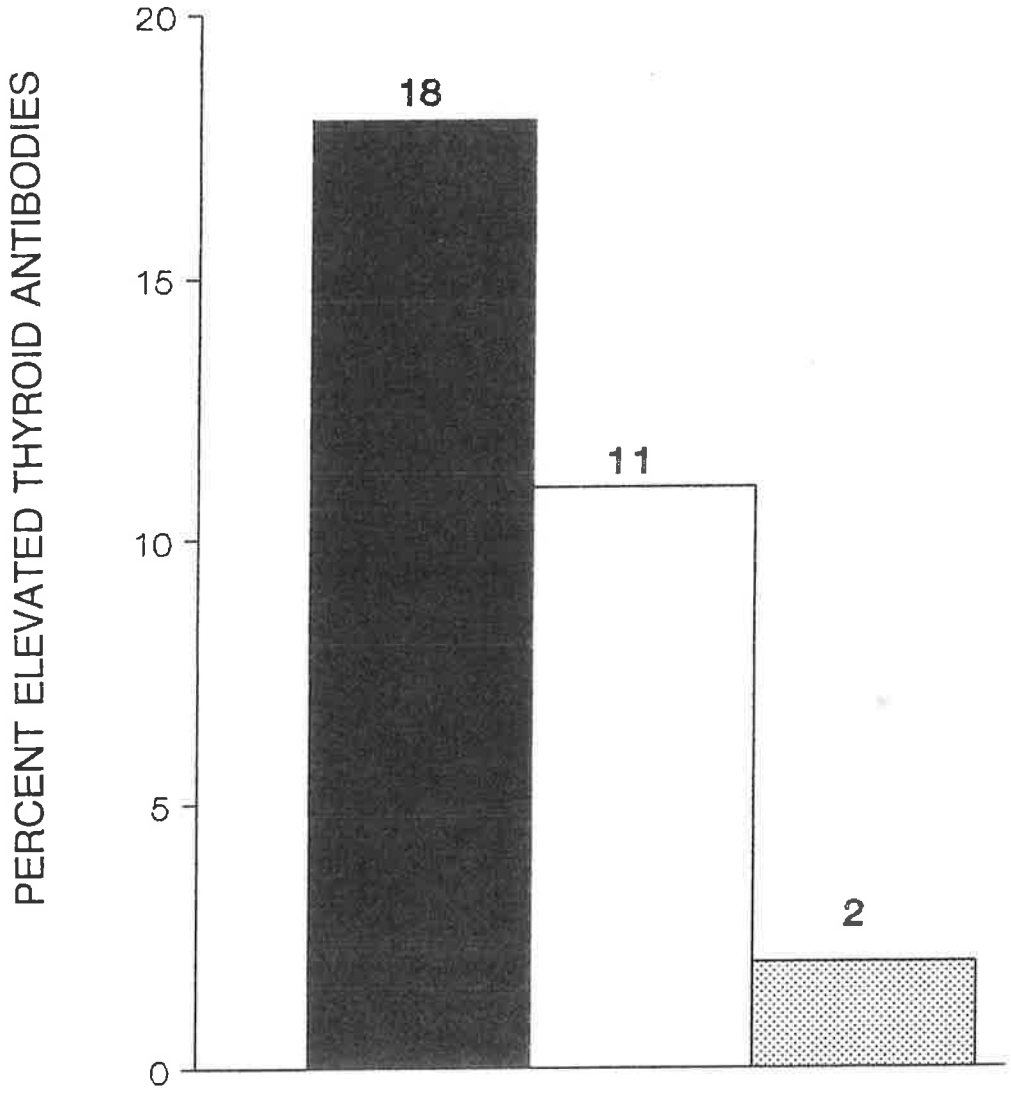


**FIGURE 9.** Thyroglobulin and microsomal antibodies in symptomatic patients with silicone breast implants ■, symptomatic patients without implants □, and normal donors ⊡.

that 33% of silicone-implant patients had elevated levels of silicone antibodies and only 4–7% of the control group had elevated levels of silicone antibodies.

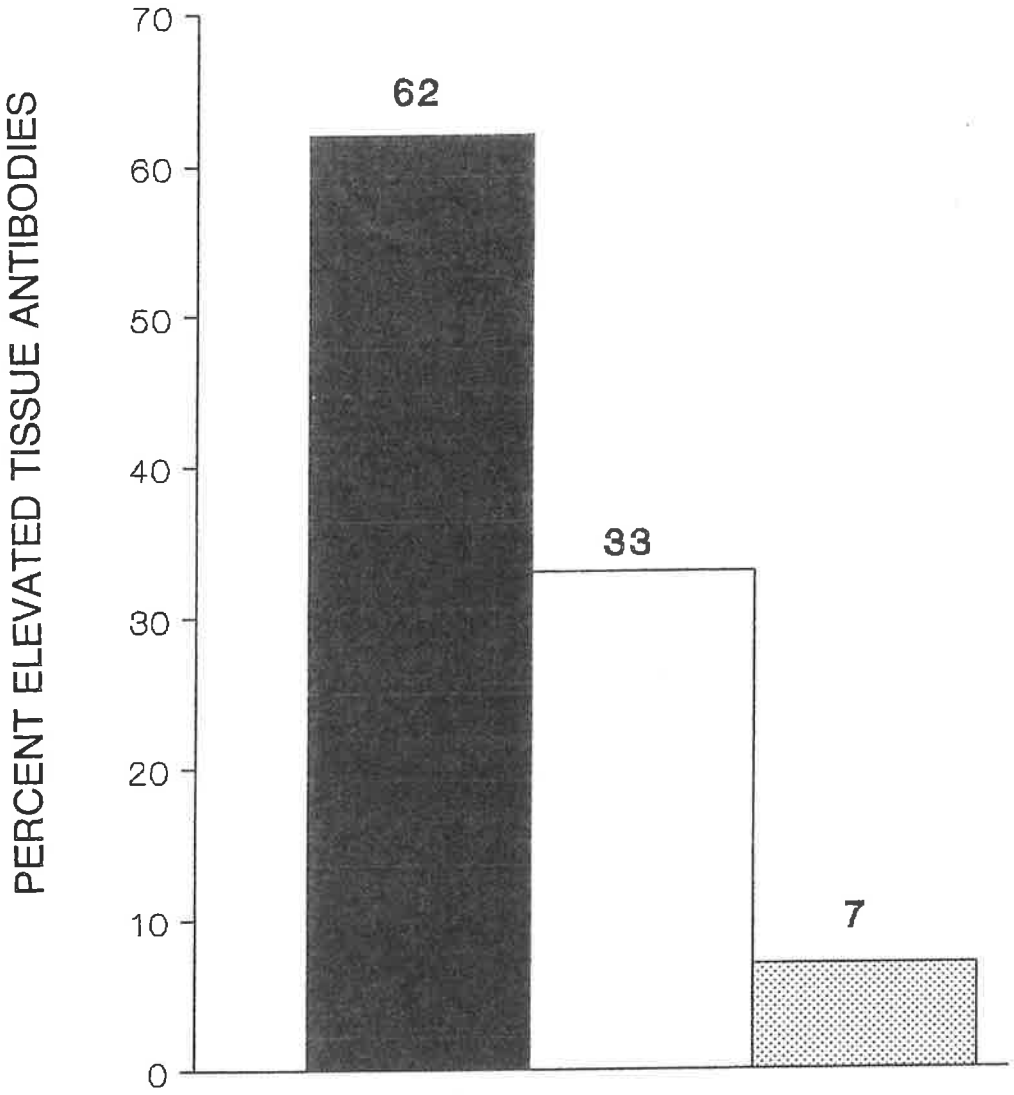


**FIGURE 10.** Antitissue antibodies in symptomatic patients with silicone breast implants ■, symptomatic patients without implants □, and normal donors ▨.

## MECHANISM OF ACTION AND DISCUSSION

*Mechanism of Silicone-Induced Atypical Connective Tissue Disease*

The exact mechanism by which silicone-induced atypical connective tissue disease occurs is not understood. However, there is little doubt that both cellular and humoral immunity are involved in the pathogenesis of this disease. On the basis of current knowledge, the following sequence of immunologic events can be hypothesized: silicone droplets are released from a

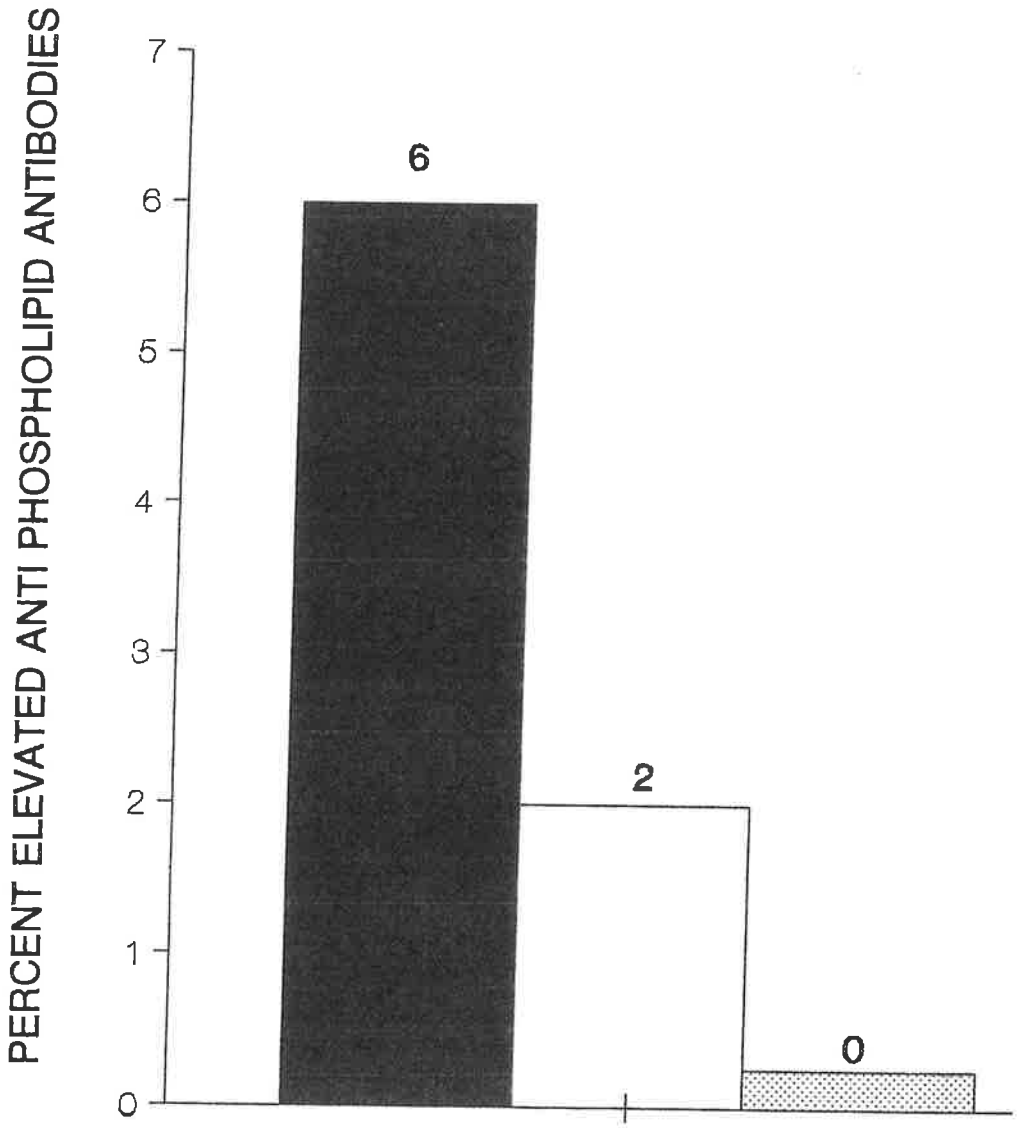


**FIGURE 11.** Antiphospholipid antibodies in symptomatic patients with silicone breast implants ■, symptomatic patients without implants □, and normal donors ⊡.

silicone bag, after which they are processed by histiocytes and macrophages; the breakdown of silicone into small spheres is followed by the release of lymphokines, which may activate cell-mediated immunity. Silicone droplets come into contact with many tissue antigens including: collagen, IgG, proteoglycans, nucleic acids, and others; some of these antigens may bind, adhere, or even penetrate inside silicone droplets and form liposome-like spheres containing antigens. These new antigens are presented by the antigen-presenting cells (APC) to specific helper T-lymphocytes, resulting in their activation. For this activation to occur, a

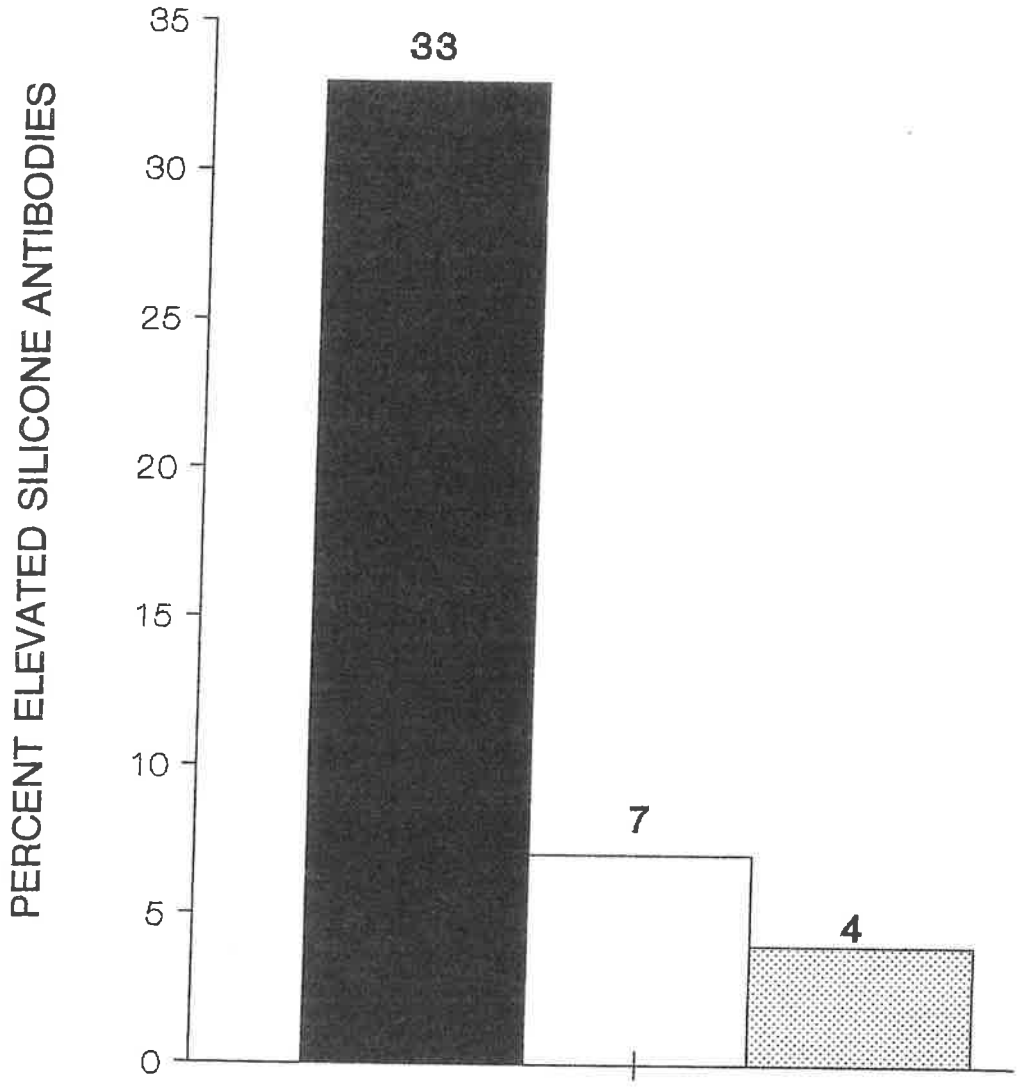


**FIGURE 12.** Antisilicone antibodies in symptomatic patients with silicone breast implants ■, symptomatic patients without implants □, and normal donors ▨.

T-cell must recognize both the antigen and DR determinants present on the APC membrane, and interleukin-1 (IL-1) must be released by monocytes/macrophages. Formation of the trimolecular (antigen/DR/T-cell receptor) complex results in the expression of IL-2 receptors on the T-cell surface. Synthesis and secretion of IL-2, which binds to these receptors, then

leads to cell mitosis. The proliferation of this clone of T-cells will continue as long as the specific antigen or silicone remains in the micro-environment. Activated T-cells will secrete numerous other lymphokines, in addition to IL-2. These include γ interferon, tumor necrosis factor β, IL-3, IL-4 (B-cell differentiating factor), and a host of mediators acting on macrophages to increase their enzymatic contents and phagocytic activity, and to degrade more silicone droplets.

Signals transmitted from helper lymphocytes to B-lymphocytes lead to the proliferation and activation of the B-lymphocytes into antibody-producing cells. Evidence indicates that IL-1 (released by macrophages), IL-2, and IL-4 (released from activated T-cells) are also needed for B-cell activation to occur. The resulting antibodies, after binding to their respective antigens, form immune complexes which can diffuse freely into the joint space, where they will fix complement and be phagocytized by polymorphonuclear leukocytes (PMN). Phagocytosis by the PMN will be accompanied by the generation and liberation of oxygen-derived free radicals, leukotrienes, prostaglandins, and neutral proteases. The end result of these immunological reactions is damage to the connective tissue (Figure 13).

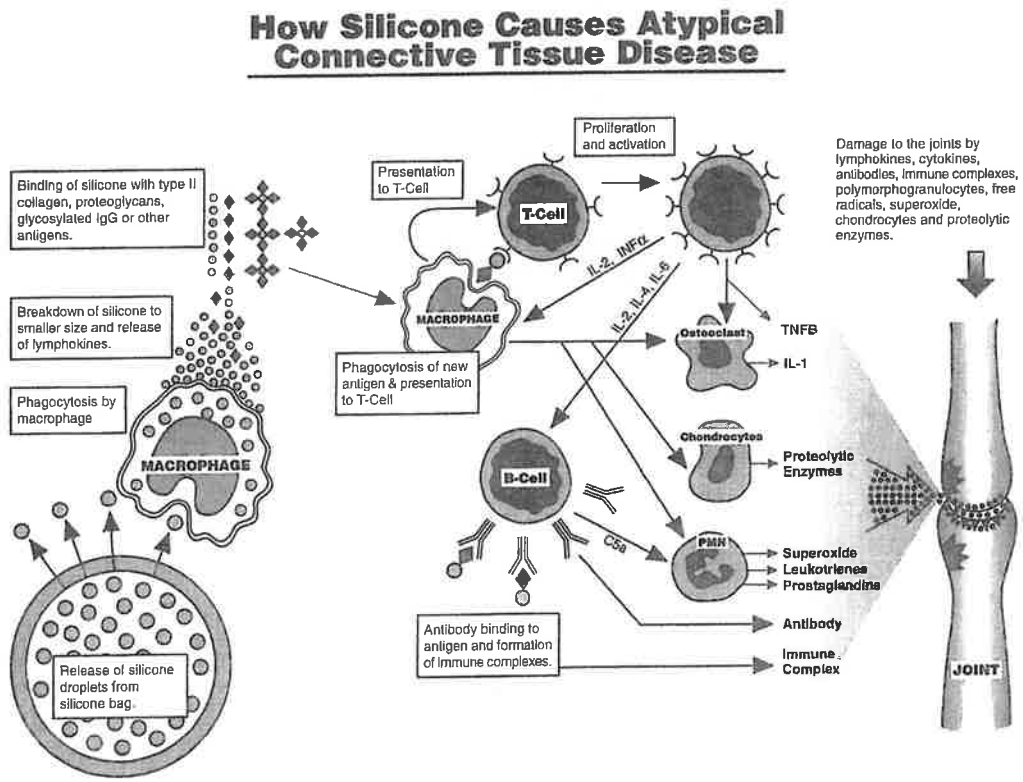


**FIGURE 13.** Damage to the joint and other connective tissues occurs in patients with silicone implants resulting from a complex chain of cellular and humoral events which ends with atypical connective tissue disorder.

*Mechanism of Silicone-Induced Autoimmune Neurologic Disorder*

The exact mechanism by which silicone-induced atypical neurologic disorder occurs is not yet clear. One may learn, however, from neuroendocrine-immune interaction and diseases such as multiple sclerosis, HIV, lyme disease, and amyloid deposits found in patients with Alzheimer's disease. In fact, the long-held view that homeostasis mechanisms are integrated by the nervous and endocrine systems has recently been expanded by information that these systems interact with the immune system. Immune responses alter neuronal and endocrine function, and in turn, neuronal and endocrine activity modifies immunologic function (Ader et al., 1991). Many regulatory peptides and their receptors, previously thought to be limited to either the brain or the immune system, are now known to be expressed by both. These findings, linking immune and neuroendocrine functions, provide explanations for the response of the pituitary and adrenal glands to infection and inflammation and the alterations in pituitary thyroid and pituitary gonadal function that occur in patients with nonendocrine disease. They also may explain how emotional state or response to stress can modify a person's capacity to cope with infection or cancer and influence the course of autoimmune disease.

The central nervous system itself can be involved in immune reactions arising from within the brain or in response to peripheral immune stimuli. Activated immunocompetent cells such as monocytes, lymphocytes, and macrophages can penetrate the blood-brain barrier and take up residence in the brain, where they secrete their full repertoire of cytokines and other inflammatory mediators, such as leukotrienes and prostaglandins. Microglia, which are embryologically and functionally related to macrophages and astrocytes, are, like macrophages and monocytes, activated by toxins, antigens, and products of cell injury arising within the brain or reaching the brain from the periphery. These cells, when activated, can secrete cytokines and inflammatory mediators (Benveniste, 1992). Endothelial and smooth-muscle cells of blood vessels in the brain can also secrete cytokines such as interleukin-1 and interleukin-6 in response to circulating antigens and toxins (Pober and Cotran, 1990).

The activation of cytokine-secreting cells in the central nervous system by the injection of bacterial toxin can be mimicked by systemic or intraventricular injection of interleukin-1 and to some extent by injections of interleukin-2, interleukin-6, and TNF-$\alpha$. Cytokines induce changes in brain function in parallel with changes in liver function; the latter include increased synthesis of $\gamma$ globulin and C-reactive protein and decreased synthesis of albumin and transferrin (Dinarello and Wolff, 1993). These changes in liver function have been termed the acute-phase response. Similarly, toxin-induced changes in cerebral function can be considered the acute-phase response of the brain.

Similar to toxins and antigens, both cellular and humoral immunity are involved in the pathogenesis of neurologic disorder induced by silicone. During this process, silicone droplets and silica are released from the bag and are phagocytized by histiocytes and macrophages. Macrophages and histiocytes break silicone down to many smaller spheres, which may result in further phagocytosis, and the release of a significant amount of lymphokines such as IL-1

and tumor necrosis factor. High levels of lymphokines and cytokine may damage a neuron through specific receptors, which can result in the appearance of neuronal antigens such as myelin basic protein in circulation. Silicone droplets come into contact with these neuronal antigens and form a liposome-like sphere containing antigens. This highly antigenic material is presented to helper T-lymphocytes, resulting in their activation and proliferation. Similar to autoimmunity, where, through a homing mechanism, the T-cell travels from the thymus to the blood and hence to the target organ, these activated lymphocytes with neuronal antigens must travel to the nervous system and penetrate the blood-brain barrier. Penetration of the blood-brain barrier by lymphocytes may be enhanced by direct action of lymphokines or silicone or silica by-products on the endothelial cells. Once they arrive at the target, leukocytes — mainly T-cells — get a foothold with the help of intracellular adhesion molecules called integrins. These molecules, which are sited on the T-cells, bear receptors that can be likened to Velcro fasteners. Counterreceptors belonging to the immunoglobulin supergene family constitute the other half of the Velcro bond. The counterreceptors grow from the endothelial lining of blood vessels at points that have been exposed to such cytokines as γ-interferon and tumor necrosis factor. These cytokines are produced on the spot by activated T-cells and macrophages. Therefore, when a T-cell moves along a blood vessel and meets a counterreceptor, they adhere to each other. The process of adhering causes the T-cell to secrete proteases, enzymes that help to create a hole in the blood vessel and enable the T-cell to tighten its cytoskeleton so that it can squeeze through the tiny hole. In this manner, leukocytes break through the blood-brain barrier to cause an MS-like syndrome, penetrate the synovial lining to cause rheumatoid arthritis, and so on for all the other autoimmune diseases.

Destruction begins when a T-cell encounters its antigen in the cleft of an HLA molecule and releases proteins and peptides, including tumor necrosis factor, a chemical relative called lymphotoxin, and γ-interferon. These chemicals have been identified as the proximate cause of demyelination. Macrophages then speed the process, partly by secreting tumor necrosis factor and partly by mounting a direct attack. It has been shown that macrophages actually strip fragments of myelin from the sheath encasing the nerve axons (Figure 14). One might suppose that autoimmune disease, once started, would proceed without interruption. Yet in multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and myasthenia gravis, periods of deterioration usually alternate with remission. In all these diseases, the pattern of decline has been shown to correlate strongly with three factors in the environment: female hormones, infection, and stress. Obviously, these factors may contribute to the worsening of clinical conditions of patients with implants. One may ask, however, the question why patients with silicone implants simultaneously produce antibodies against components of connective tissue and the neurological system? A partial answer to this question may be given from an examination of the chemical structure of silicone and the silicon dioxide backbone which is an essential component of connective neurologic tissues. These include glycosaminoglycans such as chondroitin sulfate and sulfatides. Secondly, silicone, after its release from the bag, may be disintegrated by the enzymatic contents of histiocyte vacuoles into silicon dioxide and a methyl group. These groups, which have binding capacity, could be

responsible for binding to the body macromolecules, such as myelin or chondroitin sulfate. Based on this, both immunopathological reactions shown in Figures 13 and 14 are possible.

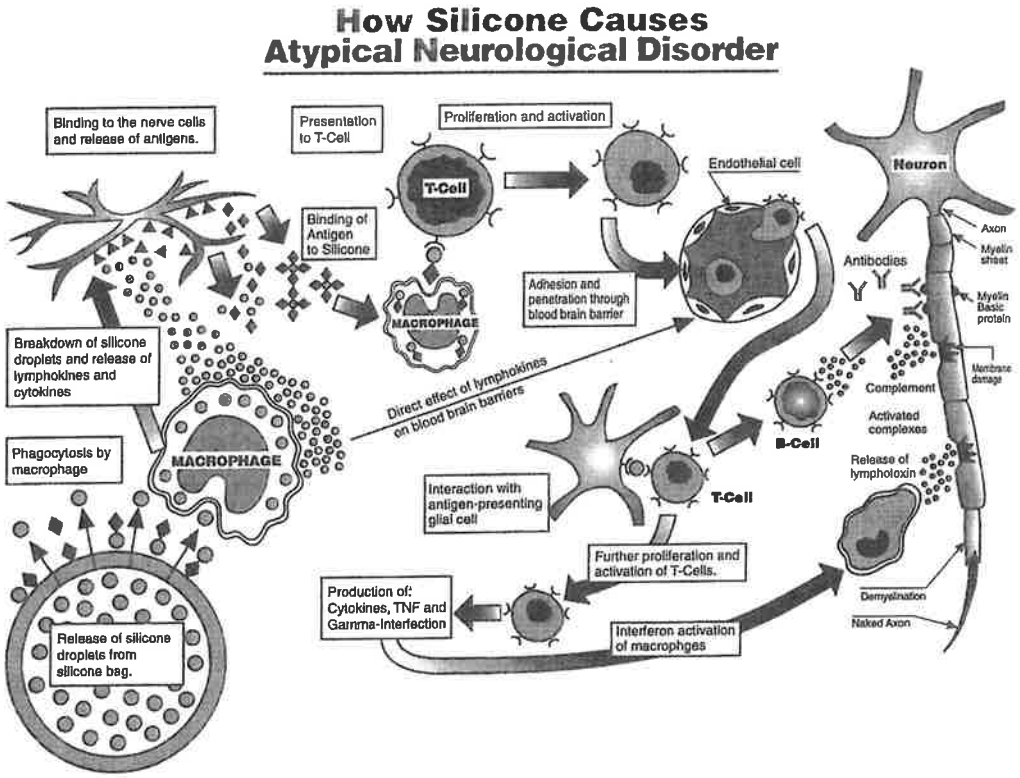


**FIGURE 14.** The demyelination of neurons that occurs in patients with silicone implants results from a complex chain of cellular events which ends with atypical neurological disorder.

In summary, based on results presented in this article, patients who present with complaints of silicone-induced immune dysfunction syndrome (SIIDS) deserve objective evaluation. However, because of the multiorgan effects of silicone and the presence of different laboratory abnormalities in different patients, there is no single test that is definitive in the diagnosis of SIIDS. Therefore, quantitative evaluation of both cellular and humoral immunity, with the major emphasis on nonspecific tissue antibodies by Western Blot assay, myelin-associated glycoprotein antibodies (MAG), and ganglioside, sulfatide, and silicone-specific antibodies, is needed to diagnose atypical connective tissue disease or atypical neurological disorder, which are the most common among these patients. A summary of these and other tests needed for aid in diagnosis of SIIDS is depicted in Table 2.

As recently discussed in a very scientific article by Ostermeyer Shoaib et al. (1994), symptoms in women with silicone breast implants or silicone injections should not be neglected nor underestimated, even if routine laboratory tests are normal. Physicians should be aware of atypical disease in women with silicone breast implants.

**TABLE 2. Antibodies or Factors which Were Found the Most Abnormal in Symptomatic Patients with Silicone Breast Implants**

| | Percent abnormal in: | | |
|---|---|---|---|
| Parameters tested | Silicone group | Chronic fatigue | Control |
| Neurologic antibodies | 69.5 | 37 | 12 |
| T-helper/suppressor ratio | 38.5 | 37 | 8 |
| B-cell | 40 | 16 | 4 |
| T-cell function | 38 | 29 | 4 |
| B-cell function | 15 | 10 | 2 |
| NK-cytotoxic activity | 67 | 33 | 16 |
| Rheumatoid factor | 29.5 | 16 | 6 |
| Immune complexes | 16 | 14 | 3 |
| C3, C4 complement | 39 | 12 | 4 |
| Antinuclear antibodies | 27.5 | 17 | 5 |
| Thyroid antibodies | 18 | 11 | 2 |
| Tissue antibodies | 62 | 33 | 7 |
| Antiphospholipid antibodies | 6 | 2 | 0 |
| Silicone antibodies | 33 | 7 | 4 |

Finally, the medical community should assume more responsibility and not publish article(s) about the lack of association between breast implants and connective tissue diseases based only on medical records that did not include neuroimmunological testing, as was the case in Gabriel et al. (1994) which was published in the prestigious New England Journal of Medicine.

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# DETECTION OF LYMPHOCYTE STIMULATION BY SILICON DIOXIDE

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*During the past several years, much debate has focused on the adverse effects of silicone breast implants on women. We describe an adaptation of mitogen testing which demonstrates a cell-mediated immune response of T-lymphocytes to silicon dioxide or silica. Among 50 patients with silicone breast implants, normal lymphocyte stimulations were demonstrated with mitogens pokeweed (PWM), concanavalin A (Con A), and phytohemagglutinin (PHA). Lymphocyte stimulation of the implant group by silicon dioxide showed a mean index of 208, approximately 20 times greater than that for the control group ($p < 0.0001$). Evaluation of working suspensions of silicon dioxide showed no detectable endotoxin present. Among six patients who showed stimulatory effect of cells by labeled thymidine uptake, monoclonal antibody assessment by flow cytometry confirmed that 94–98% of cells recovered after stimulation with silicon dioxide were T-lymphocytes. The method described in this report has been used for measuring immunologic response to beryllium, gold, zinc, and silver. It is, however, easily modified to evaluate cell-mediated immune responses to other potentially antigenic particulate materials.*

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2. Abbreviations: Con A, Concanavalin A; LAL, Limulus amoebocyte lysate; PHA, phytohemagglutinin; PWM, pokeweed mitogen; SI, stimulation index.

3. Key Words: memory lymphocytes, silica, silicon dioxide, silicone-associated disease, silicone breast implants, stimulation indices.

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## INTRODUCTION

Recently, much debate has focused on the adverse effects of silicone breast implants on women. Studies have shown the physical presence of silicon (Rudolph et al., 1978; Wickham et al., 1978; Silver et al., 1993) and silicones (Wagner et al., 1977; Montandon, 1979; Baker et al., 1982; Thomasen et al., 1990) in tissues at the site of or closely adjacent to the prostheses, including axillary lymph nodes (Wintsch et al., 1978; Truong et al., 1988; Shanklin, 1991, 1993). Antibodies to silicone elastomers have been reported in patients with silicone ventriculoperitoneal shunts (Goldblum et al., 1992) as well as patients who have had silicone mammary implants (Wolfe et al., 1993). Although antibody testing is evidence of immunogenic reaction or exposure to silicone, variations occur that suggest a dose-response effect (Vojdani et al., 1995a,b). In order to define further the immune response, we report the adaptation of standard mitogen tests, a method that demonstrates cell-mediated immune responses of T-lymphocytes to purified silicon dioxide, or silica, in these implant patients.

## MATERIALS AND METHODS

A total of 50 symptomatic patients with silicone gel breast implants and 50 normal age-matched female controls without implants or clinical symptoms were sources of lymphocytes. The average age of the women with silicone implants was 43 years; the average for the control group was 40 years. Implant patients demonstrated at least two or more symptoms previously described (Bridges et al., 1993). These common symptoms included arthralgia, myalgia, excess fatigue or flu-like symptoms, alopecia, night sweats, and skin rashes. Average length of implantation was 11.2 years with a range of 2 to 24 years. In addition to the 50 matched controls, 5 other individuals provided samples from 6 to 13 times over three to five months. Informed consent was obtained from all subjects prior to taking blood samples.

Twenty ml of blood were drawn by standard venipuncture into tubes containing acid citrate dextrose as anticoagulant. Blood was transported to the laboratory and tested within 24 hours. Lymphocytes were removed by standard ficoll-paque (Pharmacia LKB Biotechnology AB, Uppsala, Sweden) centrifugation method. The mononuclear layer was immediately aspirated by micropipette and washed three times in RPMI-1640 (Grand Island Biological, Grand Island, New York). Lymphocytes were diluted to a final concentration of $5 \times 10^5$ cells per ml in RPMI with 10% human AB serum; this was determined by hemocytometer and purity was typically 97–99% lymphocytes. Viability of all lymphocytes was confirmed, by trypan blue exclusion, to be 95% or greater before use.

Two hundred µl of cell suspension were pipetted into 15 microtiter plate wells. These were tested in triplicate in five test schemes. The first series included 25 µl RPMI-1640 with 10% human AB serum added as blank for an unstimulated set. Three comparative sets were established with 25 µl of the three mitogens. These were prepared according to manufacturer's recommendations and included pokeweed (PWM), concanavalin A (Con A, 83 mg/ml), and phytohemagglutinin (PHA). PWM and PHA were obtained from Gibco

Biological Co., Grand Island, New York, and Con A was obtained from ICN Biomedical, Inc., Costa Mesa, California. The fifth set of wells included 25 µl of colloidal pharmaceutical grade silicon dioxide (Paddock Laboratories, Minneapolis, Minnesota) from a working stock containing 0.335 g/10 ml of RPMI. Plates were sealed and incubated at 37°C for four days, the standard incubation time used by this laboratory for similar studies. Studies lasting three and five days were conducted; however, four days appeared to be the optimum amount of time and also met our previously established standard length of incubation. At the end of the fourth day, 50 µl of tritiated thymidine (0.5 µCi/ml) was added to all wells. Lymphocytes were obtained by a standard harvest after 18 hours of pulsed labelling. The cotton-fiber filter discs (Titertek, Flow Laboratories, Rockville, Maryland) containing the lymphocytes were dried overnight at 37°C.

Dried filters were carefully placed in seven-ml glass scintillation vials and two ml of Beckman scintillation fluid (Beckman Laboratories, Fullerton, California) were added to each vial. Vials were incubated at room temperature in the dark prior to placement in a beta scintillation counter (Beckman Laboratories). Beta counts were recorded for five minutes and reported per minute. Triplicate values were averaged and the results for stimulated lymphocytes and blank wells were determined. The results for mitogen and silicon dioxide were expressed as a stimulation index which was found by dividing the average counts per minute for each agent by the unstimulated count for each patient or control. Statistical analyses of mitogens were done by the two-tailed Student T test. Silicon dioxide studies were statistically compared by the two-tailed Student T test and by the Mann-Whitney test. Evaluation of the potential of nonspecific stimulation with silicon dioxide using five healthy adults without symptoms and without overt exposure to silicone was also attempted. These individuals were tested by using the above-described procedure, conducted in a serial manner for periods of three to five months at varying intervals. Statistical analyses using chi-square and one-way analysis of variance (ANOVA)were performed.

To confirm that no endotoxin was present in the silicon dioxide working stock solutions, three random samples were subjected to further testing. A Limulus amoebocyte lysate (LAL) test was performed in duplicate on each sample. The LAL method used was the quantitative chromogenic procedure (QCL-1000, Biowhittaker, Inc., Walkersville, Maryland) previously applied to other analyses of fluids (Smalley, 1990). Briefly, the procedure recommended by the manufacturer was followed; this procedure included a blank of endotoxin-free water, endotoxin standards at 27 Endotoxin Units (EU)/ml, 13.5 EU/ml, 6.75 EU/ml, and 3.38 EU/ml, and each of the test samples. In order to evaluate the specificity of reactions, 50 implant patients and 10 normal adult controls without silicone exposure were tested against beryllium dioxide and titanium dioxide. Neither agent was found to be stimulatory in any of the patients or controls tested.

Six patients had silicon dioxide tests set up in additional wells. After stimulation, lymphocytes were washed as before and cells were carefully collected from the microtiter wells and placed in RPMI. The cells were then exposed to pan-T and pan-B monoclonal

antibodies separately (CD3 and CD19, respectively) and to CD45/CD14 dual-stained monoclonal antibodies (Coulter, Hialeah, Florida). They were then assessed by using flow cytometry on an Epics Profile II (Coulter). In all cases, it was confirmed that CD45 positivity exceeded 99%; this verified the presence of human white blood cells. The cell suspension was next evaluated for the pan-T and pan-B markers as noted above.

## RESULTS

All 50 implant patients demonstrated normal lymphocyte stimulation by PWM, Con A, and PHA. For the three standard mitogens (Table 1) with p-values from 0.4 to greater than 0.6, there were no statistical differences between implant patients and normal controls. Implant patients showed an increased stimulation index to silicon dioxide when compared to normal controls (Table 1). The background of counts from the unstimulated wells ranged from 16 to 174, with an average of 32 counts per minute. The average counts per minute for the mitogens and silicon dioxide in the implant patients were as follows: PWM = 578; PHA = 7161; Con A = 10,648; and silicon dioxide = 5376.

**TABLE 1. Mean Stimulation Indexes for Implant Patients Compared to Normal Controls**

| Stimulant | Controls (n = 50) | Implant patients (n = 50) | p-values |
|---|---|---|---|
| PWM | 20.5 ±1.96 | 22.4 ± 1.92 | 0.4704 |
| PHA | 270 ± 25.2 | 305 ± 41.4 | 0.4722 |
| Con A | 476 ± 39.3 | 450 ± 49.6 | 0.6803 |
| Silicon dioxide | 11.6 ± 0.9 | 208 ± 23.1 | < 0.0001 |

The data presented in this table reflect the mean stimulation index ± SEM for each mitogen and for silicon dioxide in control and implant patients. The stimulation index is determined by the ration of stimulated counts per minute divided by the unstimulated (background) counts per minute.

The mean stimulation index of 208 for implant patients was approximately 20 times greater than that for controls, with $p < 0.0001$, a highly significant difference according to both statistical methods. The distribution of individual responses is shown in Figure 1. Studies of the implantation time compared to immune stimulation with silicon dioxide showed no correlation, $r = 0.1454$.

Among the serial controls tested, the first control (#18) had blood lymphocytes tested 9 times over a five-month period with a mean SI of 4.7 ± 1.9; control #30 had 7 blood samples tested over a four-month period with a mean SI of 5.0 ± 2.0; control #31 had 6 blood samples tested over a three month period with a mean SI of 5.2 ± 1.6; control #32 had 9 blood samples tested over a three-month period with a mean SI of 4.7 ± 1.7; and control #33 had 13 blood samples tested over a three-month period with a mean SI of 3.2 ± 0.8 (Figure 2). The p-value by chi-square was 0.6937 which indicated that the variation among these group medians was not significantly greater than expected by chance. The ANOVA had $p = 0.8563$, i.e., not

significant. No measurable endotoxin was detected in any of the samples tested by the chromogenic LAL test. Monoclonal testing indicated that 94–98% of proliferating lymphocytes by silicon dioxide were T-cells marked with CD3 antibody (Figure 3).

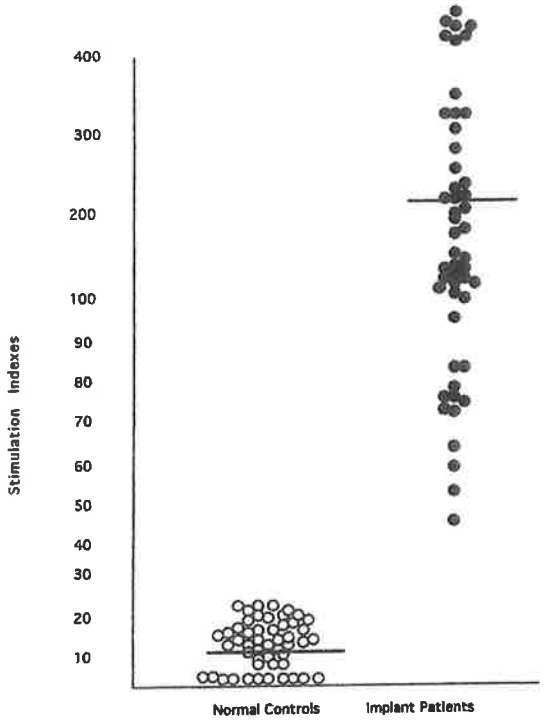


**FIGURE 1.** Comparative individual lymphocyte stimulation indices: normal controls (open circles) and symptomatic women with silicone mammary implants (solid circles).

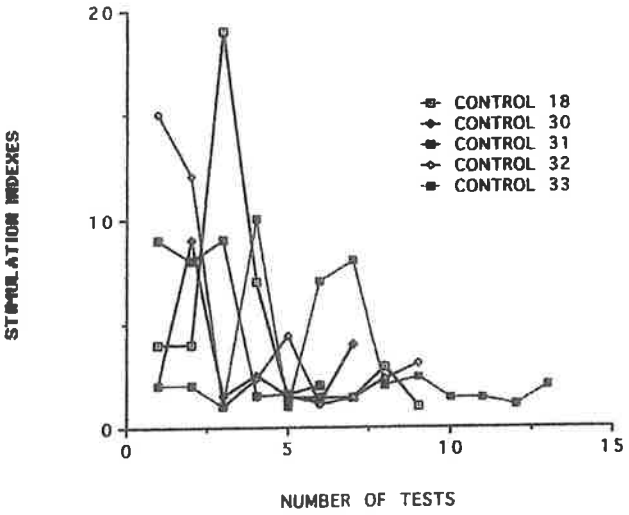


**FIGURE 2.** Serial stimulation indices for five normal controls tested over a period of three to five months.

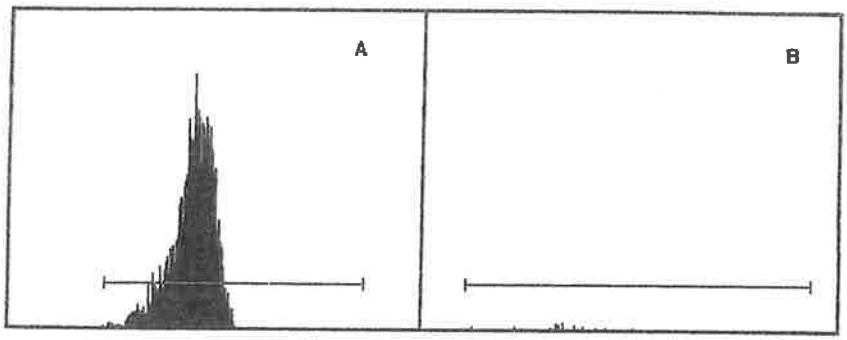


**FIGURE 3.** Representative flow cytometric histograms of pan-T response in an implant patient following stimulation with silicon dioxide (Side A) and pan-B response (Side B). The percentage of response to the pan-T monoclonal antibody in this case was 95.5% compared to only 2.3% for pan-B.

## DISCUSSION

The method used demonstrates clearly that silicone implant patients frequently develop a T-cell–mediated immunopathic response to foreign material from the prosthesis. The method is not new (Han, 1971; Geha and Merler, 1974; Chilson and Kelly-Chilson, 1989). It has been used to demonstrate similar cell-mediated immunopathic responses in berylliosis (Saltini et al., 1989) and drug-induced occupational allergy (Stejskal et al., 1986). It has also been used to assess the mechanism of topical metal allergy (Gilboa et al., 1988). Although antibody testing has been reported as evidence of immunopathic reactivity (Kossovsky et al., 1993), the silicone specific IgG antibodies vary from patient to patient depending on implant rupture status (Wolfe et al., 1993).

Among the five participants, the serial normal controls showed only three cases in which the mean of the original 50 normal controls was exceeded (Table 1). However, as shown in the statistical analyses, this variation confirmed that the results did not differ significantly from what could be expected by chance (Figure 2). This is interpreted as showing no false-positive responses in this serial phase of study among normal, healthy adults not exposed to silicone or its metabolites.

As shown by flow cytometric analysis, the predominant cell derived after stimulation in this setting was the T-lymphocyte (Figure 3). This does not preclude the stimulation of B-lymphocytes in some cases but confirms that the *in vitro* stimulation by this laboratory method is primarily of T-cells. This has also been confirmed by other investigators using a depletion methodology to show predominance of T-cell reactions (Ojo-Amaize et al., 1994). The results of the current study clearly demonstrate that there is a presence of silicon dioxide stimulated–T-lymphocytes in women with silicone mammary implants which cannot be detected in women without exposure to such prostheses.

Among 31 implant patients who were symptomatic, Ojo-Amaize et al. (1994) detected only 6 of 21 and 3 of 10 in their groups III (symptomatic patients with implants) and IV (explanted patients with symptoms), respectively. Our study showed a positive response in all 50 patients and may reflect how patient selection can cause differences in percentage of activity. Their preliminary study showed that either silicon, silicon dioxide, or silicone could induce a lymphocyte proliferation.

The results of the current study increase our understanding of the effects of silicone on the immune system. In addition, this method appears useful in distinguishing the immune disorder found in mammary implant patients due to sensitization to silicon dioxide from other altered immune disorders unrelated to these implants. Thus far, no direct correlation between the cell-mediated immunity and the presence or absence of symptoms has been demonstrated. Follow-up studies evaluating asymptomatic implant recipients and those with saline-filled implants are in progress. The method is readily modified to examine other particulate materials considered *a priori* to be antigenic in cell-mediated immune responses. Similar results for both silicone and silicon dioxide were recently reported from another laboratory (Ojo-Amaize et al., 1994).

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# SILICONE IS A POTENTIAL CARCINOGEN

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*Several recent data in the literature support the notion that silicone is a potential carcinogen, and a possible human carcinogen. This manuscript summarizes the available information and discusses the various scientific evidence.*

## I. SILICONE HAS DIRECT EFFECTS ON NATURAL KILLER CELL ACTIVITY IN PATIENTS

Natural killer cells, a cornerstone of the immune system, are responsible for controlling tumor cell growth, are involved in control of microbial infection, and have immunoregulatory properties, as well as a role in development of graft versus host disease (Louis and McGee, 1992).

In 1994, we (Campbell et al.) showed that natural killer cell activity in patients with silicone breast implants is significantly reduced, and that this suppressed activity is associated with additional immunological abnormalities (Vojdani et al., 1992).

Each patient in that study served as her own control, and it was demonstrated very clearly that the suppressed function of natural killer cell activity improved in at least 50 percent of the patients upon removal of the silicone breast implants. We proposed (in 1992) that since natural killer cells are important in the control of tumor cell growth, patients with reduced or

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impaired natural killer cell activity as a result of silicone breast implants have a higher risk of developing cancer (Vojdani et al., 1992).

## II. SUPPRESSED NATURAL KILLER CELL ACTIVITY IN EXPERIMENTAL ANIMALS

Studies by Smith et al. (1994) have shown suppression of natural killer cell activity as a result of exposure to silicone gel, and reversal of that suppression upon removal of silicone gel. Rats were implanted with silicone gel, and showed significant reduction in natural killer cell activity. This tendency was reversed following removal of implants. These studies of experimental animals confirm our observations in patients (Campbell et al., 1994) that silicone has a direct effect on natural killer cell activities and therefore has a direct effect on the immunological capability of controlling cancer cells.

## III. ADMINISTRATION OF SILICONE GEL TAKEN FROM BREAST IMPLANTS CAUSES CANCER IN EXPERIMENTAL ANIMALS

Recent studies by Potter et al. (1994), from the National Cancer Institute, clearly demonstrate that in mice who are genetically predisposed, silicone gel injection causes development of plasmacytomas; and indeed, that study was followed by a call from the editorial board of the Journal of the National Cancer Institute (Salmon and Kyle, 1994), for epidemiological studies in patients with silicone breast implants, to evaluate further the risk of hematological malignancy. During the most recent meeting of the National Cancer Institute at the National Institutes of Health (March 13–14, 1995), a workshop on the immunology of silicone was held. Several investigators presented data and studies suggesting an increased incidence of myeloma in patients with silicone breast implants.

## IV. SILICA IS RELEASED FROM SILICONE IMPLANTS

Studies by Garrido et al. (1993) and Pfleiderer et al. (1993) clearly showed that silicone is not inert, and that it biodegrades in the body and releases silica. Since silica is shown to be immunogenic and carcinogenic, it is highly probable that in individuals where silica is released, it plays an important role in the source carcinogenic mechanisms.

## V. EVIDENCE THAT SILICA IS CARCINOGENIC

Several studies have shown that silica is carcinogenic. Studies by Wagner et al. (1980) showed that after treatment with silica, rats developed a tumor incidence of 35%, compared to controls which developed only 5% incidence. There was a correlation between the site of toxicity to mouse peritoneal macrophages and tumor incidence. The investigators concluded that administration of silica causes malignant histiocytic lymphoma.

Digby and Wells (1981) have reported lymphadenopathy associated with refractile foreign material in cases of rheumatoid arthritis following replacement of affected hand joints with silicone prosthesis. They further recount a preliminary report of a case of rheumatoid arthritis where, following a series of joint replacements with silicone prostheses, complicated by infections and prosthesis fracture, a large-cell undifferentiated diffuse malignant lymphoma arose in an axillary lymph node. The investigators concluded their report as follows: "We share your earlier correspondent's anxiety about the possible long-term hazards of silicone particles, especially in patients with rheumatoid disease, which is known to be associated with defects of the immunological mechanisms." Julio Sanchez-Roman et al. (1993) described how a total of 50 subjects underwent a prospective study after exposure to silica. The study included immunological HLA typing, and tests for radiological, respiratory, and ophthalmological functions. They found that 64% of the patients had systemic disease such as Sjögren's disease, systemic sclerosis, systemic lupus erythematosus, and overlap syndrome. Antinuclear antibodies were present in 72% of the patients. The frequency of HLA DR3 was increased in the clinically affected subjects, but did not reach statistical significance. They concluded that workers exposed to silica developed a whole range of clinical, serological, and autoimmune symptoms. This confirmed the theory that silica has a direct effect on the immune system.

Based on the experimental studies by Michael Potter et al. (1994), our observation in our report of reduced natural killer cell activities in patients with silicone breast implants, the observations of Smith et al. (1994) in experimental animals; the knowledge that silica is released from silicone implants and that silica is immunogenic and carcinogenic, and recent presentations at the NIH and National Cancer Institute of a possibly higher incidence of multiple myeloma in patients with silicone breast implants, it is strongly suggested that silicone should be classified as an animal carcinogen, and at this point in time, should be classified as a potential human carcinogen.

It is further strongly suggested that the International Agency for Research on Cancer should re-evaluate its position on silicones and in the near future should establish criteria for classifying silicone as an animal carcinogen and a potential human carcinogen.

We agree with Dr. Salmon and Dr. Kyle that reports must be provided immediately to the FDA, the National Cancer Institute, and the National Institutes of Health concerning the relation between multiple myeloma and silicone breast implants, but it is also our position that other carcinomatoses — central nervous system, pulmonary, breast, gastrointestinal, or hematological — in patients with silicone breast implants, should be reported to those same agencies. We suspect that more carcinogen has gone unreported and unrecognized. We hope that, based on the above data, more attention in the media, and scientific papers, will be forthcoming.

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# SILICONE BREAST IMPLANT RECIPIENTS AND AUTOIMMUNE ENDOCRINOPATHY

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*In order to evaluate the relationship between silicone-induced immune dysfunction syndrome (S.I.I.D.S.) and autoimmune endocrinopathy, we tested 100 women, who had silicone breast implants and whose prevailing complaint was severe fatigue, for antiadrenal, antithyroglobulin, antimicrosomal, and antiparietal cell antibodies. Sixteen (16%) had adrenal, thyroid, and parietal cell autoantibodies; twenty-two (22%) had adrenal and parietal cell autoantibodies; ten (10%) had adrenal and thyroid autoantibodies; forty-seven (47%) had adrenal autoantibodies. Only five women (5%) had no detectable levels of any of these autoantibodies. These findings suggest that the immunogenicity of silicone may cause autoimmune endocrinopathy with fatigue as a prevailing symptom in silicone breast implant recipients.*

## INTRODUCTION

Fatigue is a common complaint that can be associated with many medical disorders. These include: toxic exposures, endocrinopathies, immune and autoimmune disorders, neurological disorders, infectious diseases, neoplastic disorders, adverse drug reactions, sleep disorders, depression, and organ failures such as renal, hepatic, pulmonary or cardiac diseases (Demitrack et al., 1991; Gupta et al., 1991; Goldstein, 1993). In a controlled study of 40 symptomatic women with silicone breast implants and 40 normal women, we have previously

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2. Key Words: autoantibodies, autoimmune, breast implant, endocrine, silicone.

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reported that fatigue is the most prevalent symptom (90%) (Vojdani et al., 1992). The 40 women with silicone breast implants had significant immune and autoimmune abnormalities, including elevation of thyroid autoantibodies, myelin basic protein autoantibodies, circulating immune complexes, elevated rheumatoid factor and antinuclear antibodies. Considering the significant elevation of thyroid autoantibodies in women who participated in that study, it would be important to evaluate the possibility that silicone's immunogenicity may cause an autoimmune endocrinopathy in silicone breast implant recipients.

## PATIENTS AND METHODS

One hundred women with silicone breast implants and fatigue as the prevailing symptom of disease were selected. They were between 28 and 71 years of age. All one hundred women had undergone at least one silicone breast implantation. They were all tested for production of autoantibody to adrenal, thyroid, and parietal cells. Blood was drawn in vacutainer tubes that did not contain any anticoagulants and was processed for the different antibodies. The tissue antibodies were measured by ELISA assay.

## RESULTS

Of the one hundred women with silicone gel breast implants whom we evaluated, sixteen (16%) had thyroid, parietal cell, and adrenal autoantibodies; twenty-two (22%) had adrenal and parietal cell autoantibodies, and ten (10%) had adrenal and thyroid autoantibodies. Forty-seven (47%) had adrenal autoantibodies, and five (5%) had no detectable levels of these autoantibodies.

## DISCUSSION

Studies have demonstrated the migration and accumulation of silicone in the adrenals, pancreas, ovaries, spleen, liver, kidneys, and lymphatics, following subcutaneous and intraperitoneal injections of silicone in laboratory animals (Ben-Hur et al., 1967; Rees et al., 1967; Brody and Fray, 1968). A study funded by Dow Corning was conducted with mice that were injected with silicone, from which it was concluded that silicone directly influences the function of the reticulo-endothelial system (Lake et al., 1975). Naim et al. (1993) demonstrated that silicone is a potent immunological adjuvant and concluded that silicone gel may mediate an autoimmune reaction. Several researchers have confirmed that silicone can trigger an immune reaction resulting in an autoimmune response (Van Nunen et al., 1982; Kumagai et al., 1984; Press et al., 1992; Vojdani et al., 1992). Indeed, silicone not only migrates into various organs, including endocrine glands, but may also create an immune and autoimmune response in these tissues.

Autoimmune endocrinopathies are characterized by infiltration of the affected endocrine gland with mononuclear cells. However, a relative sparing of adjacent tissues occurs (Yoshida et al., 1978; Muir et al., 1991). In patients with autoimmune Addison's disease, there is

marked mononuclear infiltration of the adrenal cortex but the adrenal medulla is spared (Sotsiou et al., 1980). The affected glands eventually undergo fibrosis and atrophy, and functioning endocrine tissue is eventually destroyed (Latinne et al., 1987; Frank et al., 1995). Adrenal autoantibodies can be found in patients with Addison's disease, and in patients with polyendocrine disease who may not exhibit adrenal failure. They are also found occasionally in patients with thyrotoxicosis, pernicious anemia, and diabetes (Baker, 1992; Salvi et al., 1988; Muir et al., 1991). The prevalence of these autoantibodies in the general population is very low. This autoimmune process results in deficient adrenal production of glucocorticoids and mineralocorticoids (Latinne et al., 1987). Demitrack and Greden (1991) reported that debilitating fatigue, an abrupt onset precipitated by a stress or feverishness, arthralgias, myalgias, adenopathy, postexertional fatigue, exacerbation of allergic responses, and disturbances in mood and sleep are all characteristic of glucocorticoid insufficiency. In several studies, similar symptoms have been reported as prevalent in silicone breast implant recipients (Van Nunen et al., 1982; Kumagai et al., 1984; Weiner et al., 1989; Vojdani et al., 1992). In the present study, we confirm that patients with silicone breast implants with these symptoms have adrenal and other endocrine autoantibodies.

## CONCLUSION

We have previously stated that silicone-induced disorders manifest themselves through a wide variety of immunological, rheumatological, and neurological syndromes (Brautbar and Campbell, 1995). This study demonstrates that autoimmune endocrinopathy constitutes yet another manifestation of silicone-induced immune dysfunction syndrome.

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# RHEUMATOLOGIC PRESENTATION AND WORKUP OF SILICONE-EXPOSED PATIENTS

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*Determination of the relationship between silicone breast implants and rheumatologic disease requires comprehensive analysis of large numbers of individuals, both with implants and without. Techniques of history taking and physical examination, predicated upon a working knowledge of rheumatologic disease, form the basis for identification of potentially associated rheumatologic conditions.*

*Symptoms are reported 6 to 7 years after prosthesis placement, with a range of 2 months to 25 years. The number of individuals with breast implants who have developed scleroderma and other rheumatologic disorders does not appear to be greater than that expected on the basis of chance alone. However, much larger populations must be studied to determine if a small risk does exist. While fibromyalgia may be an exception to that perspective, it too requires additional study.*

## INTRODUCTION

The search for the etiology of rheumatologic disease has often mirrored the stages of grief, and of most patients' responses to learning or being told they have a chronic disease. The final stage, acceptance that a problem exists and taking responsibility for its accommodation, is often achieved by a most indirect route, with many course reversals. The first step, however, in dealing with grief or a chronic disease, is often denial. The afflicted individual

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2. Abbreviations: ADL, activities of daily living; ANA, antinuclear antibody; anti-SSA, anti-Ro antibody; anti-SSB, anti-La antibody; CPK, creatine phosphokinase; ENA, extractable nuclear antigen; rnp, ribonucleoprotein; SGOT, serum glutamic oxalacetic transaminase; SGPT, serum glutamic pyruvate transaminase; SLE, systemic lupus erythematosus.

3. Key Words: fibromyalgia, polymyositis, scleroderma, silicone, Sjögren's syndrome, systemic lupus erythematosus.

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does not accept having a problem; some members of the medical profession do not believe that an organic problem exists. The second phase is often the question, "Why me? Why am I afflicted? On whom can I/we blame this problem?" Thus began the saga of rheumatologic complaints/problems among individuals with silicone breast implants.

The challenge to acceptance of a relationship of silicone to rheumatologic disease has perhaps been based partially on the preconceived notion that silicone is biologically inert (Brody, 1988). If the Bureau of Standards established silicone as an industrial standard for biologically inert materials, how could it possibly be responsible for a disease? As governmental agency credibility has come under great scrutiny in the past several decades, this governmental agency's assessment has become less compelling. The assumption of biologic inertness has since been tested and is today challenged.

Acceptance of the association between silicone and rheumatologic disease has, however, been challenged because of two other factors. One relates to the increased likelihood of identifying a second problem (rheumatologic) when an individual is already under enhanced surveillance (for breast implants), which is called the Berkson hypothesis (Fleiss, 1980). The second factor is perhaps more insidious. Common phenomena are common. If 2% of American women have had silicone implants (Hochberg, 1994), and if a rheumatologic problem is also not rare in the general population (Rothschild, 1982; McCarty, 1988), it is likely that the two will co-occur at some time. It is that frequency of co-occurrence which must be assessed. If silicone implants have a protective effect, the frequency of co-occurrence will be lower than expected. If silicone causes disease, the rate of co-occurrence will be higher than that expected solely on the basis of chance. The challenge is to assess whether the frequency of a given rheumatologic condition/disease is higher than could occur strictly by chance (statistical significance).

The difficulty of dependence on case reports is that rheumatologic disorders are relatively constant and variable in their clinical course, with many exacerbations and remissions. Placebo effect associated with nonsurgical interventions may exceed 30%, perhaps higher for surgical intervention. Lyme disease was suspected to be a separate phenomenon [from juvenile rheumatoid arthritis (JRA)] because of geographic clusters of what appeared to be JRA, otherwise considered a relatively rare phenomenon. Rheumatologic recognition of disease associations is quite firmly based on controlled studies of large populations.

While some investigators are convinced of the causation, and view epidemiologic studies as necessary to determine the degree of risk (Brautbar et al., 1994), I (as a rheumatologist) would suggest that determination of a relationship between silicone breast implants and rheumatologic disease still requires additional comprehensive analysis of large numbers of individuals, both with implants and without. Any such assessment is predicated upon the examiner's ability to obtain the pertinent historical information and review of systems, perform the pertinent examination, obtain valid laboratory and radiological studies, assess the significance of the latter, and have familiarity with a relatively broad spectrum of

rheumatologic disorders. Such an examiner would have to be trained in and have a working knowledge of internal medicine and rheumatology.

## RHEUMATOLOGIC HISTORY AND REVIEW OF SYSTEMS (ROTHSCHILD, 1982)

There is no diagnostic aid more important than a thorough patient history. When the patient complains of pain, it is important to have the patient point to the site of the pain and describe its distribution. Triggering phenomena must be identified. The mode of onset, with respect to rapidity, and the presence of any associated symptoms should also be noted. The patient should be specifically questioned with regard to pain modification by rest, exercise, time of day, position changes, activities of daily living (ADL), coughing, sneezing, and Valsalva's maneuver. A history of stiffness, swelling, deformity, heat, redness, and loss of range of motion should be sought. It is important to evaluate complaints of weakness, giving way, locking or clicking of joints, muscle pain, weakness or atrophy, and Raynaud's phenomenon.

The systems review should include queries about: rashes, pigmentary changes, hypo/hyperpigmentation, vasomotor changes, nail changes, hair loss, mucosal ulcers, headaches, paresis or altered control, paresthesias, personality or cognition changes, syncope, muscle pain or weakness, photophobia, eye or mouth dryness, excess tooth decay, dysphagia, nausea, vomiting, diarrhea, constipation, abdominal pain, mucus or blood, chest pain, hemoptysis, dyspnea, palpitations, hypertension, cyanosis, cramps, claudication, skin or mucosal ulcers, trophic changes, dysuria, fatigue, sleep disturbance, weight change, fever, chills, sweats, hearing changes, tinnitus, and seizures.

## RHEUMATOLOGIC PHYSICAL EXAMINATION (ROTHSCHILD, 1982)

The systemic joint examination begins when the patient walks into the room. Gait, habitus, posture, and the ability of the patient to undress are assessed to determine functional limitations. Alterations of structure, size, contour, and color of joints should be identified. Skin overlying joints should be evaluated with respect to smoothness or shininess, thickness, atrophy, and presence of calluses. Deformities noted on inspection should be characterized in terms of: 1) malalignment, 2) swelling, 3) subluxation (incomplete joint dislocation), 4) ankylosis, and 5) contracture. Alteration of the temperature of the skin overlying any joint should be noted. Tenderness should be localized (skin, muscle, bursae, ligaments, tendons, fat pads, or joint capsule). Any masses present should be assessed as to their nature (fluid, soft tissue, or bone). The presence of fluid or fluctuation should be assessed by ballottement techniques, wherein fluid displaced by pressure at one site produces motion perceived by a sensor at a second site. Soft tissue should be evaluated for the presence of subcutaneous nodules.

Active and passive range of motion should be measured with the joint supported in the position of least pain and spasm. Each joint should be palpated during passive range of

motion to identify: 1) stability, 2) muscle spasm, 3) gelling (stiffness that improves with repeated movement), 4) effusions, 5) locking (secondary to loose bodies, fibrosis, or bony ankylosis), and 6) crepitus. Muscle strength should be evaluated according to the following grading scale: 0, no muscle contraction; 1, contraction without joint motion; 2, joint motion but no antigravity power; 3, minimal antigravity power; 4, inability to move the joint against full resistance; and 5, normal strength against full resistance.

The presence of sclerodactyly, calcinosis, hyperpigmentation, hyperkeratosis, hypertrichosis, hyperhidrosis, Janeway's spots, and other skin lesions, should be noted. The nails should be examined for pitting, splinter hemorrhages, and clubbing. Loss of normal knuckle wrinkles may be an early sign of joint effusion. The technique of ballottement is to be utilized to determine the presence of joint effusion. The patient should be evaluated for the presence of Tinel's sign, by light percussion over the radial side of the palmaris longus tendon in the wrist. The elbow should be palpated for tenderness in the region of the olecranon bursa and lateral and medial epicondyles and for nodules along the extensor surface. The shoulder should be inspected for contour deformities and muscle atrophy. The following areas should be palpated for tenderness, defects, and crepitus: 1) the subdeltoid bursa; 2) the greater tuberosity of the humerus (where tendons of the supraspinatus, infraspinatus, and teres minor insert to form the rotator cuff); 3) the lesser tuberosity (where the subscapularis muscle inserts); 4) the bicipital groove; 5) the acromioclavicular joint; and 6) the sternoclavicular joint. Fluid in the knee should be evaluated by patella ballottement and examination for bulge sign. Knee instability, collapse of the arch of the foot, and metatarsal phalangeal and calcaneal tenderness should be tested, as well as smoothness and appropriate skin distraction of back flexion. The full technique of examination is beyond the scope of this article.

Trigger point examination is especially important. It is performed by noting pain and withdrawal on palpation of specific areas: temporalis (above the ear), anterior to tragus of ear, scalenus capitis, sternocleidomastoid, low anterior neck, pectoralis minor, manubrosternum, anterior and posterior axillary folds, low posterior neck, trapezius ridge, upper and lower rhomboids, parasagittal, iliac crest, midpoint in buttock, and rectus femoris, or vastus lateralis.

## SILICONE-SPECIFIC ANTIBODIES (BRAUTBAR ET AL., 1994; VOJDANI ET AL., 1995)

The implications of silicone-specific antibodies are discussed in detail elsewhere in this issue. Brautbar et al. (1994) report that 60% of patients with silicone breast implants who complain of fatigue and cognitive dysfunction have IgG, IgM, IgA, or IgE antibodies to silicone, especially those with rupture/leakage. Vojdani et al. (1995) noted an even higher frequency in plastic surgery practice.

## RHEUMATOLOGIC DISEASES (ROTHSCHILD, 1982; MCCARTY, 1989)

*Scleroderma/Progressive Systemic Sclerosis*

Scleroderma is a systemic disease characterized by edema and lymphocytic infiltration of subcutaneous connective tissue. It leads to subsequent atrophy and fibrosis, resulting in a loss of secondary skin structures (sweat glands and hair follicles). It may remain localized to the skin or be associated with multiple system involvement. It rarely occurs without any signs of skin involvement, or may present as focal skin involvement. While 10% of patients are diagnosed after age 60, its population frequency is approximately 3 to 12 per million. Prior to consideration of silicone effects, scleroderma has been proposed as a secondary phenomenon to graft-versus-host disease and occasionally after ethosuximide therapy.

Initially, a painless pitting edema of the hands and feet develops. Over the course of weeks or months, this produces a thickening and tightening of the skin (sclerodactyly), which becomes taut, shiny, and tightly tethered to subcutaneous structures. A waxy hardness and luster eventually develops. The face becomes expressionless, with loss of normal skin folds, and the nose, ears, and lips become smaller, thinner, and sharper. The patient is often unable to open the mouth sufficiently to separate the incisors by more than two cm. Skin involvement may be focal, giving rise to patches (morphea); may form linear streaks following the courses of nerves or blood vessels ("coup de sabre" lesions); or may be limited to the hands or feet (acrosclerosis). Fingertips shorten, thicken, and may lose their distal fat pads. Tiny, painful pits or ulcers form on fingertips and heal with scar formation. Calcinosis may break through the skin as a toothpaste-like material. Telangiectasias are quite prominent and Raynaud's phenomenon is common.

One-fourth of afflicted individuals have an arthritis which is very difficult to distinguish from rheumatoid arthritis, with morning stiffness but usually noninflammatory synovial fluid. Resorption of distal phalangeal tufts, acromioclavicular joints, and distal portions of radius and ulna is noted. Gastrointestinal involvement includes the replacement of muscle layers with fibrous tissue. Nausea, vomiting, heartburn, reduced peristalsis and dilatation of the lower two-thirds of the esophagus, increased transit time, large-mouthed intestinal diverticuli, pseudo-obstruction, and malabsorption are noted. Pulmonary involvement may present as fibrosis or pulmonary hypertension. Intimal proliferation and fibrinoid necrosis in intralobular arteries of the kidneys produce a necrotizing glomerulitis, microangiopathic hemolytic anemia, and malignant hypertension.

*Overlap Syndromes and Mixed Connective Tissue Disease*

Mixed connective tissue disease is one form of overlap syndrome. Rather than having more than one clearly defined connective tissue disease, it has a few components of several. Raynaud's phenomenon, inflammatory arthritis, decreased esophageal motility, pulmonary dysfunction, and myositis in association with diffuse hand swelling is highly suggestive of the diagnosis. Mixed connective tissue disease is often associated with high-titer antinuclear

antibody, with specificity for the ribonucleoprotein (rnp) portion of extractable nuclear antibody (ENA).

*Sjögren's Syndrome*

Sjögren's syndrome is a disorder of exocrine gland function which most typically presents as keratoconjunctivitis sicca and/or xerostomia (sicca complex). Keratoconjunctivitis sicca is a symptom complex resulting from impairment of normal lacrimal gland function. The reduced tear volume is not sufficient to maintain a normal protective film; dry spots form on the cornea and sclera. If the dry spots are not "wetted" by lacrimal fluid (supplied by blinking) in two to three seconds, the epithelium is shed and erosions are initiated. The Schirmer test is often used to assess lacrimation. A 5 x 35 mm strip of #41 Wattman filter paper is folded at right angles approximately 5 mm from the end and placed into the unanesthetized conjunctival sac at the outer third of the eyelid. Fifteen mm of wetting will normally occur in five minutes. Less than five mm is definitely abnormal.

Xerostomia is a symptom complex resulting from functional impairment of major and minor salivary glands. Ectasia is common in the terminal branches of the parotid duct system. Salivary flow can be measured with a Lashley cup. Although biopsy of a major (e.g., parotid) salivary gland reveals classic changes (lymphocytic infiltration, hyperplasia of lining cells of intraglandular ducts, and myoepithelial islands), the procedure may cause facial nerve damage. A properly performed lip biopsy is a benign procedure and is preferred, since the minor salivary glands are equally affected. Examination for greater than four lymphocytic clusters is to be pursued.

Involvement of exocrine glands is often systematic. Similar changes occur in the submucosal glands of bronchi and sebaceous glands of the skin and vaginal mucosa; dyspareunia and pancreatitis may therefore occur. Arthritis may occur, mimicking rheumatoid arthritis. Renal involvement may produce renal tubular acidosis, Fanconi syndrome, or diabetes insipidus. Serological abnormalities in Sjögren's syndrome include rheumatoid factor in 90%, ANA in 70%, and high frequency of anti-SSA and anti-SSB antibodies, the latter somewhat dependent upon associated connective tissue disease.

An important aspect of Sjögren's syndrome is its frequent association with other disease entities. Approximately one-half of the patients with Sjögren's syndrome have rheumatoid arthritis. Associations with any connective tissue disease, malignancy, sarcoidosis, or spondyloarthropathy are worth noting.

*Systemic Lupus Erythematosus*

Systemic lupus erythematosus (SLE) is a multisystem disease characterized by polyserositis and evidence of autoimmune disease or vasculitis. Definitive diagnosis of a multisystem disease with a myriad of presentations is always difficult. Study of such a disease is complicated by the nonhomogeneous nature of the patient group with the disease, if it is indeed one disease. Criteria have been developed which tend to reduce the variation of the

group to a more defined population amenable to experimental study. Such criteria are a research tool. There is no evidence that the presence of criteria defines or identifies the syndrome with any greater confidence than does the overall clinical picture.

Arthritis is the initial symptom in approximately 64% of the patient population, and eventually occurs in 95% as a polyarticular, nondeforming symmetrical arthritis. Synovial fluid is mildly inflammatory. Dermatological abnormalities include malar rash, discoid lesions (which heal with scarring), photosensitivity, alopecia areata (patchy hair loss), ecchymoses, pigmentary changes, subcutaneous nodules, panniculitis, mucosal ulcers, and Raynaud's phenomenon. Perhaps 25% of individuals with lupus develop significant renal involvement. Hematuria, red cell casts, and proteinuria may be noted. The course of renal disease in some individuals parallels elevation of anti-DNA antibody and depression of complement levels. Pleuritis and pericarditis, neuropsychiatric symptoms (e.g., encephalopathy, psychosis, headache, convulsions, chorea, nerve palsies, myelitis, cerebral vascular accidents), and retinal changes (cytoid bodies) may be noted. Hematological perturbations are common. Leukopenia (especially with lymphopenia), thrombocytopenia, and hemolytic anemia (usually Coombs' positive) are often present. Circulating anticoagulants are associated with prolongation of prothrombin, partial thromboplastin, or Russell viper clotting time, or with anticardiolipin or antiphospholipid antibody. While bleeding times may be prolonged, these individuals are especially at risk for thrombotic events (e.g., strokes, myocardial infarctions). Constitution symptoms of fever, lymphadenopathy, and hepatosplenomegaly are common.

*Polymyositis*

The terms "polymyositis" and "dermatomyositis" reflect predominant involvement of muscle and skin, respectively, but are often used interchangeably. Polymyositis is essentially a disease of the proximal musculature, affecting the neck, shoulder, and hip girdle muscles. Classically, patients have difficulty arising from a chair or reaching over their heads. The muscles may be tender, but cramps are usually not present. One-third have electromyographic evidence of a myopathic process. Serum enzyme levels reflect muscle cell leakage of creatine phosphokinase (CPK), aldolase, SGOT, and SGPT in one-third of patients. Light microscopy of muscle tissue reveals variation in fiber size and basophilia, with internalization of sarcolemmal nuclei. Mononuclear cell inflammatory infiltrates, especially in a perivascular distribution, are common, and perifascicular fibrosis is apparently diagnostic. Hypopharyngeal and esophageal muscle incoordination produces dysphagia.

The two skin manifestations classically associated with dermatomyositis are heliotrophe and Gottron's sign. The former is a periorbital lilac or purple discoloration that may be associated with periorbital edema. Gottron's sign describes an alteration of the extensor surface of joints. Hyperpigmentation of knuckles or extensor surfaces of knees gives way to a thin, wrinkled, shiny, or slight scaly, blue-red or porcelain-colored skin. A central depression may be surrounded by telangiectasias; periungual erythema may be noted. Discoloration of the neck and malar regions may be noted, ranging from lilac to erythematous or cyanotic in

appearance, secondary to telangiectasias. Although hyperkeratosis and epidermal thinning occur, accessory skin structures are preserved. Raynaud's phenomenon and calcinosis (within necrotic muscle) are other complications. Pericarditis, heart block, and cardiomyopathy occur in 25% of patients. Arthritis is typically symmetrical, with non- to mildly inflammatory synovial fluid. Restrictive lung disease may occur. ANA is found in one-third of those afflicted and 50% have rheumatoid factor.

*Rheumatoid Arthritis*

Rheumatoid arthritis can be considered as the prototype of inflammatory arthritis. It is usually characterized as a progressive, seropositive (rheumatoid factor positive), symmetrical polyarthritis, with infiltration of mononuclear cells into a proliferating synovial membrane, producing erosive disease. It affects 6% of American women and 2% of American men. The onset of rheumatoid arthritis is usually insidious and accompanied by malaise, fatigue, and occasionally by weight loss or the development of lymphadenopathy.

The role of criteria in the diagnosis of rheumatoid arthritis is controversial. The initial criteria included: tenderness in a joint, swelling in one or more joints, symmetry, morning stiffness (of at least one hour duration), subcutaneous nodules, rheumatoid factor, poor mucin clot, typical rheumatoid nodule pathology in a subcutaneous nodule, typical rheumatoid nodule pathology in the synovial membrane, and typical erosions on X ray. Definite or classical rheumatoid arthritis is diagnosed in the presence of five or seven criteria, respectively. Although invaluable in assuring uniformity in clinical studies, the role of criteria in diagnosis has not been fully delineated. It should be immediately obvious that the presence of only a few isolated criteria, such as rheumatoid factor positivity or subcutaneous nodules, is in no way pathognomonic for rheumatoid arthritis. These are nonspecific; tenderness and swelling must be observed by a physician. Bony overgrowth does not meet the criteria. With active disease, synovial fluid is inflammatory and periarticular osteopenia is invariably present on X ray. Hand deformities are characteristic (in absence of adequate therapeutic intervention), with ulnar deviation of metacarpal phalangeal joints, radial deviation of the wrist, boutonniere or swan-neck deformities of the fingers, and piano-keying of the ulna.

The pathology of rheumatoid arthritis is not limited to joints. Extra-articular manifestations include: pleuritis, pulmonary fibrosis, nodules and hypertension, Felty's syndrome, cardiomyopathy, pericarditis, valve disease, amyloidosis, neuropathy, myopathy, carpal tunnel syndrome, vasculitis, episcleritis, and anemia. Perhaps 25% of individuals with rheumatoid arthritis develop cervical subluxation, but nerve entrapment can occur at other sites. Five percent can develop a symmetrical sensorimotor neuropathy, especially if amyloidosis occurs. For individuals with rheumatoid arthritis, rheumatoid factor is present in 30–70%, and ANA is present in 10–30%.

*Vasculitis/Vasculopathy*

Vasculitis/vasculopathy describes a continuum of pathological alterations of blood vessels, which ranges from bland intimal proliferation to necrotizing inflammation. Infiltrates, when

present, may be perivascular or intramural, polymorphonuclear or mononuclear. Granulomas may occur in any of the vasculopathies, although they are more common in certain types.

Necrotizing vasculitis is characterized by necrosis of the walls of blood vessels. Perivascular lymphocytic cuffing or leukocytoclastic changes may predominate. The vascular lumen is often occluded by intimal proliferation or thrombosis. Palpable purpura and urticaria are prominent.

Polyarteritis nodosa is a disorder of small and medium-sized arteries (especially at their bifurcations), characterized by involvement of all three vessel layers. Although lesions progress through several stages, multiple stages may be present at the same time at different sites. The initial stage of fibrinoid necrosis is followed by polymorphonuclear infiltration, with destruction of the internal elastic membrane, and frequently by thrombus formation. Subsequent proliferation of fibroblasts eventually resolves with residual dense fibrosis and calcium deposition. The segmental nature of involvement in this disease often manifests as vascular nodules. These are related to periarterial inflammation, secondary fibrosis, or aneurysm formation. Almost any body system can be involved in polyarteritis nodosa, with the exception of the lungs (except for asthma). A salicylate-unresponsive, large-joint arthritis develops in 25% of patients.

*Fibromyalgia*

Fibromyalgia is basically a pattern of pain (Rothschild, 1991). The tenderness complaints are verified by application of pressure at defined trigger points (which reproduces the individual's symptoms). While the resultant pattern of pain may be at the trigger points, it is often somewhat displaced, but reproducible (Rothschild, 1991). Trigger point sites include: temporalis (above the ear), anterior to tragus of ear, scalenus capitis, sternocleidomastoid, low anterior neck, pectoralis minor, manubrosternum, anterior and posterior axillary folds, low posterior neck, trapezius ridge, upper and lower rhomboids, parasagittal, iliac crest, midpoint in buttock, rectus femoris, or vastus lateralis, and quadriceps insertion (at the patella). Hemicranial pain produced by pressure applied anterior to the tragus of the ear or sternocleidomastoid, or pain radiating to the chest or down the arm produced by pressure applied to the anterior triangle of the neck, anterior axillary fold, trapezius ridge, or rhomboids, probably can have no other explanation.

Nonrestorative sleep pattern (awakening in an unrefreshed state) is characteristic of fibromyalgia. Other characteristics include modulation of symptoms by physical activity, weather, anxiety or stress, generalized fatigue or tiredness, anxiety, chronic headache, irritable bowel syndrome, and subjective swelling or numbness.

## CURRENT STATE OF THE ART

Controlled studies to assess nonchance association of rheumatologic disease with silicone breast implants are in process. Initial reports described a phenomenon called human adjuvant

or graft-versus-host disease (Ostermeyer Shoaib et al., 1994), because of perceived similarities to other animal models of disease and notation that silicone was an immunomodulator (Miyoshi et al., 1964; Smahel et al., 1993). However, silicone-induced animal models have apparently not been inducible (Wolf et al., 1993). Because of similarities to graft-versus-host disease and the often dramatic nature of scleroderma presentations, many subsequent studies have focused on scleroderma. Early reports related to the occurrence of scleroderma are difficult to assess. One point four percent of women with breast implants developed scleroderma, compared to 1.1% of women with no implants (Hochberg et al., 1995). The number of individuals with breast implants who have developed scleroderma was not greater than that expected on the basis of chance alone. Wigley and Miller (1992) observed that 0.66% of scleroderma patients had a history of augmentation mammoplasty. Muhanna et al. (1992) found that 2 out of 350 patients with scleroderma had implants, but the scleroderma symptoms predated the implants.

Symptoms start 6 to 7 years after prosthesis placement, with a range of 2 months to 25 years (Weisman et al., 1988; Varga et al., 1989; Bridges et al., 1993; Koeger and Burgeois, 1993). While it has been suggested that 50% of individuals with severe, life-threatening disease note improvement with removal of the prosthesis, this condition is typically minor or short-lived. Improvement, when it occurs, may occur as early as 15 days after removal and continue for six to twelve months. Carpal tunnel syndrome, Raynaud's phenomenon, rashes with hypo- or hyperpigmentation, dyspnea with interstitial and pleural thickening, arthritis or arthralgias, myalgias or muscle weakness, lymphadenopathy, dry eyes, dysphagia, anemia, leukopenia, and focal tenosynovitis (producing a sausage-shaped digit) have been reported (Weisman et al., 1988; Varga et al., 1989; Bridges et al., 1993; Koeger and Burgeois, 1993).

One of the major challenges that implants present relates to the question of the very commonly associated fatigue. Is there any justification for removal of a breast prosthesis, solely for the complaint of fatigue? Psychological evaluation (especially for subtle signs of depression) would probably be reasonable for any individual who wants explantation because of fatigue. Fibromyalgia is commonly present in individuals who have had breast implants, although it is also quite common in the general population. As its occurrence is often related to stress and sleep disturbance, it is not clear whether stress or the implants are responsible. If the patient becomes convinced that the fibromyalgia is related to her implants, psychological evaluation would again appear critical in that individual's evaluation.

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# NEUROCOGNITIVE SYMPTOMS AND QUANTITATIVE EEG RESULTS IN WOMEN PRESENTING WITH SILICONE-INDUCED AUTOIMMUNE DISORDER

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*The first 23 women who presented for evaluation of neurocognitive symptoms following silicone breast implantation were studied. Their major presenting symptoms included: fatigue; difficulty with short-term memory; slow mental processing; distractibility; mood changes; confusion; shortened attention span; decreased word retrieval; problems organizing; and difficulty concentrating which correlated with abnormal mental status examination findings. Quantitative EEGs were performed and statistically compared to a reference population. All demonstrated significant deviations, but no one pattern emerged. Further controlled research to determine specificity is recommended.*

## INTRODUCTION

Recently there has been controversy and litigation over the purported effects on tens of thousands of the seven hundred thousand to two million women who have been the recipients

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2. Abbreviations: P300, Auditory Evoked Potentials; QEEG, Quantitative Electroencephalogram; UBOs, Unidentified Bright Objects; VEP, Visual Evoked Potential.

3. Key Words: breast implants, cognitive, neurocognitive, quantitative EEG (QEEG), silicone.

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of silicone breast implants in the United States. Review of the literature describes patients complaining of arthralgias, myalgias, fibromyalgia-like syndrome, chronic fatigue, connective tissue–like disorders (similar to scleroderma, lupus, arthritis, and dermatomyositis), peripheral neuropathies, Sjögren's-like symptoms, and neuropsychiatric complaints (Kumagai et al., 1984; Sergott et al., 1986; Press et al., 1992; Bridges et al., 1993; Fenske and Vasey, 1993; Hirmand et al., 1993; Lappé, 1993; Silver et al., 1993; Yoshida et al., 1993; Brautbar et al., 1994; Patten and Ostermeyer Shoaib, 1994). While most of the focus has been on rheumatologic consequences of implants, little has been written about objective measures of cognitive disruption. Lewy notes that between 34.29% and 47% of patients studied had abnormal MRI results suggesting areas of demyelination, and/or infarction or vasculitis, as usually evidenced by periventricular punctate lesions and/or "unidentified bright objects" (UBOs) on MRI (Lewy, 1993). As he points out, these changes are nonspecific, yet the radiological literature "associates them with multiple sclerosis, chronic hypertension in the elderly, and a variety of other not-so-benign conditions." SPECT studies have demonstrated diffuse cortical defects in clinically toxic patients with silicone breast implants (Simon et al., 1992).

Patients presenting to the practice of one of the authors typically complained of several neurocognitive symptoms (Table 1). Mental status testing corroborated the patient's history (Table 2). In addition to a neuropsychiatric interview and mental status examination, patients were administered a computer-enhanced or quantitative EEG (QEEG). In all cases, the results demonstrated significant deviations from a reference population, using Z-score transforms. A few subjects were also administered visual and auditory (P300) evoked potentials if requested by the referring physician.

**TABLE 1. Moderate to Severe Neurocognitive Symptoms**

| Symptom | Frequency (N = 23) | % |
|---|---|---|
| Lethargy, tiredness, fatigue | 23 | (100%) |
| Short-term memory problems | 21 | (91.3%) |
| Slow thinking or mental processing | 21 | (91.3%) |
| Sleep disturbance | 20 | (87.0%) |
| Irritability | 18 | (78.3%) |
| Sensitivity to noise or photosensitivity | 17 | (73.9%) |
| Distractibility | 16 | (69.6%) |
| Headache | 16 | (69.6%) |
| Dizziness | 16 | (69.6%) |
| Anxiety | 16 | (69.6%) |
| Depression | 15 | (65.2%) |
| Confusion | 15 | (65.2%) |
| Anger | 15 | (65.2%) |
| Shortened attention span | 14 | (60.9%) |
| Forgetfulness (incidental memory problems) | 14 | (60.9%) |
| Impatience | 14 | (60.9%) |
| Labile emotions | 13 | (56.5%) |
| Trouble finding the right word or word reversals | 12 | (52.2%) |
| Blurred vision | 12 | (52.2%) |
| Problems organizing | 11 | (47.8%) |
| Difficulty concentrating | 11 | (47.8%) |
| Overloaded by too much stimulation | 9 | (39.1%) |
| Tinnitus | 8 | (34.8%) |
| Nausea | 6 | (26.1%) |

**TABLE 2. Abnormal Mental Status Examination Findings**

| Test | Frequency (N = 23) | % |
|---|---|---|
| Serial subtractions | 16 | (69.6%) |
| Recall four objects after five minutes | 15 | (65.2%) |
| Recall past presidents | 13 | (56.5%) |
| Digit span | 12 | (52.2%) |
| 21-unit story test | 10 | (43.5%) |
| Calculations (at least 50% wrong) | 9 | (39.1%) |

## METHOD

*Patient Selection*

The patient population used in this study consisted of the first 23 women presenting for evaluation. Their ages ranged from 30 to 61 years (mean of 46.13 years), with symptoms and complaints that had a temporal relationship to silicone breast implantation. Time since initial implantation ranged from 2 to 21 years, with an average of 10.75 years. Eighteen (78.3%) were explanted between 5 and 26 months before presentation. Table 1 lists the frequency of moderate to severe neurocognitive symptom complaints. Table 2 shows abnormal mental status testing. The subjects were not compared to a control group; percentages in the tables are of the inclusive group of 23 women. Each patient received and signed an informed consent form which described the procedure, including notification of its experimental status.

## PROCEDURE

*EEG Recording*

EEG was recorded digitally using a NeuroSearch 24 EEG acquisition system. Electrodes were placed according to the International 10–20 System using a fitted electrocap. Impedances were reduced to below 5 Kohm. All recordings were made to linked ear reference and off-line montage reformatting allowed for viewing of standard bipolar montages. EEG was digitized at a rate of 128 Hz and stored to disk for off-line analysis. The patient was seated either upright or semireclined during testing. Recordings were obtained in the awake and alert eye-closed resting condition.

*Data Processing*

EEG was transferred to the QND program (Neurodata, Inc.), and visually edited to reduce extracerebral artifact. A minimum of 30 seconds of EEG data was subjected to analysis. EEG coherence, amplitude differences, and relative power were computed according to the method described by Thatcher et al. (Thatcher, 1987;[1] Thatcher et al., 1987, 1989). These measures were then used for Z-score analysis by comparison to an age-matched group extensively screened for neurological history, intelligence, and educational achievement.

[1]Thatcher, R. (1987). "Normative Data Base." Personal communication. pp. 1–10.

*Life Span Reference Database Comparison*

The Life Span Reference Database is comprised of 564 individuals with ages ranging from 2 months to 87 years (Thatcher, 1987;[2] Thatcher et al., 1987). The set of measures includes the mean and standard deviations for intra- and interhemispheric EEG coherence, amplitude differences, and relative power for each of 16 recording electrodes (the 19 electrodes of the 10–20 system minus the midline electrodes: Fz, Cz, Pz). Individual patients were compared to a subgroup most closely matched in age, with Z-scores computed for each of 192 measures.

*Interpretation*

Records were reviewed visually for detection of potentially significant transient activities. In addition, the tabular presentation of data was reviewed and summarized for the number and level of statistical deviations, and particularly for any clustering of deviations forming a pattern consistent with possible brain dysfunction.

## RESULTS

A summary of each patient's most significant complaints, along with major QEEG findings, is shown in Table 3. Numerous findings considered consistent with brain dysfunction were noted. The severity of abnormalities ranged from relatively mild to markedly severe, with a clearly defined abnormality present in almost all cases. The most common findings centered over the temporal scalp regions. Findings were seen both unilaterally and bilaterally and in different frequency ranges. There was a trend toward decreased coherence, and in several cases, increased focal slow and sharp activity over the left temporal area was noted. In 10 of the 23 subjects significant transient abnormalities in the EEG tracing (including one case with frank spike and wave) and paroxysmal activities in the awake, alert state were also noted. For a small subset of patients (N = 5), long latency auditory P300 and visual pattern reversal evoked responses were recorded. Two of these patients showed delayed P100 peak latency; one showed a P300 response lateralized to the right side.

## DISCUSSION

Significant deviations (Z-scores of 2 or greater) from the reference population were found in all subjects on QEEG. In general, the most prevalent QEEG findings appear to be consistent with specific patient complaints. In particular, there is a high incidence of memory-related symptoms (N = 21/23) and EEG coherence changes (N = 22/23), especially in the temporal regions. This correlation needs to be confirmed with larger samples and more comprehensive neurodiagnostic and neuroimaging evaluations.

While a clear temporal relationship between neurocognitive symptoms and silicone breast implants has been noted in these patients, it would be of interest to assess the specificity of these findings by performing similar analyses for patients with silicone implants but without neurocognitive symptoms, and for patients with neurocognitive symptoms but without silicone implants. It is possible that QEEG abnormalities may be related to other disease entities such as fibromyalgia, depression, chronic fatigue, or presenile dementia. Controlled studies are indicated to substantiate causal relationships.

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[2]Thatcher, R. (1987). "Normative Data Base." Personal Communication. pp. 1–10.

**TABLE 3. Summary of Severe Symptoms and QEEG Findings**

| Case # | Age | Most severe complaints | EEG and QEEG findings |
|---|---|---|---|
| 1 | 49 | Headache, slow thinking, distractibility, memory, overloaded by stimulation | Diffuse elevation of relative theta, increase in slow frequency coherence over right hemisphere |
| 2 | 30 | Blurred vision, memory, dizziness | Generalized paroxysms, decreased theta coherence with right posterior temporal region |
| 3 | 39 | Depression, tinnitus, sleep, photosensitivity | Markedly decreased theta and alpha coherence with posterior temporal regions bilaterally |
| 4 | 48 | Headache, blurred vision, slow thinking, distractibility, memory, confusion, attention, sleep, noise | Increased slow frequency coherence over right hemisphere, lack of alpha coherence over left hemisphere, elevated relative theta power, L > R |
| 5 | 43 | Headache, slow thinking, distractibility, dizziness, tinnitus, memory, confusion, attention, sleep | Focal slow transients over left temporal, lack of delta coherence with left temporal, elevated right frontal theta coherence |
| 6 | 51 | Memory, sleep | Sharp transients over left temporal, decreased theta coherence with left temporal, some right posterior slowing, diffusely elevated relative theta power |
| 7 | 36 | Headache, blurred vision, irritability, dizziness, memory | Some elevation of frontal theta coherence, lack of alpha coherence with right posterior temporal region, increased delta coherence posteriorly |
| 8 | 47 | Organization, memory, confusion, concentration, finding the right word/reversals | Small sharp transients over left temporal, increased delta coherence with left temporal |
| 9 | 39 | Headache, depression, anxiety, sleep, memory, overloaded by stimulation | Marked sharp activity over right posterior temporal, temporal slowing R > L, lack of theta coherence over posterior temporal regions bilaterally, elevated delta coherence over parietooccipital scalp and elevated theta coherence over frontal scalp |
| 10 | 32 | Organization, memory, finding the right word, dizziness | Right occipital spike and wave, increased delta coherence with right occipital, some elevation of frontal theta coherence |
| 11 | 51 | Headache, slow thinking, irritability, memory, attention, sleep | Focal sharp and slow transients with paroxysmal features over left temporal scalp, marked lack of coherence with left temporal for delta, theta, and alpha frequencies, elevated delta coherence diffusely over the right hemisphere |
| 12 | 60 | Organization, headache, slow thinking, irritability, tinnitus, memory, sleep, photosensitivity | Elevated delta coherence diffusely over the right hemisphere, excess right frontal slow activity, relative theta power elevated over medial frontal and occipital scalp |

**TABLE 3. Summary of Severe Symptoms and QEEG Findings (cont'd)**

| Case # | Age | Most severe complaints | EEG and QEEG findings |
|---|---|---|---|
| 13 | 61 | Organization, headache, blurred vision, slow thinking, distractibility, depression, tinnitus, memory, confusion, attention, concentration, finding the right word, overloaded by stimulation | Elevated frontotemporal coherence bilaterally, multifocal slowing, delayed VEP latency, asymmetric auditory P300 |
| 14 | 53 | Blurred vision, slow thinking, distractibility, memory, attention, sleep, noise | Diffusely elevated alpha coherence, focal high amplitude in theta, alpha, and beta frequencies over left temporal region, increased delta coherence with left posterior |
| 15 | 34 | Headache, slow thinking, distractibility, irritability, memory, attention, sleep, noise | Transient slowing in theta frequencies over left temporal, diffusely elevated slow frequency coherence, increased left temporal delta activity |
| 16 | 46 | Slow thinking, distractibility, memory, confusion, attention, concentration, overloaded by stimulation | Increased left frontotemporal delta coherence |
| 17 | 58 | Organization, nausea, slow thinking, distractibility, irritability, impatience, memory, confusion, attention, sleep, photosensitivity, concentration, overloaded by stimulation | Prominent left temporal delta focus, lack of delta and theta coherence with left temporal |
| 18 | 40 | Headache, blurred vision, slow thinking, distractibility, memory, confusion, attention, sleep | Paroxysmal delta focus over temporal scalp L > R, elevated relative theta power over right occipital, elevated delta coherence |
| 19 | 49 | Headache, blurred vision, slow thinking, irritability, dizziness, memory, sleep, concentration, finding the right word | Increased theta and delta over temporal regions bilaterally, particularly on right |
| 20 | 55 | Organization, slow thinking, distractibility, irritability, impatience, memory, attention, sleep, concentration, finding the right word | Increased theta coherence with prefrontal and lateral frontal regions, particularly on right |
| 21 | 59 | Organization, blurred vision, slow thinking, distractibility, memory, confusion, attention, sleep, noise, concentration, finding the right word, overloaded by stimulation | Sharp and slow wave transients, increased posterior slow activity, elevated coherence bilaterally, maximally over frontotemporal regions, delayed latency of P100 component of VEP |
| 22 | 37 | Organization, slow thinking, distractibility, irritability, depression, memory, sleep, concentrating, finding the right word, overloaded by stimulation | Focal left temporal sharp waves, lack of alpha coherence with left temporal region, increased posterior slow activities |
| 23 | 44 | Organization, depression, anxiety, memory, attention, sleep | Focal left temporal slowing, some increase in frontotemporal delta coherence, L > R |

The mechanism of pathology also requires further research. It is somewhat surprising to note the extent of focal findings in what appears to be systemic exposure. Other preliminary reports suggest a pattern of varied symptoms and widespread findings similar to demyelinating disease. Indeed, antimyelin antibodies have been reported, as well as abnormalities of GM1 ganglioside, myelin-associated glycoprotein antibodies (anti-MAG), and sulfatides in such patients, including several of those in this study. It is possible that focal findings represent the vulnerability of specific cortical regions to systemic exposure. For example, the medial temporal lobe may be more sensitive to toxic exposure than other cortical regions. These findings may be analogous to focal ischemic necrosis, which often results from systemic carbon monoxide exposure (Van Sweden and Niedermeyer, 1993). It is possible that the etiology involves multiple factors, including mechanical ones, e.g., reduction of blood flow due to particulate matter obstructing small vessels. Differences in patients' results suggest that different types of implants or silicone may cause different cortical reactions.

In summary, we report preliminary findings suggesting a correlation between neurocognitive symptoms and quantitative EEG findings in patients with silicone breast implants. These results imply a significant impact on the central nervous system in some patients. Measures of EEG coherence, amplitude, and relative power, including measures of deviation from a reference database of asymptomatic individuals, appear to be sensitive to neurocognitive symptoms reported in these patients. Based on these initial observations, additional studies of the mechanism of impact of the disease on the central nervous system, including identification of specific toxic agents, time course, and cofactors, are indicated. However, it is clinically useful to compare patients' neurocognitive symptoms with QEEG and perhaps neuropsychological testing for functional assessment, although in our experience, QEEG is a more sensitive tool than neuropsychological testing in diagnosing neurocognitive dysfunction.

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# QUANTITATIVE ASPECTS OF CELLULAR RESPONSES TO SILICONE

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*Silicone medical devices have been widely used in the recent past, especially as mammary implants. The early clinical finding is principally capsular contracture; the cellular dynamics have been described but not quantified. Quantitative histological assessment was done in a series of 100 consecutive but random patient consultations with 121 individual biopsy samples from various sources. There was an average of 5.5 slides per biopsy (range, 1–35), stained by hematoxylin and eosin. Overt silicone was seen in 109 samples (90.1%), dense capsular scar in 89 (73.6%), and mineralization in 19 (15.7%); breast tissue was present in only 35 of 121 samples, or 28.9%. A strong correlation was found between lymphocyte and macrophage reactions, especially with granuloma formation which occurred in 76 samples (62.8%). Intracytoplasmic micronization of silicone was seen 26 times in tissues with (34.2%) and 15 times in tissues without granulomas (33.3%), suggesting an independent form of macrophage response. The number of slides available was not a factor in identification of lymphocytes, which were found in 109 of 121 samples (90.1%, a different set from the 109 samples with silicone; there were four biopsies with neither). There was an increase in the severity of granulomatosis when more slides were available; this appeared to be due to wider sampling of large, often discrete siliconomas beyond the prosthetic capsule, not their identification per se. The correlation coefficient between severity of lymphocyte infiltration and granuloma formation was 0.51046, with good fit linear regression between*

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2. Key Words: granulomas, inflammatory reaction, silica, silicon dioxide, silicone-associated diseases, silicone breast implants.

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*lymphocytes and the intensity of granulomatosis as the dependent variable. These results confirm that immune processing and inflammatory cell responses are commonplace in the tissues surrounding silicone mammary implants.*

## INTRODUCTION

Currently there is a debate on the effects of silicone breast implants on women. One study claimed the "natural" incidence of autoimmune diseases to be higher after implantation (Shons and Schubert, 1992). However, reports of systemic sclerosis (Varga et al., 1989), scleroderma (Spiera and Kerr, 1993), connective tissue disease (Silver et al., 1993), and human adjuvant disease (Thomsen et al., 1990) continue to be published, various epidemiological surveys notwithstanding (Gabriel et al., 1994). Studies, both older and recent, have established the physical presence of silicon (Rudolph et al., 1978; Wickham et al., 1978; Silver et al., 1993) and silicones (Wagner et al., 1977; Montandon, 1979; Baker et al., 1982; Thomsen et al., 1990) in tissues at or closely adjacent to the prostheses, including the axillary lymph nodes (Wintsch et al., 1978; Truong et al., 1988; Shanklin, 1991, 1993). Antibodies to silicone elastomers have been reported in patients with silicone ventriculoperitoneal shunts (Goldblum et al., 1992) as well as following silicone mammary implants, especially after leakage or blatant rupture (Wolfe et al., 1993). Such evidence, while compelling for: (a) the presence of silicones and/or breakdown products *beyond* the prostheses; and (b) antigenicity of silicone; does not indicate whether or how autoimmune disease results from exposure to silicone prostheses. We report here cellular responses, often intense, consisting mostly of lymphocytes and macrophages.

## METHODS

### *Study Material*

All case materials were sent to one of us (D.R.S.) in consultation from numerous hospitals across the United States over the period January 1992 through September 1994. Many biopsies had been obtained earlier. Most came as slides previously stained by hematoxylin and eosin, but unstained mounted sections, paraffin blocks, and fixed wet tissue were all represented. All three of the latter categories were processed by routine methods in the diagnostic histopathology laboratories of the Department of Pathology; staining was by hematoxylin and eosin. A review was undertaken of 100 consecutive patient consultations on periprosthetic mammary capsular tissue; 121 biopsies were available from the 100 patients. Single samples came from 87, two each from 7, three each from 4, and four each from 2 patients. Ten of the 100 patients showed polyurethane foam remnants in capsular tissues (10.0%); granulomatosis due to polyurethane was easily distinguished from that due to silicone in all such cases and the features of polyurethane-induced reaction are not further considered in this report. Polyurethane foam granulomas were disregarded in the quantitative assessments of silicone granulomatosis in the ten cases.

*Methods*

Prior experience in microscopic identification of silicone in human tissue (Shanklin, 1991, 1993) indicated that careful examination would establish its presence without requiring dark field illumination (accomplished by dropping the condenser and slowly closing the substage diaphragm to throw silicone droplets and globules into refractive relief). The intensity of silicone presence was graded as: (a) droplets/globules; (b) bulk deposits; or (c) intramacrophagic micronization. Micronization was in turn graded as 1+ to 4+. The intensity of lymphocytic infiltration was graded as 0 through 4+, as was the formation of granulomas. The fibrous capsule was noted as loose (mild or incomplete) or dense; the latter often contained nodular or hyalin scar. The presence or absence of calcification or mineralization of capsular tissue and the presence or absence of mammary tissue were noted. Further analysis of the mineral deposits was not undertaken. The presence of neoplasm as part of the biopsy was also recorded. In all, 664 tissue slides were examined.

## RESULTS

Three general features of the biopsies are shown in Table 1. Dense capsule formation was found in 89 of 121 (73.9%). Only 19 biopsies had identifiable calcification or mineralization. Mammary tissue was present in 35 biopsies (28.9%). Six neoplasms, one benign and five malignant, were part of the biopsy materials. The benign tumor was a paraprosthetic desmoid. The malignant tumors were: one cribriform small-cell carcinoma, three ductular carcinomas (one of which was invading the prosthetic capsule), and one adenosquamous carcinoma. Our review confirmed the original diagnoses, which are the designations given here and in Table 1.

Silicone was identified in 109 of the biopsies (90.1%). All possible mixtures of globular deposits, bulk collections, and micronization were noted; these combinations accounted for 45 of the 109 samples which were positive for silicone (41.3%). The distribution of silicone by the mass and character of the deposit was related to the presence or absence of silicone granulomas which were found in 76 biopsies (Table 2). This distribution is highly significant, with a chi-square of 25.39 (D.F. = 5, $p = 0.0001$) (Table 3). Granulomas ranged from small, sometimes with just a single globule of silicone within a giant cell, to large and complex lesions containing an admixture of lymphocytes (Figures 1 and 2). These lesions often contained very large globules which were at the lower range in size of bulk deposits (Figure 2). Lymphocytes were identified in 109 biopsies; as noted, this was a different set of 109 from those with silicone in one form or another. There were only four biopsies with neither silicone nor lymphocytes. Lymphocytes were dispersed, often in juvenile fibrous tissue (Figure 3), sometimes in nodules, and were found frequently about small blood vessels (Figure 4). Isolated perivascular lesions were also found in capsular tissue (Figure 5) and in adjacent skeletal muscle, specifically the pectoralis major.

**TABLE 1. General Features of 121 Mammary Capsule Biopsies from 100 Patients**

| Finding | Number | Percent of samples |
|---|---|---|
| Number of samples per patient: | | |
| One | 87 | 71.9 |
| Two | 7 | 11.6 |
| Three | 4 | 9.9 |
| Four | 2 | 6.6 |
| Tissue findings: | | |
| Breast tissue | 35 | 28.9 |
| Silicone | 109 | 90.1 |
| Dense fibrous capsule | 89 | 73.6 |
| Calcinosis/mineralized | 19 | 15.7 |
| Lymphocytes, 1+ to 4+ | 109 | 90.1 |
| Granulomas, 1+ to 4+ | 76 | 62.8 |
| Polyurethane foam | 10/100 patients | |
| Neoplasms identified:* | | |
| Paraprosthetic desmoid tumor | 1 | |
| Ductular carcinoma of breast | 3 (1 invading capsule) | |
| Cribriform small cell carcinoma | 1 | |
| Adenosquamous carcinoma | 1 | |

*Review confirmed all original diagnoses of these tumors.

**TABLE 2. Relationship between Silicone Deposit and Granulomas**

| | Capsular tissue reaction | |
|---|---|---|
| Character of silicone deposit | Granulomatous | Nongranulomatous |
| Number of cases | 76 | 45 |
| Globules/droplets | 20 | 22 |
| Micronized | 5 | 5 |
| Globules/micronized | 17 | 10 |
| Subtotal | 42 | 37 |
| Bulk only | 17 | 0 |
| Globules/bulk | 9 | 0 |
| Micronized/bulk | 2 | 0 |
| Micronized/bulk/globules | 2 | 0 |
| Subtotal | 30 | 0 |
| Total | 72/76 [94.7%] | 37/45 [82.2%] |

Silicone was also found within nongranulomatous macrophages in the form of dispersed fine droplets, which gives the cells an epithelioid appearance (Figures 6 and 7). Their resemblance to macrophages in xanthogranuloma has prompted the use of *xanthoid* as a descriptive term. Sometimes, highlighted large droplets within these cells were found to have the refractile qualities of larger deposits of silicone (Figure 7). The distribution of micronized silicone (Table 2) is of interest. Micronization was found in 26 of 76 biopsies with granulomas

**TABLE 3. Statistical Treatment of Silicone Deposits against Silicone Granuloma Formation**

| | Granuloma | No granuloma | Totals |
|---|---|---|---|
| No silicone | 4 | 8 | 12 |
| Less than bulk | 42 | 37 | 79 |
| Bulk deposits | 30 | 0 | 30 |
| Totals | 76 | 45 | 121 |

Chi square = 25.39, D.F. = 5, p = 0.0001.

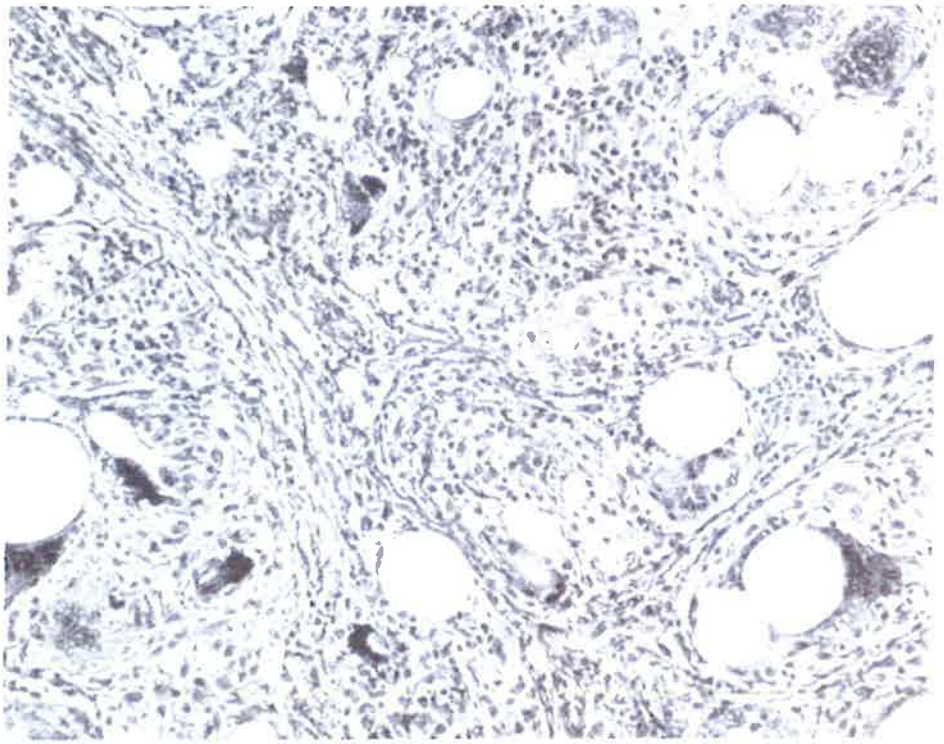

**FIGURE 1.** Silicone granuloma with small to moderate globules of silicone, and numerous giant cells, and lymphocytes. The substage condenser is down, putting a refractile cast on the alien material. H&E. Original magnification, 100X.

(34.2%) and in 15 of 45 biopsies without granulomas (33.3%). The frequencies are essentially identical; this suggests micronization as an independent process by which macrophages deal with silicones in lesser quantities, since it does not seem to occur within or closely adjacent to bulk deposits. The interdependence of lymphocyte response and granuloma formation is shown starkly by Figure 8, which is a regression plot of graded severity of granulomas versus lymphocytosis as the independent variable. Although statistical plotting programs produce an equation for the slope, there is a more limited biological meaning to the result. The reverse

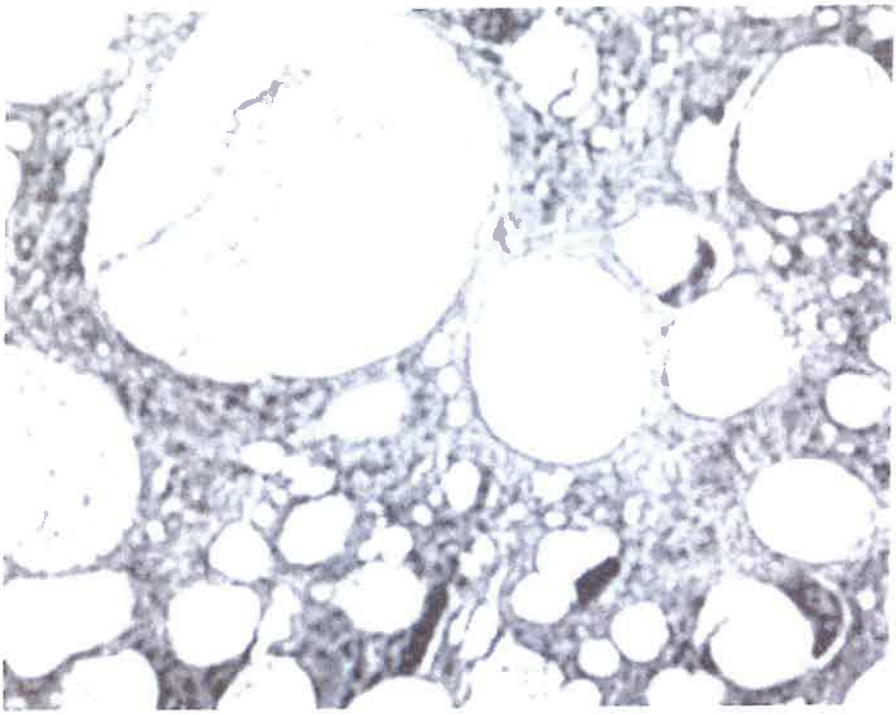

**FIGURE 2.** Silicone granuloma with moderate to large globules of silicone, and numerous giant cells and lymphocytes. The substage condenser is down, as in Figure 1, and the focus has been adjusted to enhance the visibility of the silicone. H&E. Original magnification, 100X.

plot (not shown) had a lag phase in the correlation, supporting the general understanding that the initial dominant cellular response is lymphocytic prior to granuloma formation, even though macrophages participate early in the preparation and presentation of alien or foreign material for immune processing. Their relationship is shown in Table 4.

Plasmacytes were seen infrequently (6 of 121 biopsies, 4.96%). Only one biopsy showed eosinophilic granulocytes. This was a 4+ eosinophilia with moderate plasmacytic reaction as well. One biopsy with plasma cells also had many neutrophils, one showed ductular carcinoma infiltrating the periprosthetic capsule, and one had plasma cells from the adjacent skeletal muscle present in the biopsy.

The relatively small subset of polyurethane foam cases, ten percent of the total, limits somewhat a comparison of granulomata *per se*. From this limited perspective, on a provisional basis, little or no distinction was observed outside of the obvious difference in the alien or foreign material contained. In a few instances both were present. A further specific study of this has been planned and will be reported separately.

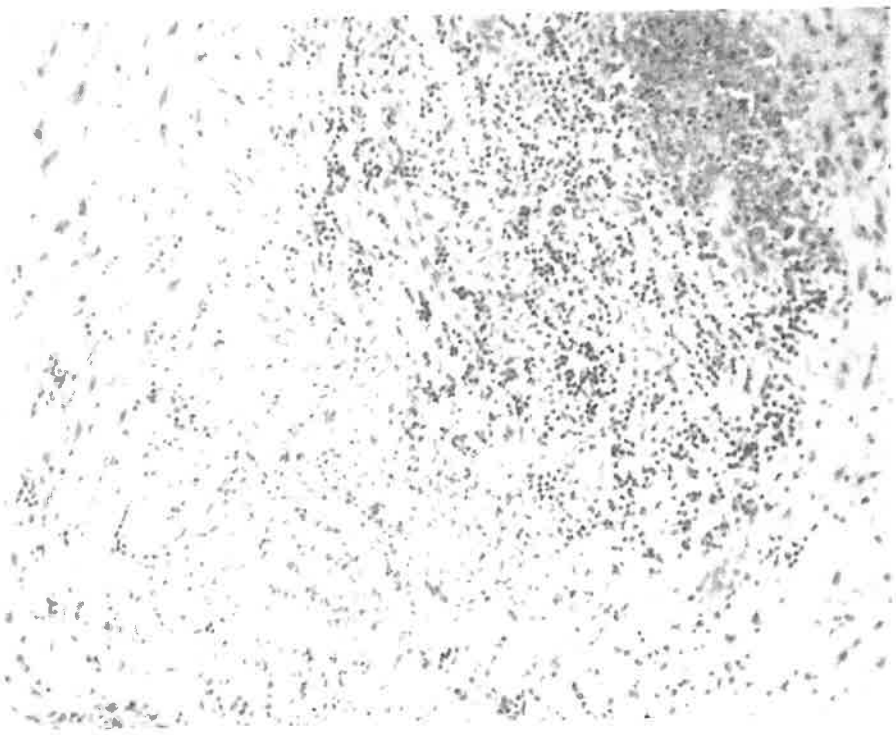

**FIGURE 3.** Immature (juvenile) connective tissue as part of a prosthetic capsule with dispersed lymphocyte infiltration. H&E. Original magnification, 100X.

## DISCUSSION

The data demonstrate clearly that cellular responses occur in women with mammary implants. The close correlation between lymphocytic response and the formation of granulomas indicates that silicones are processed by the human immune system despite the alien nature of polymerized dimethylsiloxanes. In fact, given that many individuals produce large complex granulomas, to which the term *siliconoma* has been applied (quite reasonably), and that these masses often recur two or three times after first excision, an autonomous progression seems to develop, despite removal of much or most of the silicone. Six of the one hundred patients had three or four biopsies each.

Pure lymphocytic reaction is occasionally very severe in human mammary implant capsules (Figure 4), but mixtures of lymphocytes, macrophages, and globular silicone as foreign body granulomas are common (Figure 2). Both reactions are seen frequently, if variably, in human (Shanklin, 1991, 1993) and animal material (Picha and Goldstein, 1991). Picha and Goldstein (1991) found that silica-free silicone produced little cellular reaction early and moderate fibrosis with mild lymphocyte infiltration late. Fumed (amorphous) silica resulted in much

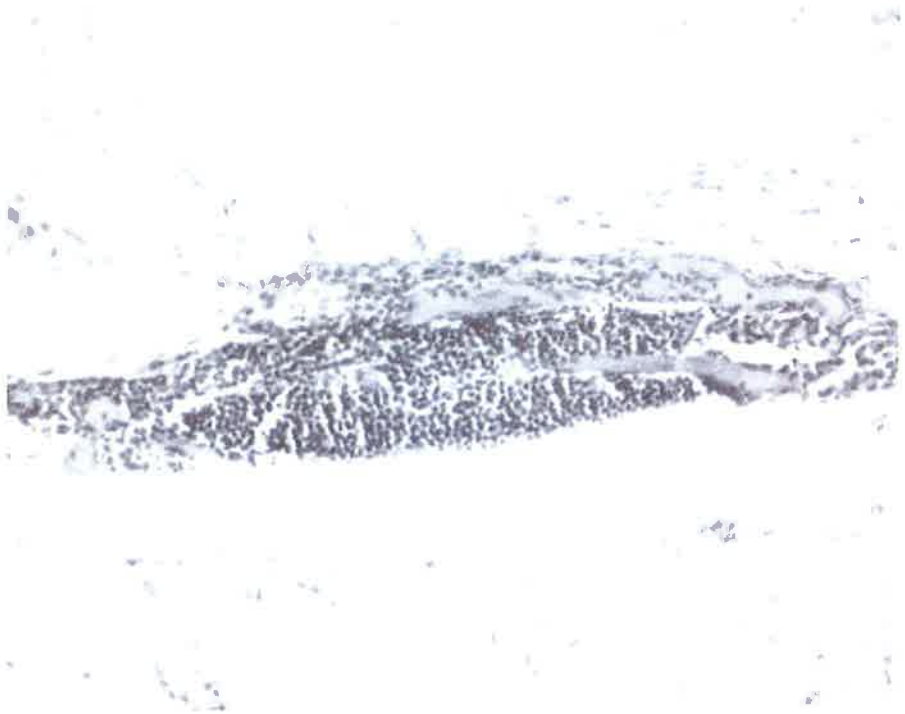

**FIGURE 4.** Dense aggregation of mature lymphocytes about a complex of small blood vessels, within a portion of dense capsule. H&E. Original magnification, 100X.

more severe lymphocytic reaction, which was progressive over the course of their experiments (Picha and Goldstein, 1991). By contrast, both silicone gel and silicone oil produced mixed cellular reaction, including macrophages (Picha and Goldstein, 1991), which are the precursors to the granulomas found often in human material (Shanklin, 1991, 1993). This distinction between types of cellular reaction parallels, and is probably based on, the memory T-lymphocyte response (Smalley et al., 1995) to components of the prosthetic envelope at the initial interface with tissue, the periprosthetic capsule. Silica accounts for a quarter of the envelope (Dow Corning Corporation, 1968, 1979), an amount which supports a strong relationship between silicon dioxide derived physically or chemically from the prosthesis and the intensity of memory lymphocyte sensitization by comparative mitogen testing (Smalley et al., 1995).

Antibody testing has also resulted in evidence for immunopathic reactivity (Kossovsky et al., 1993). Silicone-specific IgG antibodies were found by use of modified enzyme-linked immunosorbent assay (ELISA) in 34 implant patients, 19 of whom experienced implant rupture (Wintsch et al., 1978), confirming prior work (Goldblum et al., 1992). The study showed significantly higher antibody titers in implanted women compared to unimplanted

**FIGURE 5.** Isolated lymphocyte cuffing of single blood vessel, chronic perivasculitis. H&E. Original magnification, 200X.

controls and increased antibody formation following implant rupture (Wolfe et al., 1993). Interactions between antisilicone specific IgG and various connective tissue proteins have been described (Kossovsky et al., 1993). About 15% of positive immunoglobulin responders also showed reactions to connective tissue matrix proteins independent of siloxane (Kossovsky et al., 1993). The role of connective tissue cells in lesion formation is supported by the finding of increased serum lysosomal β-galactosidase in rats implanted with silicone, either solid or gel (Landon et al., 1993).

Accordingly it may be seen that human tissue reactions to the components of silicone mammary implants occur on several levels, over time:

(a) sensitization of the T-lymphocyte reaction system, most likely by silicon dioxide (silica) per se;

(b) macrophage reaction sometimes progressing into granulomas, a direct response to silicone elastomer in tissue, as one process toward antibody formation;

(c) production of silicone-specific IgG antibodies; and

(d) conformational changes in native connective tissue proteins following possible adjuvant transformation by silicone.

**FIGURE 6 .** Xanthoid effect of silicone micronization within macrophages. H&E. Original magnification, 200X.

Dense fibrous capsules were observed in 73.6% of the available biopsies, and lesser degrees of scar formation were present, sometimes along with hypermature or nodular scars. This datum is of interest in that the consensus rates for capsule formation detected, clinically developed during the February 1991 F.D.A. Symposium on Silicone Medical Devices, were 40% palpable (mild), 25% hard or indurated (moderate), and 15% hard with distortion (marked), which is a total of 80%. We consider the figure of 73.6%, derived from biopsy material, to represent a confirming datum of the less precise, experientially derived rate (Shanklin, 1991).

None of this is unexpected. Despite the alien character of polymeric silicone, the principal monomer is dimethylsiloxane in which the methyl groups are displayed outwardly on the polymer core of oxygen-silicon. This means, in probable effect, that immunopathic processing begins with protein coating of the methylated layer or zone, a feature less alien to carbon-based living forms than the totality of silicone polymers, whether solid, gel, or fluid, and that presentation to the major histocompatibility complex of macrophages proceeds more or less as it does for all foreign or alien material introduced into the mammalian or human body. The high content of silica in the envelope of these devices is clearly another factor in

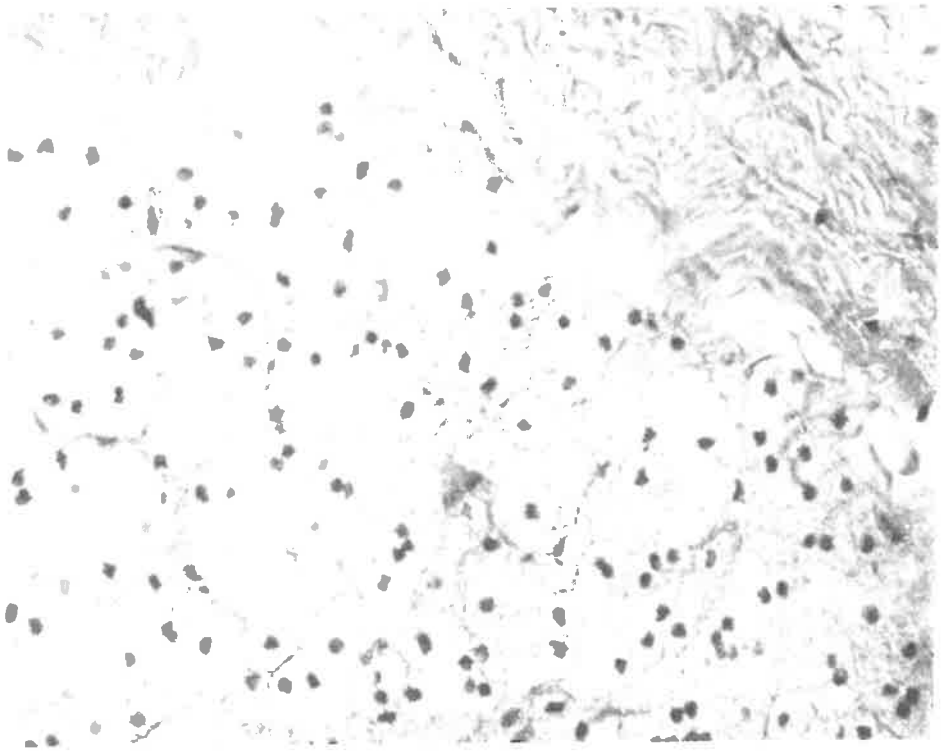

**FIGURE 7.** Xanthoid effect of silicone micronization showing some refractile globules by adjustment of the condenser. H&E. Original magnification, 200X.

**TABLE 4. Lymphocyte Versus Silicone Granuloma Matrix**

| | Lymphocytes | | | | |
|---|---|---|---|---|---|
| Granuloma | None | 1+ | 2+ | 3+ | 4+ |
| None | 7 | 24 | 8 | 3 | 3 |
| 1+ | 5 | 15 | 4 | 1 | 1 |
| 2+ | 0 | 11 | 5 | 3 | 1 |
| 3+ | 0 | 5 | 2 | 2 | 3 |
| 4+ | 0 | 0 | 5 | 5 | 8 |
| Totals | 12 | 55 | 24 | 14 | 16 |

The presence of remnants of polyurethane foam granulomas were discounted in making these assessments.

immune reaction. Even if silicone polymer is designed to coat the silica at first, the frequency with which silica and silicon are found in capsular tissue (Rudolph et al., 1978; Wickham et al., 1978; Shanklin, 1991, 1993; Silver et al., 1993) and lymph nodes (Wintsch et al., 1978; Truong et al., 1988; Shanklin, 1991, 1993) indicates release of silicon dioxide as part of implant ageing and conformation to the implant site during capsule formation. The results of

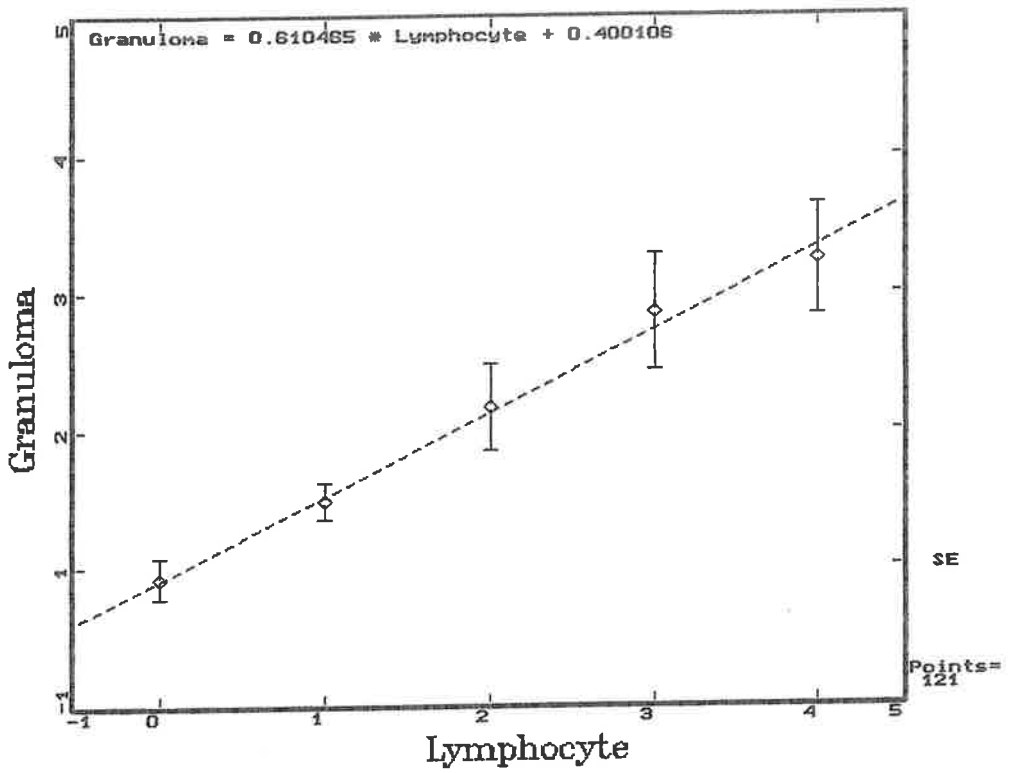


**FIGURE 8.** Regression plot of intensity of granuloma formation against lymphocyte response as independent variable. The specific regression equation for slope is not to be taken literally but as indicating relative severity of the two cellular responses. A reverse plot (not shown) indicates a lag in granuloma development as a statement of sequence of cellular events. Data from Table 4.

this study strongly support not only the fact of immune processing by cellular infiltration but also indicate something of the sequence of events, with lymphocyte responses in 90% of samples followed by progressive granulomatosis in 63%, especially after bulk deposition of silicone into periprosthetic tissues.

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# SILICONES USED IN LONG-TERM IMPLANTABLE MEDICAL DEVICES AND RESULTANT DISEASES

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*Long-term implantable medical devices require materials that are resistant to degradation by the corrosive environment of the body (or its cells) and must not release materials which cause sensitization or stimulate an immune response. Although silicones contained significant amounts of migratable low-molecular-weight cyclics (oligomers) and were known by the manufacturers to contain other migratable materials, they were thought by device users to fit those requirements. Today the true amount and nature of silicone migratables are still not openly publicized. More recent data suggest that, because of these migratables, silicone materials may not be as safe as initially thought. There were many early warnings that were, at best, missed or at worst, ignored. This review points out erroneous assumptions and some of the recent related research which may explain the chemical basis of silicone-caused diseases. It is hoped that continued exposure to silicone-caused diseases can be stopped worldwide, and agreement that silicones are involved with delayed toxicity can be reached among the medical community.*

## INTRODUCTION

Early warnings about the hazards of low-molecular-weight migratable materials in implantable devices (Bischoff, 1972) have been ignored. This is especially true with most silicone gels and elastomers which contain low-molecular-weight silicone semivolatile materials called cyclics and macrocyclics. Soft solid materials used in facial and body implants contain silicone softening or plasticizing fluids. Indications from the breast implant global settlement response and new litigation on other silicone-based devices, such as Norplant and face or body cosmetic implants, suggest that we are now in the midst of an epidemic with thousands of women and

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2. Abbreviations: CS, centipoise; CSA, Council on Scientific Affairs; DC, Dow Corning; FDA, Food and Drug Administration; GC, gas chromatography; LMWC&LS, low-molecular-weight cyclics and linear siloxanes; 2,6-cis, 2,6-cis-diphenylhexamethylcyclotetrasiloxane.

3. Key Words: delayed toxicity, immune response, migratable materials, sensitization, silicone, silicone cyclics, silicone macrocyclics, silicone migratables, silicone-related disease.

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children ill from silicone-related diseases. Causation concerning women and their children has been discussed by several authors (Kessler et al., 1992; Brautbar et al., 1994; Levine and Llowite, 1994; Teuber and Gershwin, 1994).

The composition of silicone elastomers, adhesives, and gels varies depending on the specific application for which they were originally intended. The chemical processes used in the manufacture of silicone polymers control the amount of small, low-molecular-weight polymer species known as cyclics and macrocyclics. These materials can be detected easily by gas chromatography (GC) (Carmichael et al., 1966). It is likely that the nature and the amount of these and other migratables from silicone devices are important to the type and severity of illnesses found in humans with implants. Due to the extreme secrecy assigned to the ingredients used in these devices, as well as their processes and composition, medical professionals and FDA scientists are handicapped in assuring that the devices are nontoxic. There is currently no way of knowing the number or nature of the toxic materials being delivered to humans via migration from long-term implants made of silicone.

The information being obtained in the discovery process of breast implant litigation, continues to reveal many of the erroneous assumptions that were made concerning the "safety" of silicones. Information previously withheld concerning the interactions of silicone with the body — its organs, tissues, and immune systems — is slowly becoming known. An example of such interaction is provided below in the discussion on the behavior of cyclic tetramers in animals. Testing to indicate sensitization to silicone is another example. Because the potential metabolite silica was not considered or tested, these tests to determine sensitization have been somewhat unsuccessful in previous years. Recent work has shown how silicone is transformed to silicates and silica in the blood and/or organs of humans (Garrido et al., 1994). Smalley et al. (1994a,b,c) have shown that the lymphocytes of patients exposed to a wide variety of silicones recognize several types of silica. More discussion on the importance of these two discoveries follows.

To prevent further exposure of hundreds of thousands more people to implant-related disease, future efforts toward testing of materials for true biocompatibility should be better defined before extended, long-term volume use of new materials is initiated. It is hoped that this review of silicone technology as it pertains to silicone bleed and macrocyclics, together with some old and new technical information concerning pharmacological activity of silicone, will assist in understanding causation of silicone-related diseases. It is hoped that this will help other countries in their efforts to ban silicone as an implantable material, as in cosmetic uses, where the risk of disease is greater than the benefit of the devices.

## METHODS

Several sources of information have been used for this review: 1) the general literature concerning silicone devices, their use, and complications; 2) documents obtained in litigation discovery; 3) documents released to the public by Dow Corning; and 4) the personal

experience of the author over his 42-year experience with industrial and "Medical Grade" silicone.

*Gas Chromatography Analysis Details*[1]

Quantitative gas chromatography (GC) was performed for the author on a number of critical silicone fluids and silicone gels. The conditions used were as follows: Column description: Coating 0.1 micron HT-5, Dimensions 50 m x 0.33 mm dia.; Injector program: 75°C, hold 2 min, ramp to 340°C, hold 40 min; Column temperature program: 50°C, hold 5 min, ramp to 300°C at 10°C/min, ramp to 375°C at 5°C/min, hold for 15 min; Detector temperature: 420°C; Flow rate: 2 ml/min; Pressure: 14 psi; Carrier gas: Helium.

The results shown in Table 1 indicate that the level of macrocyclics is much higher than the level indicated by Bennett and the Council on Scientific Affairs (CSA) of the American Medical Association article (1993). The CSA report quoted sizes of up to $D_{20}$. Yet macrocyclics of up to approximately $D_{40}$ were found by Carmichael et al. (1966) and in the present work, shown in Table 1. Quantities were as high as 28%, instead of the 0.5–1.2% quoted in the CSA report. Comments on the specific samples follow:

**TABLE 1. Dimethylcyclosiloxanes (Including Semivolatile Macrocyclics) and Related Linears in Specific Silicone Materials**

| Silicone product | Semivolatile content (%) | Cyclic size range $D_4 = (Me_2SiO)_4$ |
|---|---|---|
| 1. Dow Corning Injectable Silicone Fluid MDX 4-4011, lot 1 | 28 | $D_9$ to $D_{40}$ |
| 2. Dow Corning silicone gel 1975 | 28 | $D_9$ to $D_{40}$ |
| 3. Dow Corning silicone gel, pre-1968 model | 5 | $D_7$ to $D_{40}$ |
| 4. Dow Corning silicone gel, 1985 explant | 7 | $D_4$ to $D_{40}$ |
| 5. Dow Corning 1000-cs dielectric 200 fluid, lot 074715 | 0.5 | $D_4$ to $D_{40}$ |
| 6. McGhan 1980 gel, explant 1992 | 1.5 | $D_4$ to $D_{40}$ |
| 7. Experimental 1980 low-bleed gel implant | 0.05 | Mostly other than D or linear series |

1. A vial of Dow Corning (DC) Medical Grade Injectable Fluid MDX 4-4011, lot 1, was available for testing. GC testing showed 28% of the fluid to be GC-elutables, with structures of approximately $D_9$ to $D_{40}$, plus related similar-size linears. The amount of the volatile cyclic ($D_4$–$D_8$) and related-size linear siloxanes is nil; their removal was successful. The question remains, however, as to how the 28% low-molecular-weight cyclics and linear siloxanes (LMWC&LS) that were found interact in mammals. The 1978 clinical trial (the

[1]The experimental effort documented in this article, concerning quantitative analysis of silicones for their macrocyclic content (Table 1), was performed under contract for the author by Neil Spingarn of S & N Laboratories, Santa Ana, CA, in May and July, 1992.

latter part of FDA's IND 1702) of facial injectable silicone fluid was discontinued early because of severe patient complications (see also fn. 4, p. 121).[2]

2. Samples were found which represented one of the first lots of responsive silicone gel used in the new implants in about 1975. GC testing again indicated 28% GC-elutable species, with a structure similar to sample 1, above. In this situation, $D_{40}$ is approximately 10% of the molecular weight of the 1000-centipoise (cs) silicone fluid diluent that was in the gel at approximately 70–80%.

3. Samples of gel from a pre-1968 "Cronin" device showed about 5% GC-elutable species ($D_7$ to about $D_{40}$ with related linears). This level is about the same as most solid silicone elastomers.

4. An explanted Dow Corning 1985 implant (DC complaint MW3530) showed about 7% GC-elutables ($D_4$ to about $D_{40}$ with related linears). If the control test on this gel passed the DC specification quoted in the CSA study, then the indication is that depolymerization occurred, producing the adjuvants $D_4$ and $D_5$ (LeVier and Boley, 1974) while the device was implanted in a woman. This event suggests that in-place control was inadequate to ensure that all of the solid room-temperature-active catalyst was removed.

5. A sample of Dow Corning 1000-cs dielectric grade 200 fluid, lot no. 074715, showed only 0.5% GC-elutables ($D_4$, $D_5$, $D_6$ to $D_{40}$) with low levels of linears. This is a low level of LMWC&LS. If this lot were stripped of volatile materials using heat and vacuum, one might expect it to perform better than Dow Corning's MDX 4-4011, used in the above-mentioned 1978 injectable silicone fluid study.

6. A McGhan explant showed only 1.5% GC-elutables ($D_4$, $D_5$, $D_6$ to about $D_{40}$) with low levels of linears. Even though this level is lower, alleged illnesses still occur with these implants.

7. A gel sample from an implant made in a 1978–1981 research effort using nonequilibrium polymerization showed the lowest level, only 0.05% GC-elutable materials. Two pair of these implants gave moderate unilateral contracture but with no inflammation.[3]

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[2]The unpublished 1978 clinical trial is the latter part of the FDA's IND 2702.

[3]Results of experimental program on low-bleed breast implants. (See page 122, *An Experimental Breast Implant with a Gel Containing Very Low Amounts of Silicone Oil*, for additional details.)

## THE EVOLUTION OF THE MYTH THAT SILICONES ARE SAFE AND NONTOXIC

This section of this review will include some typical examples from the history of silicone developments and the errors and assumptions that caused the myth to develop.

*Cosmetic Use and Breast Augmentation Using Silicone Fluid Injection*

At the time of reported complications about the cosmetic use of injected silicone fluid, the effects of injecting silicone fluid into the body's tissue, now known to be severe, were ignored by silicone producers and surgeons as anecdotal and/or due to the use of adulterated silicone fluid promoted by Sakarui, Stein, and Kagan (Kagan, 1963). One of the misleading conclusions from implant qualification testing of this period was the interpretation that the exceedingly thin capsule which developed around silicone fluid injected into tissue was an indication of its inertness. The promoters of the Sakarui formula of injectable silicone, which has been reported to have 1% animal and vegetable fatty acids added to the silicone fluid, believed that the impurities would strengthen the thin, weak pseudocapsule. The additive was intended to cause a thicker pseudocapsule, to prevent easy rupture of the capsule, which could result in puddling, migration of, and a repeated (very extended) interaction with macrophages.

It is surprising that, among patients known to be injected in approximately 1960 with the adulterated silicone fluid, and reporting severe encapsulation and firmness, some have only little to moderate levels of systemic illness. It is unfortunate that little attention was paid to the article by the Japanese author Yoshida reporting Human Adjuvants Disease (Yoshida, 1973). In 1978, the Society of Plastic and Reconstructive Surgeons, Dow Corning, and the FDA proceeded with a final silicone injection program for facial atrophy. That clinical trial, FDA's IND 2702, resulted in the tragedy of the patient referred to as CA losing her face.[4]

*Lack of Concern about Oils in Medical Grade Silicones*

The author was aware in 1972, at the time he was persuaded to transfer to Dow Corning's Medical Products Business, that opportunities for the development of real "Medical Grade" materials were being overlooked. His transfer was an effort to help develop new silicone devices and new materials for the devices.

No concern was expressed internally over the silicone oil content of silicone elastomers or bleed from breast implants. There was significant concern over the extreme oiliness of an early lot of Responsive Gel–filled implants in 1975. That concern, however, was more toward marketing problems than the causation of illness. Seventeen years earlier it was known that polydimethylsiloxane polymers could be made free of semivolatile (macrocyclic) silicone oils

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[4]Court citation: In the District Court of the Third District in and for Salt Lake County, State of Utah CA, Plaintiff vs. Broadbent & Woolf, Inc., a Utah corporation, Robert M. Woolf, individually, Dow Corning Corporation, American Society of Plastic and Reconstructive Surgeons, and Dr. Robert Goldwyn, defendants. Civil No. C83-7367.

by using a process similar to that used for methyltrifluoropropylsiloxane polymers (solvent-resistant silicone rubber).

Polydimethylsiloxane polymers, made by equilibrium polymerization with strong acid or base catalyst, contain macrocyclics with up to 40 or more dimethylsiloxane units in a ring. Silicone fluids endblocked with trimethylsilyl groups, such as 1000-cs fluids, also contain similar-size linear molecules.

By using cyclic trimers and nonequilibrium polymerization with sodium or lithium catalyst, polymers can be made free of these macrocyclic and related linear species, thereby making less toxic polymers per the recommendations of Bischoff.

*An Experimental Breast Implant with a Gel Containing Very Low Amounts of Silicone Oil*
Using the above techniques, an experimental breast implant gel was prepared by the author that had an extremely low macrocyclic content of 0.05 percent (see Table 1). The control concept was to have only polymer species of a rake-type structure, sufficiently branched so that their entry into the envelope was very limited and very little silicone could pass through as bleed. Devices in a very small marketing trial showed that the slightly higher consistency gel and lack of softening of the envelope by small silicone migratables interfered with performing closed capsulotomies. This was disappointing to the plastic surgeon but obviously a safer device when exposed to mild trauma, like hugs. Another surgeon reported moderate unilateral contractures in two patients, but no inflammation.[5]

*Lack of Concern about Reaction with Macrophages*
At a Plastic Surgery national meeting early in 1973, Dicran Goulian, M.D., indicated and warned that the safest gel consistency would be one that could not be picked up by macrophages.[6] This extremely interesting comment suggested that the evaluation of silicone gels of various consistencies be performed using boluses in prepared pockets in tissue planes. Movement of the tissue in relation to the gel sample in the tissue planes would slow encapsulation, as compared to evaluation in muscle, and allow for more exposure to macrophages and transfer to other areas of the body. My manager stated that "We (Dow Corning) know all we needed to know about the toxicity of silicone." The proposed study was not considered. In about 1977, however, such a study was performed at American Heyer-Schulte showing that silicone fluid and gels, with consistency up to a firm, zero-slump or nonflowable type, were transferred in a particulate fashion to the vital organs.[7]

*Contracture with Feverish Inflammation and Severe Pain: A Typical Occurrence?*
In approximately 1977, while I was at American Heyer-Schulte, our personnel director reported that a friend with implants had severe contracture with feverish inflammation and

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[5]Early unpublished results of very small market trial, in 1981 and 1982.
[6]Personal communication, conversation in person, 1973.
[7]Unpublished results, except for multidistrict litigation deposition disclosure.

severe pain causing sleepless nights. Since I was working closely with a surgeon concerning American Society of Testing and Materials (ASTM) specifications at the time, I asked him to see the woman. The lady with this complication reported seeing the surgeon, but I had to call him a few weeks later to learn that her situation was not unusual but a "typical contracture." In my opinion, this is an indication of severe silicone bleed involvement with macrophages.[8]

*The Transfer of Migratable Silicones from Device to Tissue and Blood*

One of the most serious concerns, expressed at the FDA Alternatives To Silicone Breast Implants Workshop of October 21, 1994, was which solvent should be used to determine the amount and type of extractables from devices. Many biomaterials engineers and other medical professionals, having vested interests in having devices available, believe and infer publicly that low-molecular-weight materials (oils) cannot cross the aqueous media between the device and adjacent tissue. Therefore, they strongly suggest that only saline should be used as extraction media. Many device manufacturers believe this to be a reasonable fact. I strongly believe that using saline is wrong, since it will not extract the oily, low-molecular-weight silicones. A range of solvents with various polar and nonpolar characteristics should be used to determine which extractables with the potential to transfer to tissue and blood are in implant materials.

This issue is extremely important because the FDA apparently has no mandate from Congress to regulate materials used in devices. Currently, the FDA apparently will allow any level of migratables in silicone for long-term implantation.

The following description of the commercial process for disperse dyes used for coloring polyester and nylon should serve as an example in explaining and proving how low-molecular-weight molecules can transfer between a particle's surface (dye) and polymeric material surfaces in a aqueous medium. The uptake of toxic molecules from materials used in device construction by cells and tissue is the reverse process, where low-molecular-weight materials transfer by contact from the implant to the cells and/or tissue.

Many desirable colored dyes are very insoluble in even hot water, a preferred medium for dyeing fabric. These dyes are prepared in extremely fine particle size so that, with the help of dispersants and surfactants, Brownian motion will keep most of the particles in suspension without stirring. Fabrics then can be immersed in an aqueous hot bath of these particles to transfer dye molecules to the fibers by simple intermittent contact. Prescription plastic eyeglass lenses also are colored commercially in this manner.

*The Importance of Chemical Variation in Gels and the Effect on Silicone Gel Bleed Rates*[9]

Silicone "bleed" from a gel-filled breast implant consists of mobile, migratable (or strong solvent–extractable) silicone molecules that are not tied to the gel network. They must be of a

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[8]Personal communication, telephone conversation, 1977.

[9]Personal knowledge and discovery in injectable silicone and breast implant litigation.

suitable structure (cyclic or linear) in order to enter the elastomer shell and diffuse through the shell membrane. The exact amount and nature of the migratables changed significantly during the evolution of the breast implant device from those migratables in the original "Cronin" implant in that the fluid gel implants contained linear fluids at about 70–80% of the gel. High levels of macrocyclics were also in some of the fluid gel implants introduced in about 1975.

The original silicone gel used in the "Cronin" implant was based on a polymer that had such a low amount of tetramethyltetravinylcyclotetrasiloxane reactive cross-linking sites that not all of the polymer chains had reactive vinyl groups on them. This yielded a gel with about 50% migratables of a complex branched nature. In the 1968 to 1974 time frame, as consistency was reduced to softer more liquid gels to accommodate surgeons (by reducing the siliconehydride crosslinker), migratables increased. A portion of the migratables had to be of lower molecular weight and more of them linears which, in turn, caused a lowering of both modulus and strength of the envelope. The recent GC testing indicates about 5% macrocyclics and related linears in a pre-1968 Dacron-patched, seamed Cronin model (see sample #3, Table 1).

In 1975, the Dow Corning Task Force, assigned to coordinate and rush the completion of the development of the new fluid gel–filled breast implant, had reports that salespersons' samples had high bleed rates. At the time, laboratory studies did not confirm the high bleed rates using other drums of ingredients. The responsive gel introduced in 1975 was formulated with between 70 and 80% nonreactive linear medical grade 1000-cs fluid. All this fluid would be extractable along with a portion of the nonvinyl-containing portion of the reactive polymer as mentioned above. One 1975 lot of gel tested recently by GC showed 28% macrocyclics (see sample #2, Table 1). This high level of macrocyclics was most likely the cause of the high bleed rates mentioned above. The macrocyclics and related low-molecular-weight linear molecules cause more swelling of the envelope to allow for higher bleed rates and also a larger loss of modulus and strength of the envelope which increases the likelihood of rupture.

An additional mechanism which increases bleed rates is compression of the device which leads to expansion of the envelope. While the envelope is in the stretched state, silicone bleed molecules migrate into the stretched area of the membrane. Half of the bleed molecules in the envelope are "pumped" to the exterior of the device when it is relaxed. The remainder returns to the interior of the device. Recently, it has been reported that the pseudocapsule surrounding the device can be stretched up to 35%.[10] I believe that this daily stretching causes the pumping of bleed directly into the breast area tissue.

The change in the manufacture of medical grade silicone fluid from a simple chlorosilane hydrolysis to polymerization using catalysis by solid particles, with surface sulfuric acid reactivity, led to a very fast, less-controllable process. The result, apparently, was the creation

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[10]Deposition of Robert L. Pizali (p. 138), Citation: Superior Court of California, County of San Diego, Kali Korn vs. Dow Corning et al., Los Angeles, CA., Case No. SC014350.

of lots or drums of fluids with high levels of low-molecular-weight cyclics and linear siloxanes (LMWC&LS). Once the larger LMWC&LS. ($D_7$ or $D_8$ and above) are made in a polymer, they cannot be removed using heat and vacuum. It remains unknown how many women are suffering from the effects of these high bleed rate devices, because very few explanted devices have been tested for LMWC&LS content.

*Comment on Two Dow Corning Studies of $^{14}C$-Labeled Cyclic Silicones*

The 1970s effort by Dow Corning in pharmacological silicones is becoming well known to many. Bennett and Aberg (1975), in a 147-page monograph, described preclinical testing for using 2,6-cis diphenylhexamethylcyclotetrasiloxane (2,6-cis) in a clinical study in humans for metastatic carcinoma of prostatic origin. This study also noted the fact that 2,6-cis or its metabolites crossed the placental barrier of pregnant mice. A lesser known $^{14}C$ study (abstract only published, Le Beau and Gorzinski, 1973) compared 2,6-cis to octamethylcyclotetrasiloxane ($D_4$). The methods and data of each study are summarized in Table 2. The $D_4$ study used a dose of only 1 mg/kg. The Bennett and Aberg study used 150mg/kg of 2,6-cis. A direct comparison at the high dosage rate should have been made, but apparently never was conducted. Use of the autoradiographic technique, which illustrates the organs to which the silicone was transferred, was very impressive and should be used in future evaluations of this type.

## RECENT RESEARCH THAT WILL HELP IN UNDERSTANDING CAUSATION

*A New Chemical Path Related to Chemical Causation*

Relatively new research by Garrido seems to explain the long incubation period of silicone-related disease. Garrido, Pfleiderer, and colleagues have shown, using NMR of $^{29}Si$, that an oxidation process within the body's organs and blood converts polydimethylsiloxanes to partially oxidized silicates and silica (Pfleiderer et al., 1992, 1993; Garrido et al., 1993, 1994). It appears that polydimethylsiloxanes from bleed or exposed gel, macrocyclics from gel or elastomers, and the silicone polymers in silicone rubber, particularly wear debris, can be oxidized to silicates and silica. The NMR patterns which were found explain the structures in relation to the various stages of oxidation.

The second step in this proposed causation of disease mechanism concerns the stimulation of disease by silica materials as is described by Haustein et al. in the article "Silica-Induced Scleroderma" (1990) and other literature (Haustein and Ziegler, 1985; Poliard and Collett, 1954).

These mechanisms explain why the toxic effects of breast implants are worse after rupture and exposure to fluid-type gels; it is due to the large amount of gel that macrophages pick up. Also, the reason such a long incubation period is required for the development of some systemic illness is shown to be the smaller amount of gel bleed and the migration of silicone fluids from other silicone rubber devices. The low-bleed-rate devices used in the ongoing FDA

**TABLE 2. Comment on Two Dow Corning Studies of $^{14}C$-Labelled Cyclic Silicones [ACTA Volume 36, Supplement III, 1975, Chapter 10 (Schmiterlow and Sjogren, 1975) and Abstract No. 18 of the 1973 Program of the Society of Toxicology (Le Beau and Gorzinski, 1973)]**

Introduction: One conclusion of the ACTA study was: "The substance 2,6,cis-diphenylhexamethylcyclotetrasiloxane (2,6-cis) obviously passes the placental barrier, a fact to which special attention should be paid." Abstract 18 states, "Thus, enterohepatic circulation was evident for both compounds" (2,6-cis and octamethylcyclotetrasiloxane). The study details are outlined and specific comments made.

| Study details | ACTA study | Abstract # 18 | |
|---|---|---|---|
| Dose rate | 150 mg/kg body weight<br>0.150 g/kg body weight | 1 mg/kg body weight<br>0.001 g/kg body weight | |
| Material used | $^{14}C$-labeled 2,6,cis-diphenyl-hexamethylcyclotetrasiloxane | $^{14}C$-labeled 2,6,cis-diphenyl-hexamethylcyclotetrasiloxane | $^{14}C$-labeled octamethylcyclo-tetrasiloxane ($D_4$) |
| Method of analysis | Autoradiograms and discussion on the distribution of silicone | Recovery of $^{14}C$ species and metabolites | |
| Recovery results of $^{14}C$ in 48 hrs | | 80% eliminated | Implied same as 2,6-cis |
| Recovery at end of 3 to 4 days | | 89 +/- 5 (n = 6) | Implied same as 2,6-cis |
| Method of administration | | Oral IV | Oral IV |
| Method of elimination | | | |
| Expired air | | 3.3% 2.8% | 23% 18.9% |
| In urine | | 60 % 65% | 55.5% 71.9% |
| In feces | | 28% 20% | 8.4% 1.8% |
| Total recovered | | 91.3% 87.8% | 86.9% 92.6% |
| Average recovered | | 89.5% | 89.75% |
| Amount through bile | | 45% | 11.5% |

Comment: From this tabulation of data, it appears that the $D_4$ was merely more volatile. The dose used in the abstract #18 study was also miniscule compared to that used in the ACTA Chapter 10 study. The obvious conclusion concerns the dose rate and suggests that a repeat study be done with a dose of 150 mg/kg body weight using $^{14}C$-labeled $D_4$ through $D_{40}$ and related linears (the real range of macrocyclics and low-molecular-weight linears in breast implants). The techniques of both studies, or at least the ACTA study, should be used.

critical need program may take much longer to initiate disease than the older standard devices. The textured surface of newer devices has been evaluated in terms of the release of silicone particles from the exterior envelope (Copeland et al., 1994). "The capsules that had formed around virtually all textured-surface implants had silicone fragments present either in extracellular spaces, in vacuolated histiocytes, or in the form of foreign-body granulomas in surrounding fibroadipose tissue but not in capsules associated with smooth-walled implants." It will be interesting to see if the migration of this silicone will cause more serious disease.

*Antisilicone Antibodies*

It is interesting that antisilicone antibodies were first identified in two patients who showed severe, apparently immune-mediated, reactions to ventriculoperitoneal shunts (Goldblum et al., 1992). It is amazing that these devices were used for three decades before the cause of this complication was identified. Wolf and coauthors successfully proved that antisilicone IgG antibody levels varied, possibly in relation to the silicone exposure level (Wolf et al., 1993). A larger study, "Antibody to silicone and native macromolecules in women with silicone breast implants," by Vojdani and others, identifies additional antisilicone antibodies, including Myelin Basic Protein Antibodies (Vojdani et al., 1994).

## DISCUSSION

*Some Hypotheses as to the Interaction of Materials with the Immune System and Tissue*

Based on the research of Garrido, Smalley, and their associates, one might be tempted to make a sweeping statement that silicones are uniquely dangerous since their migratables are oxidized to silicates and silica-type structures which cause disease. Other organic polymeric material–based implants, however, cannot have migratables that will oxidize to silica. We must remember that Human Adjuvants Disease, originally called to our attention by Yoshida, was a result of the use of both silicone and paraffin (oils) (Yoshida, 1973). The only similarity between the two materials appears to be that they both are difficult to oxidize, which could indicate a longer-term residence of migratables in the cells that are performing the oxidation process. Assuming that the oxidation is occurring in macrophages, the immune system could then be exposed to specific cytokines in a chronic manner, causing disease.

A second possibility for causation of disease may be the direct interaction of silicone cyclics and macrocyclics with cells or specific tissue. Radiographic studies of radio-labeled $D_4$ and 2,6-cis showed that the cyclics were retained in a significant amount in fat and most organs. Garrido has shown that silicones circulate in the blood for years. As a macrophage expired, the silicones, including macrocyclics, would be deposited on or in specific tissues. At this point, the smaller molecules would penetrate the underlying tissue. As a new macrophage engulfed the polymer droplet on the surface, it also might be tricked into attacking the tissue/silicone cyclic mix, resulting in an immune sensitization to that tissue.

*Regulation and Recent Events Concerning Availability of Silicones for Long-Term Implants*
At the recent symposium, "Biomaterials and Medical Devices, An Industry in Transition" October 24–25, 1994, sponsored by Gorham/Interteck Consulting, it was learned that in the short term, improved and less-toxic silicones are unlikely to be developed. Discontinuance by Dow Corning and other suppliers of all products used in long-term implant devices (over 29 days tissue contact) created a crisis for small manufacturers of critical-need devices. Members of Congress and the Medical Device Manufacturers Association apparently have encouraged the FDA to make silicone materials available for critically needed devices such as heart pacemakers and orthopaedic devices. The FDA has admitted that it has never regulated raw materials suppliers, and is not authorized by law to do so (Marlowe, 1994). The FDA can only regulate device manufacturers. Two small manufacturers, NuSil Technology and Applied Silicones Corp., have worked hurriedly, in cooperation with the FDA, to make a wide variety of silicones available during the last 18 months and have made presentations at the Gorham Conference (Petraitis, 1994; Winn, 1994). The latter document indicates that 3.96% migratable silicone is still present in one of their elastomers. Only time will tell if this level of migratable silicone and the associated risk is worth the benefit of the device in which the material is used.

There is a new plan to use confidential FDA Master Files on each silicone raw material manufactured, to indicate that it is not substantially different from silicones supplied by Dow Corning or others. Both physical properties and toxicological test results will be in the confidential master files. The files will then be used by the FDA to approve the use of materials for a final device. The nature of the chemical structure and degree of toxicity of the materials used will continue to be kept secret.

## CONCLUSIONS

It is becoming more apparent that long-term medical implants will not be truly safe until tests are developed to demonstrate that the materials are safe with regard to sensitization and lack of long-term immune system response. A truly safe silicone material should not cause a mammal to develop a sensitivity to silica or antibodies to silicones. New test methods are critically needed to determine the safety of all types of polymeric implantable materials and their metabolites.

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# CELLULAR TRANSPORT OF SILICONE FROM BREAST PROSTHESES

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*Silicone gel is known to escape from clinically intact breast prostheses, through a process known as gel bleed through the elastomer shell. Multiple observers report the presence of silicone in regional lymph nodes of patients with ruptured or clinically intact breast prostheses. The mechanism of transport of silicone droplets away from the prosthesis to lymph nodes is described.*

*Using a data base of more than two hundred explanted breast prostheses and their associated capsular tissues, the path of silicone droplets has been observed. Silicone droplets are picked up by macrophages in the lumen of the capsule. The macrophages become incorporated into the capsule, where mobility of the cell is unimpeded due to the absence of a basement membrane. Macrophages move deep into collagen layers of the capsule and aggregate in deep soft tissues in perivascular locations. Macrophages containing droplets of*

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2. Abbreviations: FTIR, Fourier Transform Infrared Spectroscopy.

3. Key Words: breast, macrophage, prosthesis, silicone.

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*silicone are observed in regional lymph nodes draining the prosthesis site. The observation of silicone in sites distant from the prosthesis was confirmed using microscopically guided Fourier Transform Infrared Spectroscopy (FTIR).*

*The authors conclude that at least some of the silicone found distant to breast prostheses arrives chemically unchanged at regional lymph nodes, carried in droplets by tissue macrophages. This process occurs in patients with clinically unruptured prostheses as well as in those with ruptures.*

## INTRODUCTION

Since the introduction of silicone breast prostheses in the 1960s (Cronin and Gerow, 1964), it has been observed that placement of the implant is associated with a host response known as a capsule (Bingham et al., 1988; Brohim et al., 1992). Recent thinking has been that this capsule has potentially beneficial effects in limiting the dissemination of silicone in the event of a rupture of the elastomer shell. This phenomenon is known as a "contained rupture." However, other investigators have documented the presence of silicone in lymph nodes of patients with clinically unruptured implants (Hausner et al., 1978; Tabatowski et al., 1990, Silver et al., 1993). This observation raises questions concerning the capability of the capsule to contain silicone gel from breast prostheses.

The authors hypothesize that rather than impeding the movement of silicone from the implant site, the cells forming the capsular tissues actively participate in "clearance" of droplets of silicone from the capsular lumen. Because of the anatomic structure of the capsular tissues, the only limit to the egress of foreign material is the number and phagocytic capacity of the macrophages.

## METHODS

All observations were made on a group of more than 200 patients cared for at the University of Florida College of Medicine between 1977 and 1994. Available mammographic, histopathologic, and cytopathologic materials were reviewed. Operative notes were reviewed for observations of implant integrity.

Patients had implants removed in the process of staged reconstruction after cancer surgery, or due to symptoms related to implants placed for cosmetic reasons. Specimens accompanying the implants included cell washings from the capsule space and samples of capsule tissue obtained at the time of operation.

Cell washings were obtained by injecting 10cc of sterile saline into the capsular space and aspirating free fluid. This fluid was placed in 10cc of modified Eagle's medium. Samples prepared were cytospins, fixed in 95% ethanol and stained with Papanicolaou stain, according to methods previously published (Caffee et al., 1995).

Capsular tissues for light microscopic evaluation were fixed in 10% buffered formaldehyde and embedded in paraffin. Hematoxylin and eosin and Masson's trichrome stained slides were reviewed.

The identity of foreign material, identified light-microscopically as silicone, was confirmed using FTIR microspectroscopy, according to methods previously published (Hardt et al., 1994).

## RESULTS

*Intracapsular Space*

The cell population in the capsular space was observed to be mixed, with a predominance of mononuclear macrophage cells. Occasional eosinophils, polymorphonuclear leukocytes, or lymphocytes accompanied the mononuclear cells.

In the case of ruptured implants or implants with gel bleed, the macrophages had normal-sized nuclei, but reduced nuclear cytoplasmic ratios. Occasional multinucleate cells were present. Cytoplasm of the mononuclear cells was crowded with various-sized vacuoles containing water and clear, refractile, but nonbirefringent foreign material (Figure 1). This foreign material was identified as silicone using FTIR.

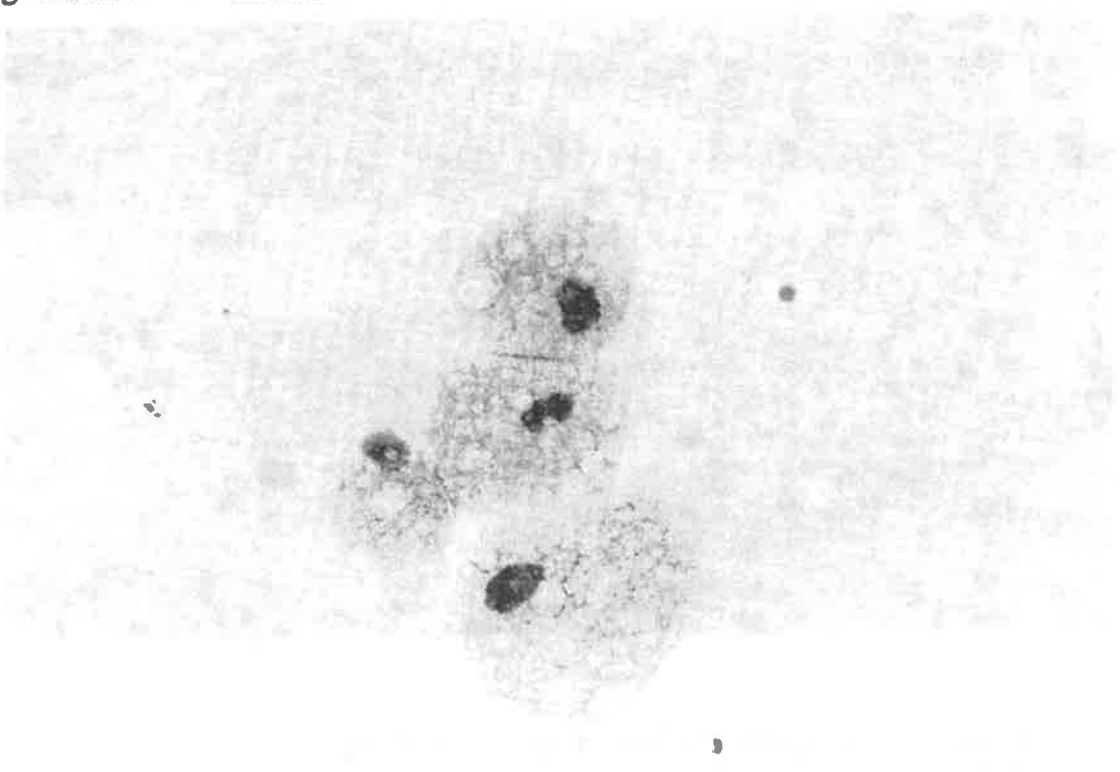

**FIGURE 1.** Cytology of intracapsular space. The predominant cell in the capsule of patients with ruptured implants or implants with gel bleed is the mononuclear macrophage. These cells are characterized by a reduced nuclear to cytoplasmic ratio due to the expansion of the cytoplasmic volume by numerous rounded vacuoles of refractile foreign material. The identity of the compound was confirmed to be silicone using microscopically guided FTIR. Papanicolaou stain at 600X.

*Capsule*

Light microscopic examination of the capsular tissue revealed an organized structure composed of layers of mature collagen with an associated capillary network. In addition to the collagen-producing fibroblasts, vacuolated mononuclear macrophages were commonly observed, as well as multinucleate macrophages in a foreign-body configuration. Foreign-body giant cells were observed in some cases in the intracapsular space, but most often were confined to the capsular layers or the soft tissues deep within the collagen layers. Mononuclear macrophages were widely distributed throughout the intracapsular space as well as throughout the collagen layers and deep soft tissues. Macrophages were conspicuous at the surface as well as in the most superficial layers of the capsule in ruptured implants and those with observable gel bleed (Figure 2). In the deep soft tissues, mononuclear macrophages were often aggregated, surrounding the vascular spaces of the capillary network (Figure 3). Occasionally, the mononuclear macrophages were seen within the lumens of vessels (Figure 4).

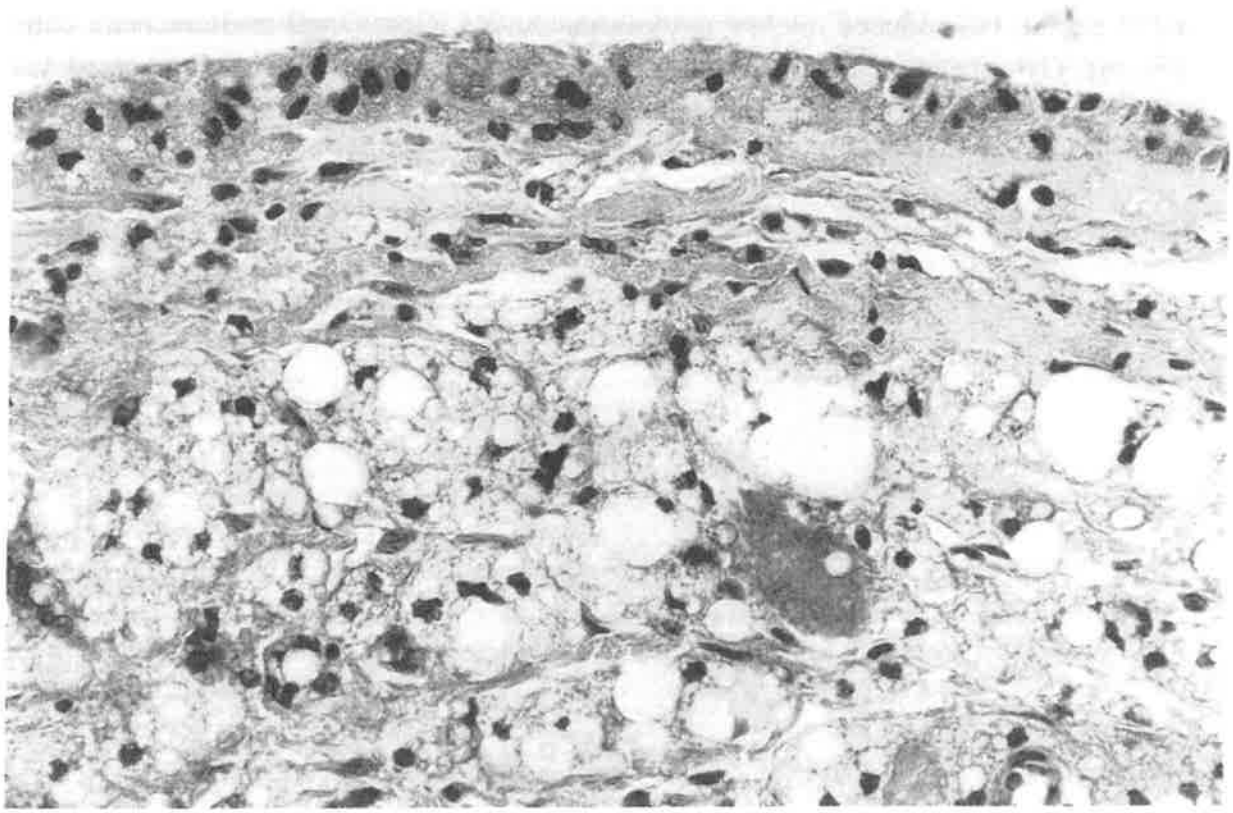

**FIGURE 2.** Superficial capsule. The layers of the capsule directly opposite the prosthesis indicate that the mononuclear macrophages of the capsular space become incorporated into capsular tissues. The most superficial layer of the capsule (at top) is composed predominantly of mononuclear macrophages of appearance similar to those in the lumen. The cytoplasm is expanded due to the presence of multiple vacuoles containing refractile foreign material. The identity of the compound was confirmed to be silicone using FTIR. In deeper layers of the capsule, the mononuclear and multinucleate histiocytes are dispersed throughout the collagen layers. Trichrome stain at 400X.

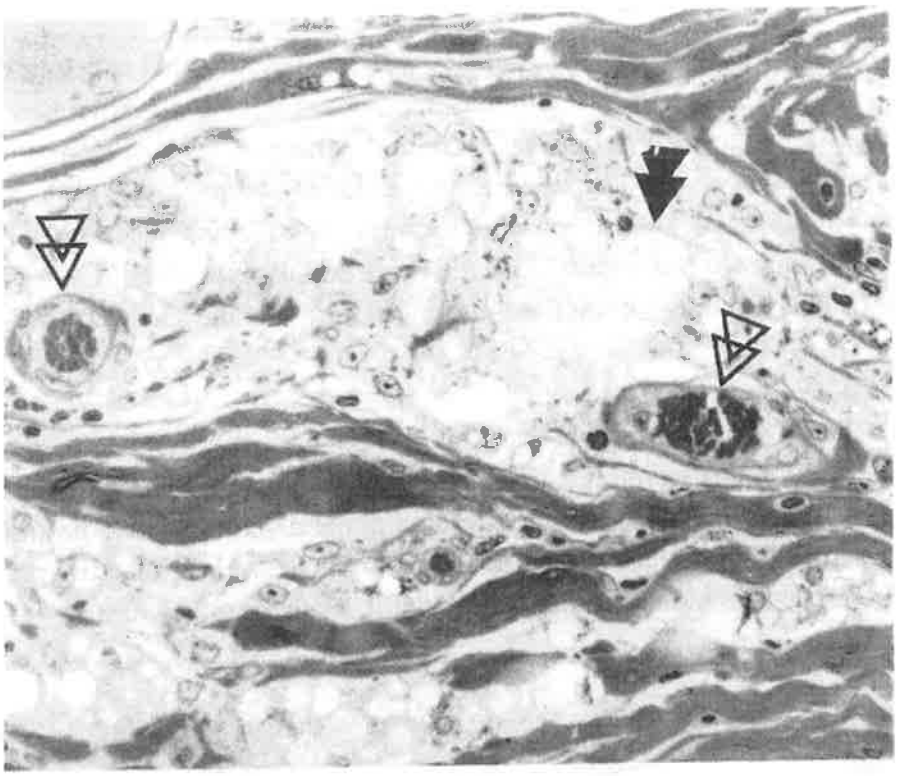

**FIGURE 3.** Perivascular aggregates of macrophages. Deep within the capsule, separating strands of skeletal muscle (note cross striations) and innumerable histiocytes are seen. These are characterized by expansion of the cytoplasm due to rounded vacuoles of refractile foreign material. One especially large vacuole is indicated by the solid arrow. Hollow arrows indicate the location of vascular spaces, all of which are surrounded by aggregates of the histiocytes. Electron microscopic thick section, stained with toluidine blue at 600X.

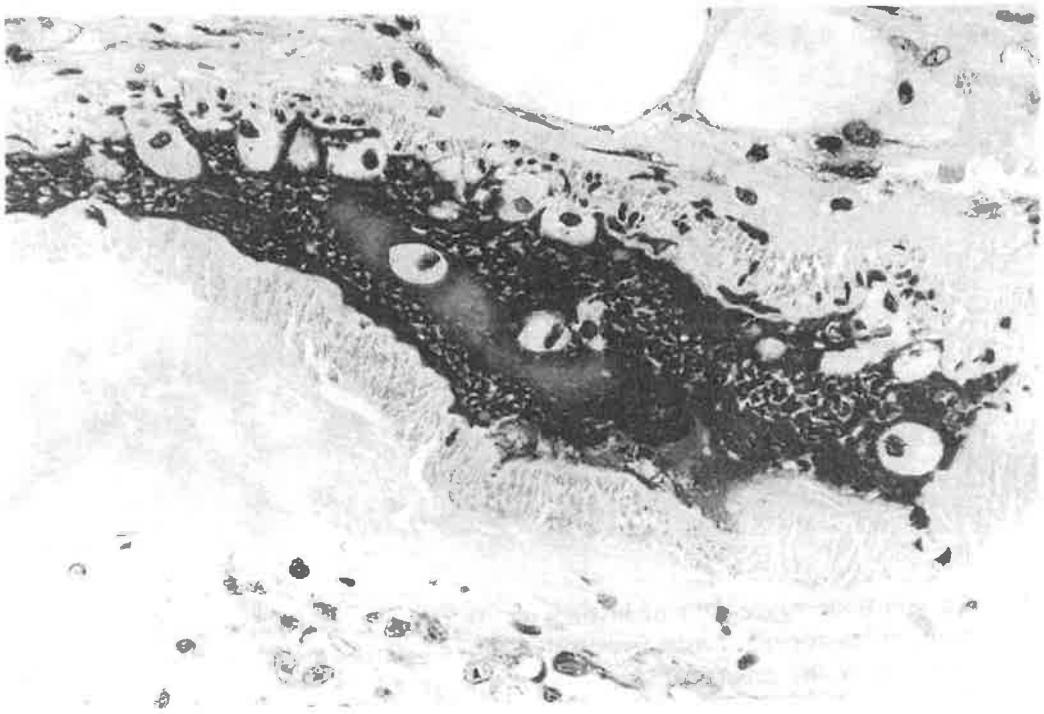

**FIGURE 4.** Macrophages in vessel. Deep within the capsular collagenous layers, a vessel is shown. The dark-staining red blood cells in the lumen highlight the pale-staining mononuclear cells, many of which are located near the vessel wall. Similar appearing mononuclear cells are in the soft tissue surrounding the vessel. Hematoxylin and eosin at 600X.

Conspicuously absent from the capsular anatomy was a basal lamina or basement membrane, such as is commonly observed in epithelial lined structures. Such structures may limit the mobility of cells capable of migration, and their absence may explain the presence of numerous macrophages deep within the capsule. Evidence of an epithelial lining of the breast implant–related capsules was not observed, except in rare instances in which squamous metaplasia of the capsule had occurred. In the three capsules in which this was observed, the change was focal, and did not involve the majority of the capsule surface.

*Regional Lymph Node*

Mononuclear macrophages were observed singly, or more commonly in aggregates, within the regional lymph nodes examined. The macrophages were vacuolated, and in many cases contained observable droplets of refractile foreign material, confirmed to be silicone by FTIR. One patient with a polyurethane foam–covered implant had irregular fragments of foreign material; FTIR spectrum indicated that polyurethane was present (Figure 5).

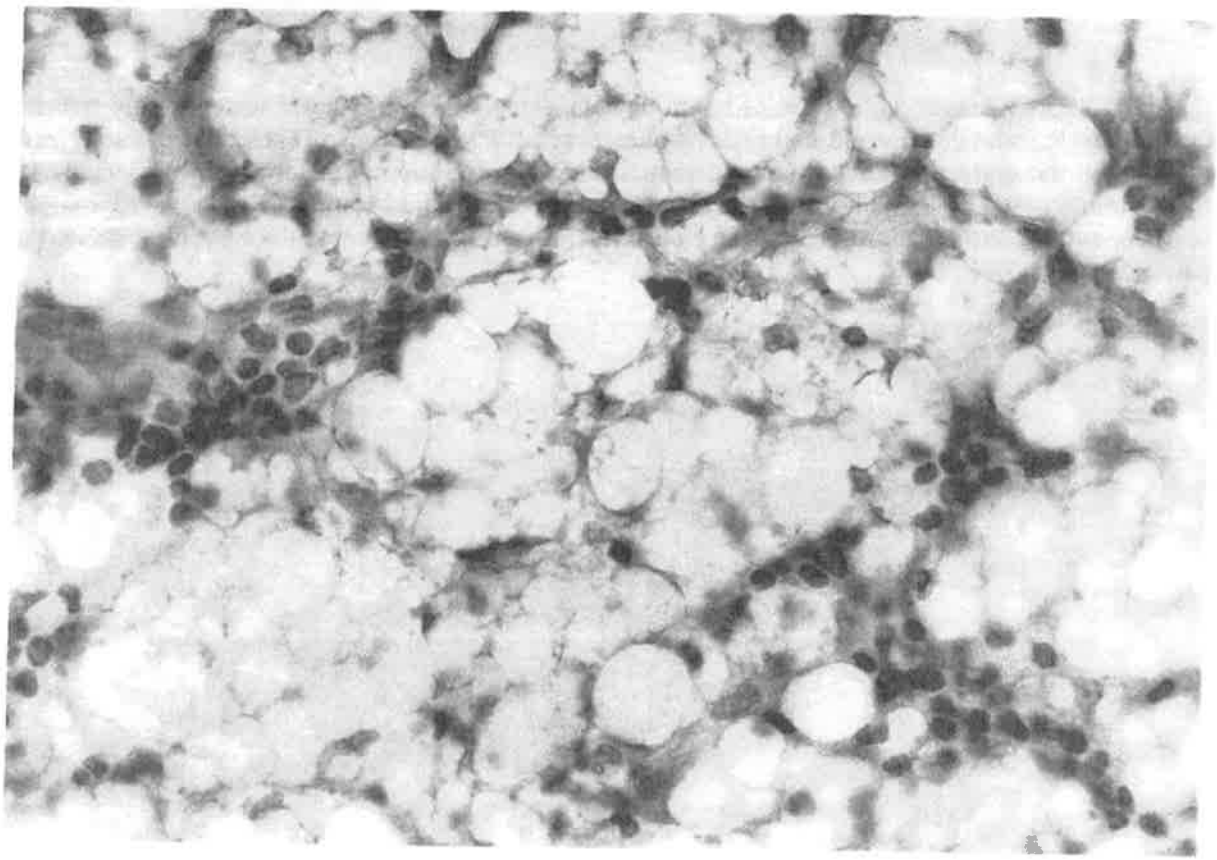

**FIGURE 5.** Lymph node aggregates of histiocytes. In patients who had lymph nodes available for review, aggregates of macrophages were frequently noted which resembled those macrophages observed in the capsular space, in the superficial layers of the capsule, and in the soft tissues deep within the capsule. In the example shown from a patient with axillary adenopathy after placement of a polyurethane foam–covered implant, irregular fragments of foreign material are noted in some of the vacuoles. FTIR indicated the presence of polyurethane foam in the lymph node. Hematoxylin and eosin at 600X.

## DISCUSSION

The lining anatomy of breast implant–related capsules is identical to that of synovium. Synovial lined spaces, or bursae, are known to occur as the body attempts to reduce friction. The observation of synovial-lined bursa formation in association with breast implants (Emery et al., 1994) is important, because synovial lining is known to have transporting capabilities (Barland et al., 1962).

Bursae have been observed to occur in response to other prosthetic devices. This phenomenon is used therapeutically in reconstructive surgery of the hand. Rods of silicone elastomer (rubber) are placed so as to induce formation of bursae, the rod is removed, and the bursa provides a friction-free space to accommodate tendon grafts (Farkas et al., 1973).

The authors conclude that anatomic evidence is sufficient to prove that placement of breast prostheses causes bursa formation. The bursa occurs secondarily to the mechanical disruption of tissue that occurs during implant placement. Because of the pendulous, mobile nature of the prosthesis, a constant source of friction is present. Friction causes the movement of particulate matter from the surface of the prosthesis. Particles are removed from the capsular space in a mechanism similar to that observed in removal of particulate matter from joints (Key, 1926). In joints, removal of particulates related to wear and tear assures maintenance of the gliding function of joints. The responsible cells are tissue macrophages.

Because of the absence of basal lamina and basement membrane, macrophages are free to carry particulate matter through the collagen layers to deeper tissue sites, and eventually to regional lymph nodes. As such, the body is constantly laboring to remove silicone from the surface of the prosthesis. Such particle movement is not peculiar to silicone, however, and may be expected to occur in association with any implanted biomaterial which causes friction.

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# SILICON-29 MAGNETIC RESONANCE OF SILICONES IN THE BODY

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*In order to assess the sensitivity of* in vivo *$^{29}Si$ magnetic resonance (MR) for monitoring implanted silicone products in the body, we developed the hardware and techniques required to obtain $^{29}Si$ MR data from samples of silicone gel with a 1.5 Tesla clinical MR system. Silicone gel samples from Même® mammary prostheses (Cooper Surgical)[1] were studied in their virgin states, as well as after having been in a saline bath for ten months, and* in vivo, *23 weeks after having been implanted subcutaneously in a rat. Virgin gel which had been removed from a prosthesis was found to have a longitudinal relaxation time, $T_1$, of 1.6 sec ± 0.3 sec; gel within an intact prosthesis had a $T_1$ of 2.5 sec ± 0.5 sec. However, relaxation time measurements of the implanted silicone gel yielded a $T_1$ value of 14.6 sec ± 5.1 sec, and the gel which had been in a saline bath for ten months had a $T_1$ of 11.5 sec ± 1.6 sec. We have attributed these changes in $T_1$ to the "bleeding" of a component of silicone from the silicone gels. This conclusion suggests two important possibilities. Firstly,* in vivo *$^{29}Si$ relaxation time measurements may be able to demonstrate whether or not silicone has been exuded from a silicone gel–filled mammary prosthesis. Secondly, MR detection*

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2. Abbreviations: CT, computed tomography; Esca, electronic spectroscopy chemical analysis; FID, free-induction-decay signal; MR, magnetic resonance; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; ppm, parts per million; RF, radio-frequency; SNR, signal-to-noise ratio; $T_1$, longitudinal relaxation time; $T_2$, transverse relaxation time; TE, echo time; TR, repetition time.

3. Key Words: breast prostheses, magnetic resonance, MRI, MRS, silicon, silicone.

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[1]These polyurethane-covered prostheses were manufactured successively by Markham Medical, Natural-Y, Natural-Y (aesthetech), Cooper Surgical, and Surgitek (Kerrigan, 1989).

*of the silicone component of the gel which can "bleed" from even an intact prosthesis is greatly facilitated by the fact that it must have a $T_1$ of less than 1.6 sec in a magnetic field of 1.5 Tesla.*

## INTRODUCTION

The need for a noninvasive and sensitive technique for characterizing interactions between silicone-based biomaterials and the body is demonstrated by the current controversy over the use of silicone gel–filled mammary prostheses, and by the lack of a reliable method for assessing the *in vivo* reaction to implanted silicone prostheses and the silicone products that can leak from an intact mammary prosthesis (Mandel and Gibbons, 1979; Baker et al., 1982; Brandt et al., 1984) The most commonly used techniques for detecting the presence of silicone in tissue include gas-liquid chromatography (Baker et al., 1982), scanning electron microscopy with an elemental detection x-ray analysis probe (Winding et al., 1988), and Esca (electronic spectroscopy chemical analysis). These techniques, however, can only be applied to excised tissue samples, and the sample preparation which is often required can itself introduce foreign materials into the sample. Moreover, the fact that silicone gel is radiopaque can limit the effectiveness of X-ray mammographic imaging, although computed tomography (CT) has been reported to be as reliable as MR imaging for the detection of intracapsular ruptures of silicone gel–filled prostheses (Eklund et al., 1988; Gorczyca et al., 1994). Proton magnetic resonance (MR) imaging and spectroscopy have successfully been used to detect ruptured breast prostheses as well as silicone products which have escaped an implant and collected in the liver (DeBruhl et al., 1992; Gorczyca et al., 1992; Garrido et al., 1993). However, these $^{1}H$ MR techniques are complicated by the intense background MR signals from protons in water and fat, and the fact that proton MR cannot detect compounds such as $SiO_2$ (a component of the prosthesis envelope). Even saline-filled mammary prostheses have been suspected of causing symptoms of rheumatic diseases, and so the effects of the prosthesis envelope must not be overlooked (Cook et al., 1994). To enable highly sensitive detection of silicone gel and envelope components which have escaped a prosthesis, as well as to determine if any break-down products are present, we propose that the combination of $^{1}H$ and $^{29}Si$ MR imaging and spectroscopy methods be used. This would also be able to detect any changes over time that may have occurred as a result of interactions with the body. Thus, the goals of this project were to develop the techniques required to obtain *in vivo* $^{29}Si$ NMR data, and to assess the feasibility of *in vivo* $^{29}Si$ imaging and spectroscopy of silicone gels and their exudates.

Silicon MR spectroscopy has been used to analyze lymph nodes and liver samples excised from rats which have received injections of an aqueous polysiloxane emulsion and others which have had silicone gel–filled prostheses implanted for 9 to 12 months, as well as to analyze blood samples from women with silicone gel–filled implants (Garrido et al., 1993, 1994) These spectra demonstrated the presence of polysiloxane, as well as hydrolyzed silicone, silica, and some highly coordinated silicon complexes, in a chemical shift spectrum

spanning almost 200 ppm (parts per million of the $^{29}Si$ resonant frequency). The chemical shift frequency of silicon nuclei in polysiloxane chains has been shown to be highly sensitive to the Si-O-Si bond angle, the length of the polysiloxane chain, and the proximity of the nucleus to the chain end (Harris and Robbins, 1978; Sternberg and Priess, 1993). Consequently, we anticipate that any chemical modifications occurring in implanted silicone gel in the body will be well described by *in vivo* $^{29}Si$ spectroscopy.

$^{29}Si$ magnetic resonance studies, however, suffer from the low NMR sensitivity of $^{29}Si$ nuclei (0.0075 relative to that of $^{1}H$ nuclei), and so have previously been carried out only in high-field MR spectrometers, to obtain an adequate signal-to-noise ratio (SNR). Also, in a 7.05 Tesla field the $^{29}Si$ transverse ($T_2$) and longitudinal ($T_1$) magnetization relaxation times have been measured to be approximately 1 second and 30 seconds, respectively (Hall and Webb, 1989, Dorne 1994). The relatively low sensitivity of $^{29}Si$ nuclei requires that the MR signal be acquired and averaged a considerable number of times, but the time between successive acquisitions should not be less than $T_1$ for an adequate SNR to be achieved. This combination of MR properties indicates that *in vivo* $^{29}Si$ MR would require an inordinately long acquisition time. However, if $^{29}Si$ magnetization relaxation is dominated by the dipole-dipole interaction, then at a lower field (1.5 Tesla, for example) the relaxation times will also be lower. Making use of the following expressions for magnetization relaxation times in a liquid-like spin system (Abragam, 1961),

$$T_1^{-1} = 2(k/\omega_0)[\tau_c\omega_0/(1+\omega_0^2\tau_c^2) + 4\tau_c\omega_0/(1+4\omega_0^2\tau_c^2)], \text{ and} \quad (1)$$

$$T_2^{-1} = (k/\omega_0)[3\tau_c\omega_0 + 5\tau_c\omega_0/(1+\omega_0^2\tau_c^2) + 2\tau_c\omega_0/(1+4\omega_0^2\tau_c^2)], \quad (2)$$

where k depends only on physical constants and the mean distance between magnetically interacting nuclei, $\tau_c$ describes the correlation time of the relative nuclear motions, and $\omega_0$ is the spin precessional frequency (12.7 MHz at 1.5 T and 59.9 MHz at 7.05 T), we determined that for $T_1/T_2 = 30$, the value of $\tau_c\omega_0$ must be 6.13; and for $T_1 = 30$ sec, $k/\omega_0$ must be equal to 0.0519 $sec^{-1}$. Thus, when $\omega_0$ is changed from 59.9 MHz to 12.7 MHz, the value of $\tau_c\omega_0$ is 1.30, $k/\omega_0$ is 0.245 $sec^{-1}$, and $T_1$ and $T_2$ become 1.8 sec and 610 msec, respectively. These estimated relaxation times suggest that if *in vivo* $^{29}Si$ MR experiments are to be carried out in a clinical 1.5 Tesla MR unit, the required recovery interval between successive acquisitions can be as low as 1.8 seconds. In this case, a $^{29}Si$ spectrum for which the signal is acquired and averaged 128 times could be acquired in less than four minutes.

## METHODS

Magnetic resonance studies were carried out in a 1.5 Tesla GE Signa® MR imaging system with spectroscopy capabilities. Radio-frequency (RF) excitation pulses were produced with a custom-made circular surface coil tuned to 12.7 MHz, and the same coil was used to detect the MR signal. The sensitive region of this coil extends approximately 30 mm from the coil

center. The MR pulse sequences employed are illustrated in Figure 1. They include a simple free-induction-decay (FID) acquisition in which the MR signal was acquired after a single 90° excitation pulse, and a spin-echo sequence in which a 90° excitation pulse was followed by a 180° refocusing pulse and the resulting "echo" signal was acquired (Abragam, 1961). The echo time, TE, is the time from the center of the 90° RF pulse to the center of the echo.

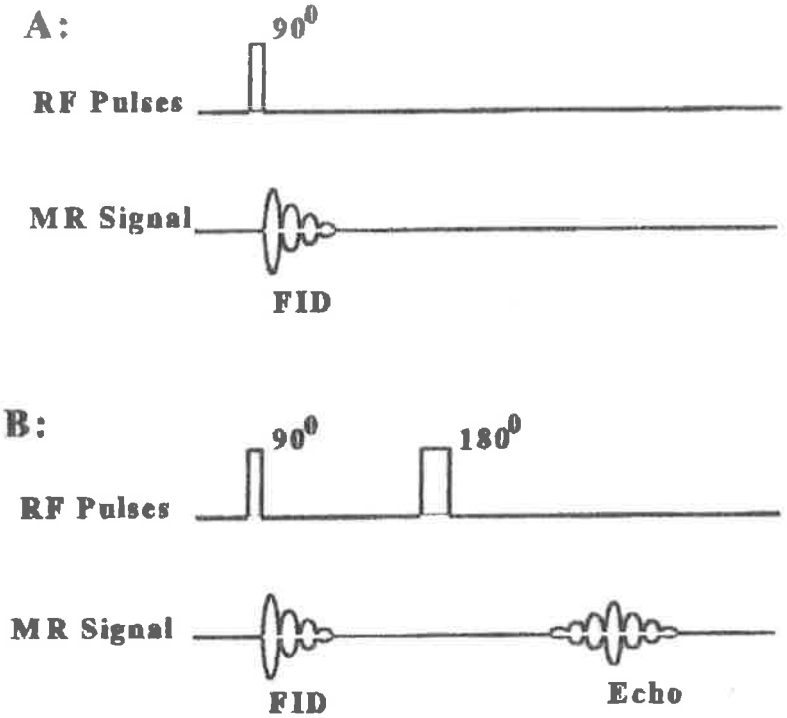


**FIGURE 1.** A) A simple spectroscopy sequence in which the free-induction-decay (FID) signal is acquired, and B) a spin-echo sequence in which the "echo" signal is acquired. The time from the 90° excitation pulse to the center of the echo is known as the echo time, TE, and the time between successive 90° pulses is the repetition time, TR.

Longitudinal relaxation times, $T_1$, were measured by acquiring $^{29}Si$ spectra with different repetition times, TR, between successive acquisitions. The total signal intensity, $S_1$, was measured from the amplitude of the single peak in each spectrum, and these values were fit to the expression

$$S_1 = S_0[1 - \exp(-TR / T_1)], \tag{3}$$

using a two-parameter nonlinear least-squares-fit algorithm to determine the values of $T_1$ and $S_0$. Similarly, transverse relaxation times, $T_2$, were computed by measuring total signal intensities, $S_2$, with a spin-echo sequence with different echo times, TE, and fitting the measured signal intensities to the expression

$$S_2 = S_0 \exp(-TE / T_2). \tag{4}$$

All of the silicone gel samples studied were taken from identical Même® mammary prostheses (Cooper Surgical). One sample of the gel (19 ml) was stored in a sealed glass

container throughout the study and is referred to hereafter as the "virgin" gel. A sample of this silicone gel (~ 5 g) was also implanted subcutaneously on the back of a 250 g female Sprague-Dawley rat. This rat was part of a larger study of the migration of silicone products through the body. The gel sample was studied *in vivo* after having been implanted for 23 weeks. Additional $^{29}Si$ relaxation time measurements were carried out on the silicone gel within an intact Même® prosthesis, as well as on a sample of Même® gel which had been placed in a bath of sterile saline and sealed in a glass container for ten months.

## RESULTS

$^{29}Si$ relaxation time measurements obtained from the virgin silicone gel sample are shown in Figure 2. The total signal intensity is plotted as a function of TR and TE. The relaxation times measured for each of the gel samples studied are listed in Table 1. These measurements show that in a 1.5 Tesla field the value of $T_1$ for $^{29}Si$ in this virgin gel is 1.6 sec ± 0.3 sec, whereas $T_2$ has a value of 172 msec ± 28 msec. The quoted uncertainties are the measurement standard deviations computed by the nonlinear least-squares-fit algorithm. Surprisingly, the measured $T_1$ value for $^{29}Si$ in silicone gel which had been implanted in a rat for 23 weeks was 14.6 sec ± 5.1 sec, and the corresponding value of $T_2$ was 158 msec ± 5 msec. The magnetization decay curves, obtained *in vivo*, are plotted in Figure 3. An *in vivo* $^{29}Si$ spectrum of the implanted silicone gel is shown in Figure 4. This spectrum was acquired using the FID acquisition sequence shown in Figure 1 with a repetition time of four seconds, has a signal-to-noise ratio (SNR) of 8, and is the result of averaging the MR signal 128 times. To the best of our knowledge this is the first $^{29}Si$ spectrum ever to be acquired *in vivo*.

**TABLE 1** **$^{29}Si$ Magnetization Relaxation Times in Silicone Gels, in a 1.5 Tesla Magnetic Field**

| Silicone gel sample | $T_1$ (sec) | $T_2$ (msec) |
|---|---|---|
| "Virgin" gel | 1.6 ± 0.3 | 172 ± 28 |
| Intact Même® prosthesis | 2.5 ± 0.5 | 177 ± 33 |
| Silicone gel in saline bath for ten months | 11.5 ± 1.6 | 158 ± 5 |
| Silicone gel implant in a rat for 23 weeks (in vivo) | 14.6 ± 5.1 | 152 ± 5 |

The silicone gel within the intact prosthesis has a $T_1$ of 2.5 sec ± 0.5 sec and a $T_2$ of 177 msec ± 33 msec, whereas the gel which had been bathed in saline for ten months has a $T_1$ value of 11.5 sec ± 1.6 sec and a $T_2$ of 152 msec ± 5 msec.

## DISCUSSION

Transverse relaxation times of $^{29}Si$ in silicone gel were measured to lie within the range of 158 msec to 177 msec in a 1.5 T field. Longitudinal relaxation times of the same samples, however, ranged from 1.6 sec to 14.6 sec; this value increased while the gel was implanted in a rat. An *in vivo* $^{29}Si$ spectrum of silicone gel which had been implanted in a rat for 23 weeks

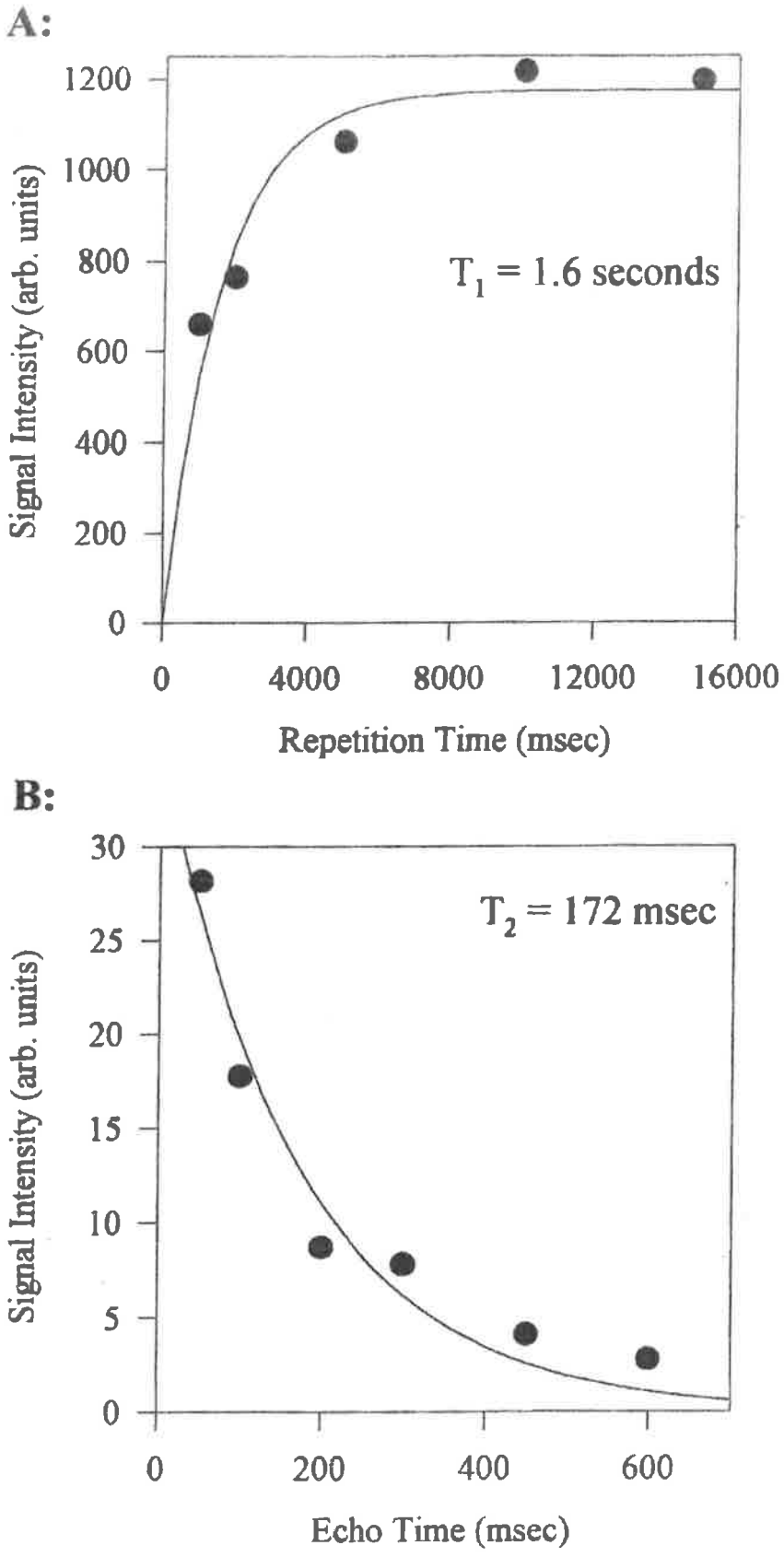


**FIGURE 2.** Plots of the $^{29}Si$ MR signal intensity, for a sample of virgin silicone gel from a Même® mammary prosthesis: A) as a function of repetition time (TR); and B) as a function of echo time (TE). The solid line plots show the results of nonlinear least-squares fits to equations 3 and 4, to determine the values of $T_1$ and $T_2$, respectively.

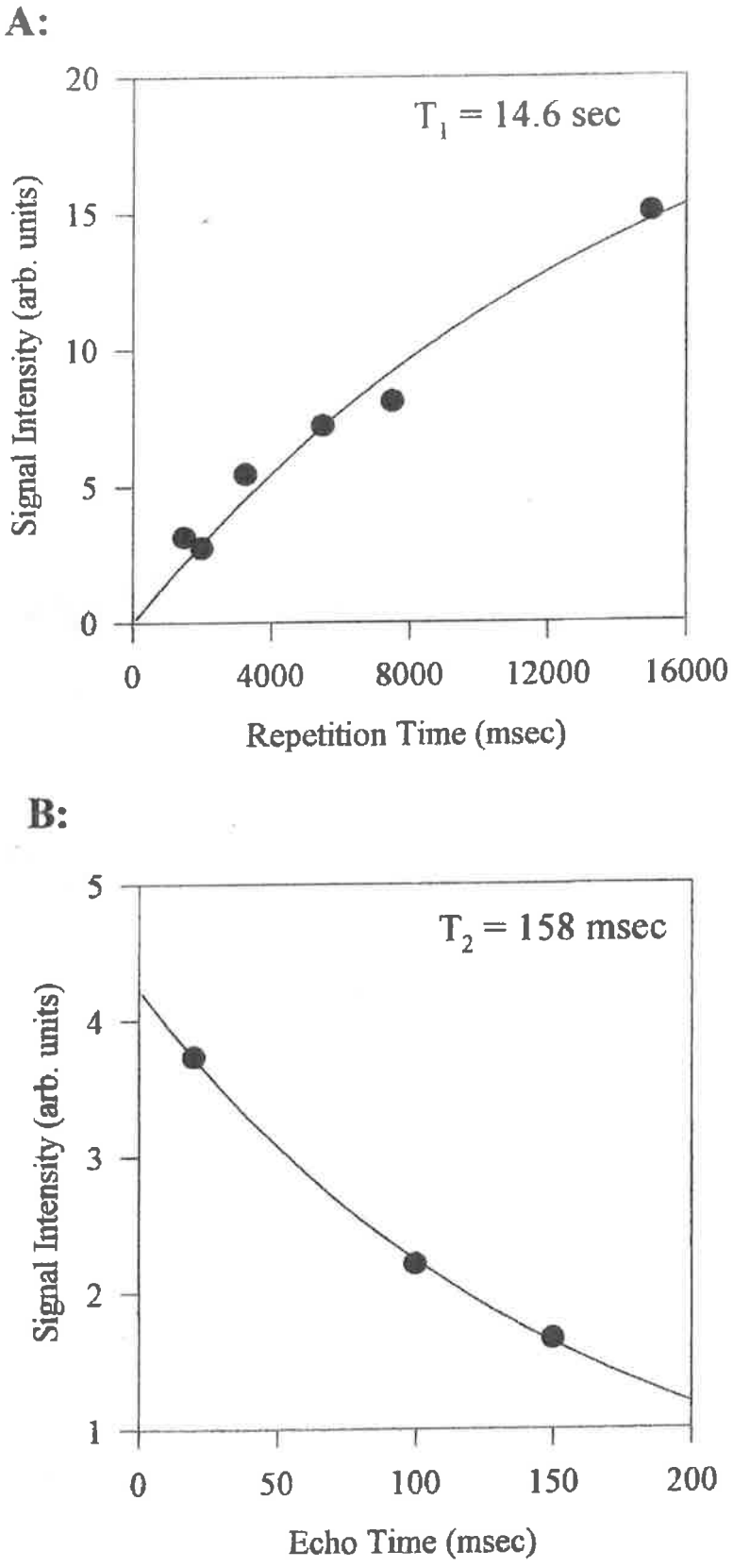


**FIGURE 3.** Plots of the *in vivo* $^{29}Si$ MR signal intensity, for a sample of silicone gel which has been implanted subcutaneously in a rat for 23 weeks: A) as a function of repetition time (TR); and B) as a function of echo time (TE). The solid line plots show the results of nonlinear least-squares fits to equations 3 and 4, to determine the values of $T_1$ and $T_2$, respectively.

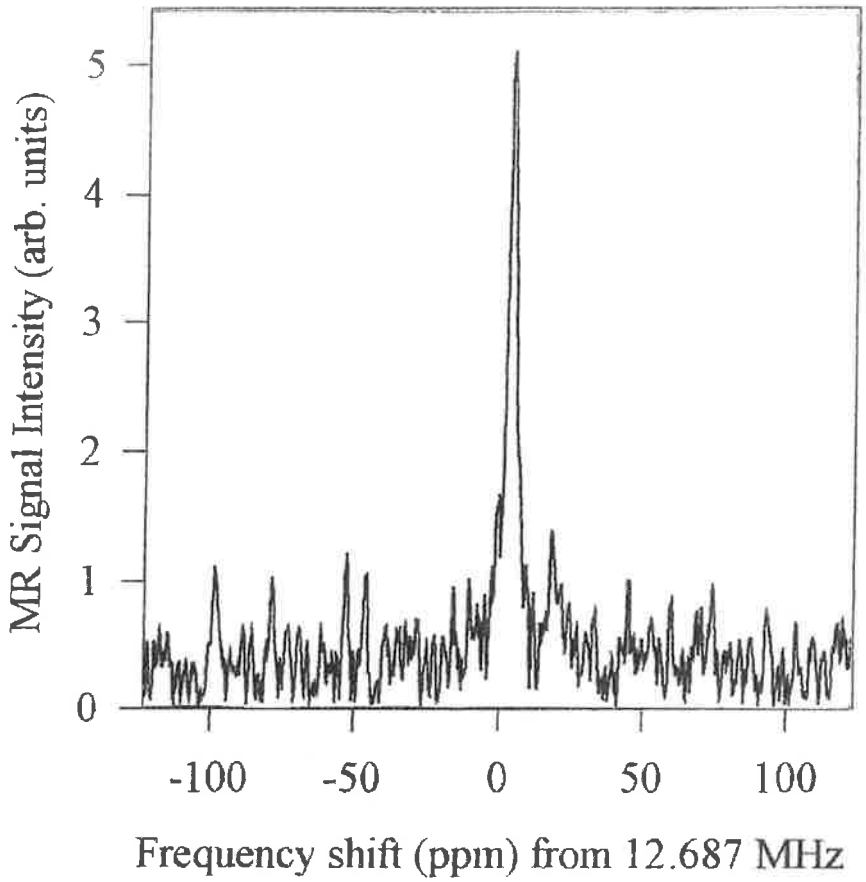


**FIGURE 4.** An *in vivo* $^{29}$Si spectrum of silicone gel which has been implanted subcutaneously in a rat for 23 weeks. This spectrum is the result of averaging 128 FID signals, which were acquired with a repetition time of four seconds.

($T_1$ = 14.6 scc) was acquired with a repetition time of 4 sec; 128 signal averages yielded an SNR of 8. The quantity of gel that was implanted was approximately five grams, and so, even in this worst-case scenario, the smallest quantity of gel that is detectable (with a SNR of $\forall$ 3) is roughly two grams. Assuming that freshly implanted silicone gel would have a $T_1$ of 1.6 sec (the value measured for the intact prosthesis gel), and using the same $^{29}$Si MR techniques, we would be able to detect as little as one half of a gram of silicone gel, with an SNR of 3 and an acquisition time of eight and a half minutes.

The longitudinal relaxation time of $^{29}$Si in silicone gel changed considerably while the gel was implanted in a rat. Although the relaxation times may have been influenced by the formation of a constricting fibrous capsule around the gel, the simplest and most plausible explanation for the observed changes is that the relaxation times measured are actually the net result of two different chemical environments in the silicone gel. The "bleeding" of an oily fluid from silicone gel has been well documented (Barker et al., 1978; Bergman and Van der Ende, 1979; Caffee, 1986) and has been monitored with proton MR spectroscopy (Stroman et al., 1994). Magnetic interactions between the more solid silicone polymer matrix (relaxation rate = $1/T_{1solid}$) and the more fluid silicone component (relaxation rate = $1/T_{1liquid}$) can cause the observed longitudinal relaxation rate ($1/T_{1obs}$) to be a weighted average of the relaxation rates of these two components, according to the expression (Abragam, 1961).

$$1 / T_{1obs} = \rho_{solid} / T_{1solid} + \rho_{liquid} / T_{1liquid}, \quad (5)$$

where $\rho_{solid}$ and $\rho_{liquid}$ are the relative fractions of nuclei contributing to relaxation in each of the two components (i.e., $\rho_{solid} + \rho_{liquid} = 1$). The observed changes in $T_1$ which occurred while the gel was implanted may therefore have been the result of the more fluid silicone component "bleeding" from the gel. The loss of this portion of the gel thus reduced its contribution to the longitudinal relaxation, and the observed $T_1$ value increased as a result. Moreover, the same mechanism can explain the observed differences in $T_2$ values between the virgin and implanted silicones. This mechanism is not limited to implanted silicones, however, and these relaxation time changes should be observable in any situation in which a component of the silicone is able to exude from the gel for a period of time.

This conclusion was verified by comparison with the results of relaxation time measurements on an intact Même® mammary prosthesis, from which we assumed that little or no silicone had escaped, and on a sample of gel, also from a Même® prosthesis, which had been in a saline bath in a sealed glass container for ten months. Transverse relaxation time measurements yielded $T_2$ values of 177 msec for the intact prosthesis gel, and 152 msec for the silicone gel in the saline bath. Longitudinal relaxation times were measured to be 2.5 sec and 11.5 sec, respectively, and so demonstrated the same trends in both $T_1$ and $T_2$ as those observed in comparing virgin gel to silicone gel implanted in a rat. Thus, it is likely that the exudation of liquid silicone from the gel was responsible for the observed increases in $T_1$ values, and decreases in $T_2$ values, which occurred in both of these cases.

This result also has two important corollaries. Firstly, the time course of alteration of a silicone gel–filled prosthesis can be monitored *in vivo* with $^{29}Si$ relaxation time measurements. As liquid silicone is exuded from a breast implant, the $T_1$ of $^{29}Si$ in the remaining silicone gel can be expected to increase by as much as a factor of nine. Secondly, the exuded component of the silicone must have a $T_1$ value which is less than the lowest value measured in virgin silicone gel, and so $T_{1liquid}$ cannot be greater than 1.6 sec. The shorter $T_1$ of this component of silicone will greatly facilitate its detection *in vivo* with $^{29}Si$ MR techniques. It is this component of the silicone gel which is most likely to migrate away from a prosthesis and be deposited in various tissues throughout the body.

## CONCLUSIONS

The feasibility of *in vivo* $^{29}Si$ spectroscopy has been demonstrated. The feasibility of *in vivo* $^{29}Si$ imaging, however, will depend on acquisition time constraints and thus on the relaxation properties of the silicone products being imaged. Longitudinal relaxation times of $^{29}Si$ in silicone gels have been observed to vary from 1.6 sec in virgin silicone to 14.6 sec in implanted silicone. The observed changes in $T_2$ were less dramatic but still varied from 152 msec to 177 msec. We have attributed these changes solely to the exudation of liquid silicone from the gel over time. An important consequence of this conclusion is that the exuded

silicone must have a $T_1$ of less than 1.6 sec and a $T_2$ of greater than 177 msec, in a magnetic field of 1.5 T. MR detection of the exuded silicone will therefore be greatly facilitated by the fact that the interval between successive acquisitions can be as low as 1.6 sec. Moreover, by virtue of their different relaxation times, we should be able to distinguish exuded silicone near a prosthesis from the silicone gel remaining within the prosthesis. Also, *in vivo* MR relaxation time measurements should be able to demonstrate whether or not silicone has been exuded from a silicone gel–filled mammary prosthesis.

## ACKNOWLEDGMENTS

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# IMMUNOLOGIC MARKERS IN SILICONE BREAST IMPLANT RECIPIENTS

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*Autoimmune disorders and rheumatic symptoms in breast implant patients have been reported frequently in recent years. The determination of serologic markers for autoimmune disorders has been done mostly without regard to the confirmed immunologic status of these patients. Our recent development of a specific T-lymphocyte stimulation testing method for silicone-associated disease has made it possible to examine for various markers in confirmed immune-positive mammary implant patients. In a study group of 231 such women, 153 were ANA-negative (66.2%); 78 had either positive ANA patterns (64 patients) or cytoplasmic autoantibodies (14 patients) (33.8%). Only eight of the ANA-negative women were anti-DNA positive (5.2%); 32 were positive for RAF (20.9%). Of the 64 ANA-positive women, 8 were also positive for anti-DNA (12.5%) and 12 were positive for RAF (18.8%). Western Blot testing demonstrated antibody patterns that differed from heretofore-defined classic rheumatic diseases. This study confirms a lack of so-called classic autoimmune response in women with silicone-associated disease.*

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2. Abbreviations: ANA, antinuclear antibody; RAF, rheumatoid arthritis factor; SI, stimulation index.

3. Key Words: antibody profiles; antinuclear antibody; lymphocyte stimulation; silicone; silicone-associated disease; stimulation index.

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## INTRODUCTION

Attempts to augment the human breast have been made since the early 20th century. The mos recent major attempt has been with various silicone-based devices. Concerns about the safet of silicone mammary implants were raised in the 1970s and finally, in 1988, an advisor committee of the federal Food and Drug Administration heard evidence of medica complications following their use. Vasey et al. (1994) reviewed the clinical findings in 5 women evaluated for silicone-associated disease, presenting evidence of a relationshi between the silicone implants and the development of rheumatic symptoms. Gabriel et al (1994) reported that silicone breast implants had no positive association with lupu erythematosus, scleroderma, or rheumatoid arthritis, when defined by classical but narrov criteria. Critical examination of their data reveals poor statistical power, such that correlatio detection was below a meaningful level. Recently, studies on cell-mediated immune processe have been developed which explain part of the immune reaction to silicone or its metabolites This is a memory T-lymphocyte test which can serve as an objective standard of specifi patient response to silicone devices (Ojo-Amaize et al., 1994; Smalley et al., 1995). Th present study is a cross-correlation of autoantibodies with well-defined T-cell responses i randomly selected silicone-implant patients.

## MATERIALS AND METHODS

Two hundred thirty-one symptomatic women with silicone gel mammary implants were studied retrospectively. Their symptoms included excess fatigue, arthralgias, myalgias, join swelling, sicca syndrome, alopecia, atypical rashes, poor memory, and others, similar to and consistent with those reported by Bridges et al. (1993). Patients were included in this study i their T-cell stimulations were considered positive (SI > 25) (Smalley et al., 1995). The normal control population of adults without implants, symptoms as noted, or other overt exposure to other silicone devices or materials had a mean stimulation index (SI) of 10.0. The level at two and a half times this mean was used as the threshold for a positive response (Smalley et al., 1995). The patients were further divided into three groups: SI between 2.5 and 5.0 times the normal mean; SI between 5.0 and 10.0 times the normal mean; and SI over 10.0 times the normal mean.

*Autoantibody Testing*

All 231 sera were individually tested for antinuclear antibodies (ANA), rheumatoid arthritis factor (RAF), anti-DNA, and autoantibodies by Western Blot.

ANA testing was by a Hep-2 cell line (Sanofi Diagnostics Pasteur, Chaska, Minnesota). All sera were initially screened at a dilution of 1:40. Any positive response was further defined according to the type of fluorescence pattern: homogeneous, speckled, nucleolar, mixed (more than one pattern), or cytoplasmic (Fritzler, 1992). RAF testing was done by a nephelometric method on a QM300 (Sanofi Diagnostics Pasteur) with a positive response above 35 IU/ml in accordance with the recommendation of the manufacturer. Testing for

autoantibodies to extractable nuclear antigen peptides was by Western Blot (Immunovision, Springdale, Arkansas) including anti-Sm(26, 25, 18, and 16 kd); anti-RNP(68, 33, and 22 kd); anti-SCL70(105 and 70 kd); anti-SSA(60, 54, and 52 kd); anti-SSB(50 and 43 kd); and anti-Ku (86, 80, and 66 kd). A positive band on the blot was noted only when staining intensity exceeded a 1+ reaction on the scale of 1+ to 4+. Representative atypical banding patterns in Western Blots are shown in Figure 1 along with a negative control. Testing for autoantibodies to double-stranded anti-DNA was by enzyme immunoassay per the manufacturer's protocol (Clark Laboratories, Inc., Jamestown, New York).

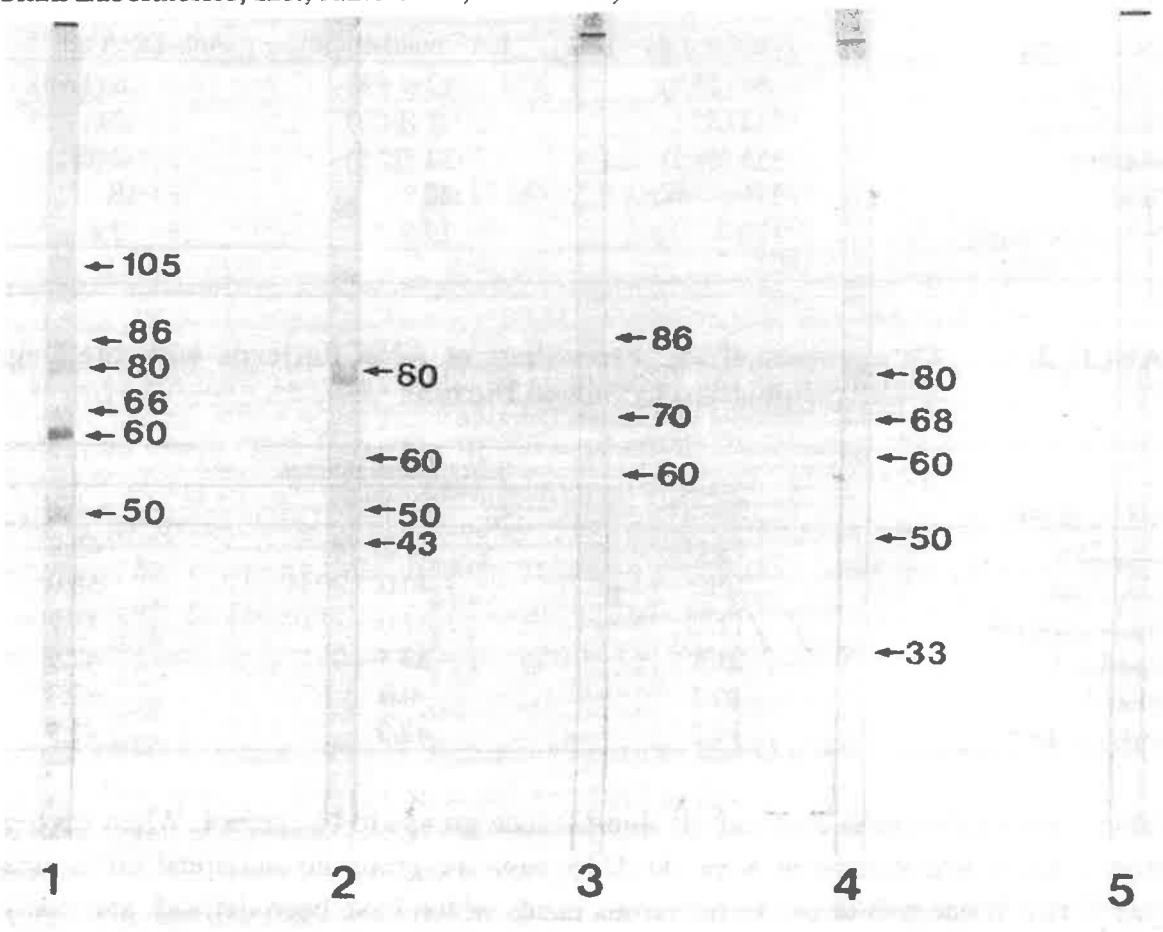


**FIGURE 1.** Representative Western Blots from four different silicone-implant patients are shown. Minor variations in band position are due to the use of different lots of antibody over time.

1. Atypical pattern: anti-Ku banding (86, 80, 66 kd) and independent bands at 105, 60 and 50 kd;
2. Atypical pattern: anti-SSB banding (50 and 43 kd) and independent bands at 80 and 60 kd;
3. Atypical pattern: mixed banding at 86, 70, and 60 kd;
4. Atypical pattern: mixed banding at 80, 68, 60, 50 and 33 kd; and
5. Negative control.

## RESULTS

As shown in Table 1, of 231 women with confirmed T-cell–mediated immune response to implant-component silicon dioxide, 153 were negative for ANA (66.2%). Sixty-four (27.7%) had positive ANA patterns and 14 (6.1%) were ANA-negative but with cytoplasmic fluorescence sometimes seen in other autoimmune syndromes (Fritzler, 1992). There were 46

women who were positive for RAF (19.9%); 18 were positive for anti-DNA (7.8%) (Table 1). The distribution of ANA is compared to the level of the T-cell SI in Table 2. Other than the mixed fluorescence, negative and other ANA patterns had similar distributions of T-cell indices.

**TABLE 1. Summary of Autoantibodies Present in Silicone Breast Implant Patients (n = 231)**

| | | Positivity of ancillary tests | |
|---|---|---|---|
| ANA pattern | Number (%) | RAF number (%) | Anti-DNA number (%) |
| Positive | 64 (27.7) | 12 (18.8) | 8 (12.5) |
| Cytoplasmic | 14 (6.1) | 2 (14.3) | 2 (14.3) |
| Negative | 153 (66.2) | 32 (20.9) | 8 (5.2) |
| Total | 231 | 46 | 18 |
| Percent of series | 100.0 | 19.9 | 7.8 |

**TABLE 2. Comparison of the Percentage of ANA Patterns with the Degree of T-Cell Stimulation by Silicon Dioxide**

| | Stimulation indices | | |
|---|---|---|---|
| ANA pattern | 25–50 | 50–100 | > 100 |
| Negative | 13.1% | 41.2 | 45.7 |
| Nucleolar | 10.0 | 40.0 | 50.0 |
| Homogeneous | 11.1 | 37.0 | 51.9 |
| Speckled | 23.8 | 33.3 | 42.9 |
| Mixed | 16.7 | 0.0 | 83.3 |
| Cytoplasmic | 14.2 | 42.9 | 42.9 |

Table 3 shows the mean RAF for all fluorescence groups to be limited. When each positive pattern group was compared with the ANA-negative group no statistical differences were found. The Western Blot shows numerous bands which have been defined, and many as yet undefined. The autoantibodies which have been defined are shown in Table 4. ANA-positive and -negative patients showed similar levels for many of the peptide-specific autoantibodies (Table 4).

**TABLE 3. Comparison of ANA Patterns with Mean RAF Results**

| ANA pattern* | Mean RAF (IU/ml) | SEM | p value |
|---|---|---|---|
| Negative | 61 | 13.2 | |
| Homogeneous | 79 | 23.6 | 0.6327 |
| Speckled | 42 | 3.3 | 0.5502 |
| Mixed | 81 | 12.0 | 0.7069 |
| Cytoplasmic | 51 | 5.0 | 0.8568 |

* No nucleolar-pattern sera had positive RAF.

**TABLE 4. Comparison of ANA Patterns with Percentage of Specific Peptide Autoantibodies Determined by Western Blot**

| | Specific peptides | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| ANA pattern | 105 | 80 | 70 | 68 | 60 | 54 | 50 | 43 |
| Negative | 19.6% | 23.5 | 24.2 | 22.2 | 33.3 | 28.8 | 29.4 | 28.1 |
| Nucleolar | 20.0 | 0.0 | 40.0 | 30.0 | 30.0 | 30.0 | 40.0 | 0.0 |
| Homogeneous | 14.8 | 18.5 | 22.2 | 22.2 | 37.0 | 33.3 | 25.9 | 33.3 |
| Speckled | 19.1 | 23.8 | 28.6 | 42.9 | 19.1 | 19.1 | 38.1 | 28.6 |
| Mixed | 16.7 | 33.3 | 0.0 | 16.7 | 16.7 | 0.0 | 50.0 | 50.0 |
| Cytoplasmic | 21.4 | 14.3 | 35.7 | 28.6 | 14.3 | 14.3 | 14.3 | 21.4 |

## DISCUSSION

Although the study by Gabriel et al. (1994) failed to identify the number of patients actually tested for ANA, the reported data suggested the number was low. Nearly a third of immune-positive implant recipients in our study had positive ANA patterns. This finding correlates well with prior studies of mammary implant patients evaluated for rheumatic symptoms (Solomon, 1994). This frequency of ANA positivity far exceeds the 2% false positivity expected among normal middle-aged individuals (Fritzler, 1992). We found a much higher level of RAF than Solomon (1994). This may be due to Solomon's use of 40 IU/ml as the threshold for positivity. We used 35 IU/ml in conformity with the protocol from the manufacturer. In retrospect, 20 RAF-positive sera were between 35 and 40 IU/ml in our study, and would have been considered negative by Solomon (1994).

Anti-DNA studies found only 18 women with positive results (7.8%). This supports the Mayo Clinic study, which concluded on weak statistical ground that implant patients do not have classical lupus erythematosus (Gabriel et al., 1994).

Banding consistent with anti-SCL70 occurred frequently in both ANA-positive and ANA-negative sera when tested by Western Blot (Table 4). This correlates with the findings of Bridges et al. (1993). In addition, we found mixed patterns of other autoantibodies to peptides associated with Ku, RNP, SSA, and SSB. The Western Blot on these patients was not characteristic of classically defined illnesses such as lupus, Sjögren's syndrome, mixed connective tissue disease, or scleroderma.

For example, 75% of patients with diffuse scleroderma have antibodies to SCL70 which consists of autoantibodies to two peptides with molecular weights of 105kd and 70kd (Wilson and Sanders, 1992). Our study found 14.8–21.4% of the implant patients had antibody to p105 irrespective of the ANA pattern (Table 4). By contrast, from 0.0–40.0% of these patients had autoantibody to the companion peptide, p70 (Table 4). Antibodies to the Ku protein, which consists of three peptides previously described, occurred in about 10% of patients with

classic systemic lupus (Wilson and Sanders, 1992). We found autoantibody to one of the K peptides (p80) in 0.0–33.0% of women with a known T-cell response. Another atypic finding in the Western Blot data was autoantibodies to peptides p60 and p54, which a associated with antibody to SSA(Ro). This antibody typically occurs in about 35% of patien with classic systemic lupus and 60% of Sjögren's syndrome patients (Wilson and Sande 1992), but in the implant population a different profile appeared. We found antibodies to p6 in 16.7–37.0% and from 0.0–33.0% for p54 (Table 4). These findings are clearly differe from any previous reported observations, suggesting that the autoantibody responses i implant patients are not typical of so-called classic autoimmune disorders.

In evaluating the statistical association with the Western Blots, data were analyzed by Cl square; no significant difference in occurrence of banding was found, $p = 0.5705$. Therefor the distribution of atypical banding was not related to a specific fluorescent pattern or lac thereof.

The presence of various autoantibodies in a significant number of symptomatic implar patients is taken as evidence for a range of atypical immune responsiveness consistent with primary cellular immune response. The appellation silicone-associated disease or silicon associated disorder is understood as an inclusive term for a new form of autoimmunity, on caused by an alien material (silicones and related substances) which mimic known and bette defined autoimmune diseases. Silicones are man-made, not found in nature, and the ter *alien presence* better conveys this fact than the more commonly applied *foreign body*. Furth studies of correlations between antibody production and cellular response should assist i understanding the mechanisms of silicone-associated disease; our recommendation is th T-lymphocyte memory testing be made an integral and central part of all such future work.

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# A MOTOR NEURON DISEASE SYNDROME IN SILICONE BREAST IMPLANT RECIPIENTS

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*Six (n = 6) women developed motor neuron disease syndrome (MNDS) at a mean latency period of 11 years (range 2–23 years) after receiving silicone gel breast implants (n = 5) or saline breast implants (n = 1). In addition to MNDS, patients had myalgia, fatigue, arthralgia, joint swelling and stiffness, rash, headache, Sjögren's syndrome, and Raynaud's phenomena. Some had autoantibodies such as anti-$GM_1$, ANA, or antimyelin antibodies, and abnormal serum levels of immunoglobulins. Three patients died during the study. Five patients had sural nerve biopsy, all of which revealed loss of myelinated fibers. Five patients had a biceps muscle biopsy, all of which revealed neurogenic atrophy. Five patients underwent implant removal, all of which were found to have ruptured implants with silicone spilled into tissue. Foreign material such as silicone breast implants might cause a MNDS, probably indirectly through an autoimmune mechanism. Further investigations of the syndromic nature of MND associated with silicone breast implants are needed.*

## INTRODUCTION

A syndromic nature of motor neuron disease (MND) or amyotrophic lateral sclerosis has been proposed (Patten, 1987), indicating a syndrome of MND can be due to various causes such as hyperthyroidism, hexosamidase A deficiency, cervical spondylosis, lead poisoning, or exposure to insecticides and pesticides. An autoimmune pathogenesis in MND has been considered as well (Patten, 1987; Drachman and Kuncl, 1989). Basically, it has been concluded that a disease or toxin that causes damage to the upper and lower motor neurons can cause the syndrome of MND (Patten, 1987).

Many clinicians have noted a causal relationship between silicone breast implant surgery and the onset of autoimmune disease (Kumagai et al., 1984; Sergott et al., 1984; Vojdani et al.,

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2. Key Words: ALS, disease, implants, MND, silicone.

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1992, 1994; Bridges et al., 1993; Freundlich et al., 1994; Ostermeyer Shoaib and Patten, 1994; Ostermeyer Shoaib et al., 1994; Silverman et al., 1994; Solomon, 1994; and Vasey et al., 1994). We report here on six women who developed MND syndrome after receiving silicone breast implants.

## PATIENTS AND METHODS

All patients were diagnosed with MND by at least two other Board Certified neurologists before they were referred to our service at Baylor College of Medicine. All patients had evidence of upper and lower motor neuron involvement with or without bulbar signs. Patients underwent history and physical examination, and laboratory testing as outlined previously (Patten, 1987).

## ILLUSTRATIVE CASE REPORT

In 1983, patient 5 underwent a mastectomy at age 36 for fibrocystic disease. She received breast reconstruction using Dow Corning silicone gel–silicone elastomer breast implants, 600 cc on each side. In 1984, she developed weakness of her left leg, fatigue, severe myalgia and arthralgia, severe headache and memory problems. In 1985, she developed weakness and atrophy of the intrinsic hand muscles. Her myalgia and arthralgia became unbearable and she was referred to a pain clinic. Routine laboratory testing as well as an EMG were normal. She was referred to a psychiatric hospital for pain management, where she spent three months without any improvement in her symptoms. She then developed a bilateral foot drop, worse on the left than right, and it became necessary for her to use a cane. She started to have weakness in both arms and blurred vision. In 1986, her weakness grew progressively worse, necessitating the use of a wheelchair. She suffered from hair loss, Sjögren's syndrome, morning stiffness, Raynaud's phenomena, and erythematous rash on her face and under her left breast and left arm. She also experienced hot flushes, chills, low-grade fevers, recurrent fungal infections of fingers and toes, recurrent urinary tract infections, and constipation. She was diagnosed with ALS, and in 1987, was referred to a specialist for ALS, who confirmed the diagnosis. She was told she had half a year more to live. At that time, on examination, her tongue was normal. She had weakness of upper and lower extremities, and bilateral atrophy of intrinsic hand muscles. Her deep tendon reflexes and sensory examination were normal. Her gait could not be tested because she was wheelchair-bound. An EMG showed widespread denervation, fasciculations, and giant units, but her tongue was normal. Biceps muscle biopsy showed chronic neurogenic atrophy.

She then presented to us for a further opinion. We found a positive ANA, anti-$GM_1$ antibodies, antimyelin antibodies, decreased IgG and IgA, and an abnormal D-xylose breath test indicating small bowel bacterial overgrowth. EMG showed widespread signs of denervation. Nerve conduction velocities were normal. Sural nerve biopsy showed demyelination with inflammation, and findings of vasculitis. We felt she had an autoimmune

disease associated with silicone breast implants. Therefore, we recommended removal of the prostheses. In 1987, she underwent implant removal, but not removal of the surrounding implant capsule. Her left implant was found to be ruptured with silicone spilled into tissue. Two weeks later, she had no more low-grade fevers, her pain lessened, and constipation and recurrent urinary tract infections resolved. She was also treated with prednisone and oral cyclophosphamide and was then able to raise her arms. Her condition began to fluctuate. She received plasma exchange and gammaglobulin infusions over one and a half years, which stabilized her neurological symptoms, but pain, headache, Sjögren's syndrome, frequent rashes, and swelling of hands and feet persisted. In addition she had an abnormal sleep study, showing an arterial $PO_2$ of only 44%, indicating respiratory insufficiency.

In 1989, a repeat EMG showed absent sensory potentials throughout, except for the right radial which was borderline slowed and small. In an attempt to find out whether all silicone had been previously removed, she underwent an ultrasound and chest MRI. Marked residual silicone and the implant capsule were found. In 1992, she underwent more surgery to remove the implant capsule and residual silicone. After surgery, weakness decreased. She could raise both arms over her head, hold a cup of coffee, and dress herself. Swelling of hands and feet resolved, and she could wear rings on her fingers for the first time since 1985. Sexual intercourse, which previously had been impossible because of severe vaginal dryness and respiratory distress, now became possible. Whereas previously she used artificial tears throughout the day for dry eyes, she now only needed one drop in the morning. Her pain and headache improved to the point that she did not need any more pain killers and her rash disappeared. Morning stiffness that used to involve her entire body was now only present in her neck.

After a few months, her condition again worsened. She went into respiratory failure several times and had to be intubated. She underwent further treatment, including plasma exchange and oral and intravenous cyclophosphamide, and was weaned off the respirator. In December of 1993, she again fell into respiratory failure and died.

## RESULTS

All six patients were caucasian women. Five had received silicone gel breast implants (patients 1, 4, and 6 for augmentation, patients 3 and 5 for reconstruction after mastectomy for fibrocystic disease) and one (patient 2) had received saline-filled silicone breast implants for augmentation. The mean age of first implantation was 33 years (range 29–37). The mean age of onset of symptoms was 43 years (range 38–50). The mean latency period between implant surgery and onset of clinical symptoms was 11 years (range 2–23 years).

All patients had upper and lower motor neuron involvement without any significant sensory findings, except for patient 5. Patients 1 and 3 also had bulbar involvement. The patients' symptoms and laboratory and tissue biopsy findings are listed in Table 1.

**TABLE 1. Clinical Symptoms and Findings in the Patients**

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 |
|---|---|---|---|---|---|---|
| age | died at age 49 | died at age 47 | 45 | 54 | died at age 47 | 50 |
| age of implantation | 31 | 29 | 35 | 27 | 36 | 37 |
| age of onset of symptoms | 42 | 39 | 41 | 50 | 38 | 48 |
| latency period | 11 | 10 | 6 | 23 | 2 | 11 |
| symptoms besides MNDS | fatigue, rash | fatigue, myalgia, stiffness, tingling, memory problems, nausea, recurrent fungal infections of finger and toe nails | fatigue, stiffness, gel-phenomena, rash, Sjögren's syndrome, hair loss, Raynaud's phenomena | fatigue, myalgia, arthralgia | fatigue, myalgia, arthralgia, stiffness, joint swelling, rash, hair loss, Sjögren's syndrome, tingling, nausea, Raynaud's phenomena, memory problems, headache, blurred vision, low-grade fevers, lymphadenopathy | fatigue, arthralgia, stiffness, Raynaud's phenomena |
| age of implant removal | 47 | 44 | 44 | not done | 40 | 49 |
| condition of implant | both ruptured | left ruptured | both ruptured | not done | left reptured | both ruptured |

**TABLE 1. Clinical Symptoms and Findings in the Patients (cont'd)**

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 |
|---|---|---|---|---|---|---|
| implant capsule biopsy | FBGC, inflammation, silicone | FBGC, inflammation, silicone | FBGC, inflammation, silicone | not done | FBGC, inflammation, silicone | FBGC, inflammation, silicone |
| pectoralis muscle biopsy | not done | myositis | neurogenic atrophy, perifascicular atrophy | not done | myositis | neurogenic atrophy |
| sural muscle biopsy | demyelination | demyelination | demyelination | not done | demyelination, inflammation, vasculitis | demyelination |
| biceps muscle biopsy | neurogenic atrophy | neurogenic atrophy, inflammation | neurogenic atrophy | not done | neurogenic atrophy | neurogenic atrophy |
| abnormal lab findings | anti-$GM_1$ AB | anti-$GM_1$ AB, anti-MAG AB, antisilicone AB, antimyelin, ANA, antiasialo AB, elevated CPK, increased IgM, decreased IgG, IgA, C3 | ANA, decreased IgA | none | anti-$GM_1$ AB, ANA, antimyelin AB, decreased IgG, IgA | decreased C3 |

FBGC = foreign body giant cells, AB = antibodies

All patients showed widespread evidence of denervation on needle EMG. Nerve conduction studies were normal, except for those of patient 5. All five patients who had a sural nerve biopsy taken were found to have loss of myelinated fibers, and all five patients who had a biceps muscle biopsy were found to have neurogenic atrophy.

Patient 1 died of respiratory failure after seven years of disease. The findings at autopsy were compatible with progressed MND. The pathologist confirmed the loss of myelinated fibers on sural nerve biopsy. Patients 2 and 5 died after eight and nine years of disease, respectively.

## DISCUSSION

Silicone is biologically and chemically active. It has been demonstrated that both silicone and silica (up to 30% of the elastomer shell and the gel of a breast implant) are cytotoxic (Kessel et al., 1963; Allison et al., 1966; Kossovsky et al., 1987) and immunostimulatory agents (Pernis and Paronetto, 1962; Heggers et al., 1983; Mancino et al., 1984; Kossovsky et al., 1987). They are efficiently taken up by macrophages from the implant surface and react with the membranes surrounding the secondary lysosomes, causing death of the macrophage and general damage to the adjacent tissue (Kossovsky et al., 1987).

Garrido et al. (1993) demonstrated in an animal model that silicone migrates from the implant to the liver and new silica compounds are formed. Silica itself is known to cause scleroderma-like illness and arthritis (Caplăn's syndrome) in coal miners (Rodnan et al., 1966).

Denaturation of native macromolecules by interaction with silicone has also been reported (Kossovsky et al., 1987, 1993; Kossovsky and Petrovich, 1994; Vojdani et al., 1994). Denatured macromolecules then develop antigenic characteristics and become the target of an immune response. A cross-reaction of the immune response to normal tissue could thus explain an autoimmune reaction.

Silicone and silica elicit both cellular and humoral immune responses (Heggers et al., 1983; Kossovsky et al., 1987, 1993). Vojdani et al. (1992) actually measured antisilicone antibodies in women with silicone breast implants. Other investigators found novel antibodies and proteins in sera of silicone breast implant recipients when compared to normal controls. In studies by Naim et al. (1993) and Dow Corning Corporation,[1] rats were injected with a homogenized gel form of silicone in the presence of bovine serum albumin (BSA). In this

[1]Klykken, P.C., Galbraith, T.W., Woolhiser, M.R., Duwe, R.L., Mudgett, S.L., Nash, G.E., and Malczewski, R.M. (1993). A humoral adjuvancy study of Dow Corning silicone fluids alone 360 fluid, 20 cs.; 7-2317, 1000 cs) and Dow Corning 360 fluid, 20 cs., mixed with Dow Corning mammary gel (Q7-2159A) or McGhan mammary gel in the rat. March 9, 1993, Dow Corning Corporation, Midland, MI 48640.

model, it was demonstrated that silicone gel has adjuvant activity similar to that of complete Freund's adjuvant in amplifying the anti-BSA antibody response. These studies have shown that silicone can act as an adjuvant, enhancing the ability of the immune system to produce antibodies to a foreign antigen.

A growing number of patients have been reported who developed an atypical autoimmune disease with rheumatological and neurological symptoms (Kumagai et al., 1984; Sergott et al., 1984; Vojdani et al., 1992, 1994; Bridges et al., 1993; Freundlich et al., 1994; Ostermeyer Shoaib and Patten, 1994; Ostermeyer Shoaib et al., 1994; Silverman et al., 1994; Solomon, 1994; Vasey et al., 1994). The clinical symptoms and laboratory features of this autoimmune disease from the silicone breast implants are clearly distinguishable from the known classical rheumatological and neurological diseases. Therefore, it has been concluded that women with breast implants tend to develop a new syndrome that we call "Adjuvant Breast Disease" (Ostermeyer Shoaib et al., 1994; Patten and Ostermeyer Shoaib, 1995).

We recently reported one hundred women who developed adjuvant breast disease with nervous system involvement at a mean latency period of six years after silicone breast implant surgery or silicone fluid injections (Ostermeyer Shoaib et al., 1994). A high number of the patients (60%) had ruptured implants. Therefore, we believe patients with implant rupture and spills of silicone into tissue are at higher risk for developing a systemic disease. In this study, the mean latency period was longer (11 years), and all patients who underwent implant removal were found to have ruptured implants. Our patients with MNDS also had the rheumatic and neuromuscular symptoms, as well as laboratory findings (Table 1) that were described in other women with adjuvant breast disease (Kumagai et al., 1984; Sergott et al., 1984; Vojdani et al., 1992, 1994; Bridges et al., 1993; Freundlich et al., 1994; Ostermeyer Shoaib et al., 1994; Silverman et al., 1994; Solomon, 1994; Vasey et al., 1994). Thus, it appears that our patients developed adjuvant breast disease with symptoms of an MNDS due to an underlying autoimmune response to siloxane, a foreign material that has been shown to act as an adjuvant to immune system responses (Kossovsky et al., 1993; Naim et al., 1993).

We conclude that attention should be paid to those patients who develop an MNDS after receiving foreign material. Patients with such a condition might benefit from removal of the foreign body, e.g., silicone breast implants. The surrounding capsule tissue must be removed together with the implants since it presents antigenic character, being full of leaked silicone, inflammatory reactions, and damaged tissue. Additional immunosuppressive therapy should be considered for each individual patient.

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# CAUSAL INFERENCE IN SYNDROMES ASSOCIATED WITH SILICONE BREAST IMPLANTS: PSYCHOGENIC AND ENVIRONMENTAL FACTORS

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*At least three models can explain the occurrence of a silicone-associated disorder (SAD) among women who have undergone breast implantation: 1) a factitious model, in which systemic symptoms are coincidental to implantation; 2) a psychogenic model, in which symptomatology results from psychosomatic processes; and/or 3) a causal model, in which silicone is responsible for some or all of the symptoms experienced by implant patients with an SAD.*

*A factitious model would require substantial selection bias on the part of treating physicians. This is unlikely, in light of the multiple, independent reports of common symptom complexes in silicone-exposed patients, dating back 30 years. However, it is possible that SAD is overreported as a result of misdiagnosis of closely related conditions such as fibromyalgia. The psychogenic model can account for a portion of the reported subjective symptomatology, but psychosomatic factors cannot fully explain the range of objective clinical and laboratory findings in SAD.*

*Support for the causal model comes from positive pathological and laboratory reports of silicone- or silica-specific serological and cellular responses. Many of the findings typical of SAD patients correspond to demonstrable pathogenic properties of silicone reported in the literature on animals, including the ability to evoke silicone-reactive antibodies; to produce granulomatous reactions; to interact with collagen to produce autoimmune disease; to depress natural killer cell function; to stimulate local cytokine production; and to cause fibroblastic reactions and lymphoproliferative disease. These findings reinforce the idea that a silicone-associated diathesis is* bona fide, *and that an as yet indeterminate*

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2. Abbreviations: EM, eosinophilia myalgia; SAD, silicone-associated disorder; TOS, toxic oil syndrome.

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*number of women have pathological sequelae causally related to exposure to silicone following breast implantation.*

## INTRODUCTION

Since 1964 an autoimmune-like syndrome associated with injection or implantation of provocative agents such as paraffin oils and later silicones of unknown purity has been described in women and some men (Miyoshi et al., 1964). Beginning in 1982, reports appeared in the western literature specifically linking certain systemic autoimmune disorders to silicone gel breast implants (Van Nunen et al., 1982; Baldwin and Kaplan, 1983). Since then, numerous case reports of autoimmune-like conditions appearing in women with silicone gel–based breast implants have appeared. (See Brautbar et al., 1992; Germain, 1991; Lappé, 1993; and Busch, 1994 for reviews.) Nonetheless, numerous preliminary epidemiological studies based largely on questionnaire responses or record reviews have so far failed to associate implant status with classic autoimmune disease (Wong, 1994).

The resulting uncertainty surrounding a putative causal linkage between silicone and autoimmunity makes it ethically imperative to explore alternative explanations for the autoimmune-like conditions which arise in breast implant patients. In this review, I explore three alternative hypotheses that may account for the present state of scientific knowledge.

## EXPLANATORY MODELS

The most common presenting symptoms of women with systemic illness after breast implantation include chronic fatigue, myalgia, polyarthralgia, cognitive dysfunction, memory loss, sicca, rashes, and neurologic disturbances, including neuropathies of the extremities (Solomon, 1994). Many of these symptoms appear only after a protracted latency following breast implantation (i.e., 2–12 years).

The exact nature of the relationship between these symptoms and silicone gel implantation is still under investigation and is presently the subject of intense clinical and epidemiological study. For the purposes of this article, the symptoms and clinical conditions associated with silicone are grouped together as an entity termed the Silicone-Associated Disorder (SAD).

When considering if a *bona fide* silicone-related symptom complex exists, one must rule out the possibility that some or all of the attributed symptoms are factitious, artifactual, or due to causes other than silicone. Elevated antinuclear antibodies and related autoantibodies may be nonspecific and/or induced by extrinsic factors. Many different environmental and pharmaceutical agents, notably omeprazole, captopril, and penicillamine, can generate elevated ANA values.

An incipient autoimmune illness may also be purely coincidental to the presence of a breast implant. Some cardiac medications, especially inderal, have been associated, albeit rarely,

with autoimmune diseases such as systemic lupus erythematosus. The symptoms of SAD overlap certain classic autoimmune states, notably Sjögren's syndrome (see Freundlich et al., 1994), making differential diagnosis critical in any breast implant patient.

Some diagnostic signs of SAD are also typical of disorders whose etiology remains uncertain. Patient complaints of fatigue, sleep disturbances, parasthesias and Raynaud's phenomenon, headaches, concentration problems, and musculoskeletal pain are common to chronic fatigue syndrome (Stoff and Pellegrino, 1992), fibromyalgia (Doherty and Jones, 1995), and multiple chemical sensitivity syndrome (Cullen, 1987; Brautbar et al., 1992). While improved diagnostic criteria (e.g., trigger point analysis in fibromyalgia) permit differentiation among these conditions, their clinical similarities may actually reflect a common etiology. Several of the most prevalent symptoms in each of these disorders are also potentially psychogenic in origin. These include myalgias, depression and anxiety, irritable bowel syndrome, and memory and concentration problems.

These observations are compatible with three hypotheses that may explain the occurrence of illness in silicone gel–implanted women:

1) *The Factitious Hypothesis*: The appearance of symptomatology or a specific disease entity in a breast implant patient is purely fortuitous and coincidental to the presence of breast implants.
2) *The Psychogenic Hypothesis*: Symptoms appear in breast implant recipients as a result of suggestion or other psychological phenomena.
3) *The Causal Hypothesis*: Silicone is responsible for *bona fide* systemic, immunological illnesses in some breast implant patients.

*Factitious Hypothesis*

According to the factitious model, silicone breast implants are simply a coincidental finding in symptomatic women who were otherwise predisposed to develop autoimmune disease and related symptomatology. The existence of numerous case reports is explained by the relatively high prevalence of autoimmune disease in the at-risk population of women between the ages of 25 and 45.

In this model, the incidence of autoimmune disease within the breast implant population would be expected to be identical to that in the general population. The reported spate of negative epidemiological studies cited above supports this model, since all but one have found no increased prevalence of disease in implant populations compared to appropriate controls. Laboratory reports may similarly be challenged. The apparent association between elevated anti-nuclear antibody titers and early rupture (Press et al., 1992) has not proven replicable (Claman and Robertson, 1994). Other studies of ANA levels have failed to find any distinction between breast implant patients and controls (Peters et al., 1994). However, the largest series of symptomatic breast implant patients examined to date for laboratory findings (N = 3193) included about one third with elevated ANA antibodies (titer > 1:40), compared to

less than 3% of a smaller number of asymptomatic but similarly implanted control (Silverman et al., 1995).

The factitious model accounts for the multiple reports of autoimmune-like illness as over reporting by clinicians who are biased towards diagnosing otherwise common symptom patterns as SAD. Making such a finding only requires that there be a sufficiently prevalent disorder in the population at large with at least some of the symptoms in question from which to construct the factitious disorder. In theory, a SAD complex could be created by "building on" a common disorder that generates the prodromal signs and symptoms of a reactive autoimmune-like problem.

Fibromyalgia is a candidate condition. It is reported in anywhere from 3.7–20% of patients who visit rheumatology clinics and is highly prevalent in the at-risk population, occurring in some 1% of a typical Anglo-Saxon population (Bennett, 1993). Fibromyalgia typically presents with multiple symptoms that mirror SAD, including musculoskeletal pain, fatigue stiffness, and, in about one third of the affected patients, Raynaud's phenomenon parasthesias, sicca, and peripheral numbness and tingling (Bennett, 1993). Unless a careful differential diagnosis is performed (e.g., by ascertaining the number and distribution of tender "trigger points"), it is possible to misdiagnose idiopathic fibromyalgia as SAD.

The key question raised by the factitious hypothesis is whether SAD is a distinct disorder that can be differentiated from related conditions by objective clinical measurements. The history of the discovery of SAD and its diagnostic characteristics suggests this is likely. The first widely recognized reports of a silicone diathesis outside of Japan, where the term "human adjuvant disease" originated, were submitted by physicians who had little or no prior knowledge of the disease complex or its expected symptomatology. There is no cross-referencing or other evidence of sharing of case-specific data in the earliest two reports appearing in the western literature; yet, both U.S. and Australian investigators described essentially similar patients (Van Nunen et al., 1982; Baldwin and Kaplan, 1983), and ascribed their autoimmune-like symptomatology to an association with silicone breast implants.

Recent independent studies establish *bona fide* criteria for a unique silicone-associated disorder complex (Borenstein, 1994; Freundlich et al., 1994; Solomon, et al., 1994). The fact that these diagnostic criteria were developed and confirmed independently by the three groups greatly strengthens the credibility of the view that SAD is a distinct clinical entity. Even as a "real" disorder, however, the possibility remains that SAD can be explained by causal factors other than silicone.

*Psychogenic Hypothesis*

According to the psychogenic model, the symptomatology experienced by patients presenting with a putative diagnosis of SAD is psychogenic in origin and unrelated to biological properties of silicone. This model predicts that SAD occurs in a distinct subpopulation of implant recipients who are particularly prone to somaticization and/or suggestion. Several

different sources for this suggestion exist. Support groups, newsletters, symposia, and televised news stories about sick breast implant patients may unintentionally provide an archetype for the expected symptom complex by describing symptomatology and case studies in great, and often graphic, detail. As support for this speculative proposition, certain symptoms common to SAD patients, notably myalgia, headaches, memory loss, confusion, and mood swings, may be amenable to suggestion. When such symptoms appear in certain circumstances, such as psychogenic depression, they clearly can have a psychological component. But these same symptoms may also be found in patients with clinically proven disease, e.g., multiple sclerosis.

Somaticization of complaints can occur following a dramatic physical event such as a rupture or powerful imagery (e.g., in 1991 when the television show *Eye to Eye with Connie Chung* graphically showed implant surgery and its attendant problems). Future patients experiencing these events may undergo somaticization and relate normal body aches and pains to their implants. For these symptoms to congeal around a stereotypical disease or psychosis, it is only necessary for there to be a predetermined model of signs and symptoms with a strong psychosomatic component and a peer group to encourage the phenomenon (McHugh, 1995). Continuing input by sympathetic onlookers, some of whom may be found in support groups, regarding "appropriate" symptomatology and behaviors can then reinforce the legitimacy of expressing certain symptoms publicly.

Support for this hypothetical sequence of events comes from the observation that SAD-like illness is a relatively recent phenomenon (circa 1982) and appeared to become prevalent only after widespread publicity was given to some early breast implant cases (e.g., Stern v. Dow Corning, 1984). A further proliferation of cases also appeared to occur following the FDA hearings held in later 1991 and early 1992, although documentation of the exact nature of these events remains to be performed.

The plausibility of this psychogenic model for SAD is also reinforced by the similarities between the breast implant saga and classic descriptions of known or likely psychosomatic illness. Some of the same symptoms found in SAD are also reported in disorders alleged to have a high psychogenic component, such as chronic fatigue syndrome (Stoff and Pellegrino, 1992), sick building syndrome, and multiple chemical sensitivity syndrome (Meggs, 1993). The similarities between these disorders and breast implant disease has been noted previously (Brautbar and Vojdani, 1992).

In psychogenic illness generally, it is documented that belief in the authenticity of the illness by authority figures helps to perpetuate artifactual illness-manifesting behavior (McHugh, 1995). This theory would postulate that as more physicians become convinced of the existence of a silicone syndrome and describe its stereotypic symptoms in the literature, other physicians may "find" their patients expressing appropriate symptomatology.

If the psychogenic model were valid, one would expect to find relatively unique psychological characteristics in women who seek cosmetic surgery that predispose them to somaticize problems. Several older studies have demonstrated that implant-seeking women have a high degree of intrapsychic conflict, poor self-image and esteem, and some degree of sexual inhibition (Edgerton and McClary, 1958; Druss, 1973; Baker et al., 1974; Shipley et al., 1977). Recently, mild to moderate depression, with or without anxiety, has been described as a common finding in symptomatic breast implant patients (Prange et al., 1995). However, little or no data yet exist that establish a unique psychosomatic personality type associated with breast implantation, nor is there evidence that breast implant recipients are predisposed to reporting more symptomatology than are nonimplanted women.

In opposition to the psychogenic model, some psychologists who have studied breast implant patients find them to have stronger self-images after augmentation than before (Hetter, 1976), and by inference, more resistance to psychosomatic conversion than previously assumed. Contemporary research teams dispute the idea that the observed psychological factors (e.g., mild to moderate depression or anxiety) adequately explain the serious disturbances in concentration and psychomotor performance measured in a subset of breast implant patients (Prange et al., 1995).

To be credible, proponents of the psychogenic model must also be able to demonstrate how psychosomaticization can lead not only to vague skeletal and muscular complaints, but to the frank autoimmune-like illness seen in some implant patients. The conversion of psychogenic symptoms to an autoimmune condition is problematic. While the elaboration of autoantibodies has been associated with psychosis (Kurtz and Muller, 1994), a comprehensive review of the literature revealed only two instances in which psychogenic factors were associated with development of factitious autoimmune disease symptomatology (Foseca and Rubio, 1993; Kossard et al., 1993).

Another prediction from the psychosomatic hypothesis is that women who get breast implants for cosmetic reasons will be predisposed to experience and report more symptomatology than will those who get them for reconstruction purposes (e.g., after cancer surgery). A retrospective examination of the medical records from both groups shows that reconstruction patients report more, rather than less, symptomatology (morning pain and stiffness) compared to cosmetic breast surgery patients (Gabriel et al., 1994).

Even allowing for a partial contribution of psychosomatic factors to symptoms such as these, they do not appear sufficient to describe the full ambit of laboratory and clinical signs found in SAD patients.

*Causal Hypothesis*

The third model posits that the association between silicone and immunologic sequelae is causal. The evidence that silicone can cause a syndrome with a strong autoimmune component includes the following:

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*Causal Hypothesis*

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- silicone gel is immunogenic and possesses adjuvant-like properties when tested in animals (Naim et al., 1993);
- some silicone-associated symptomatology shows a temporal relationship to implantation and/or rupture (Solomon et al., 1994);
- a rough dose-response relationship can be inferred from early elevations of antinuclear antibody levels following *in vivo* rupture (Press et al., 1992);
- injection of suitable experimental animals (DA rats) with silicone gel coupled with collagen produces an autoimmune condition (Naim, 1995);
- heightened silicon- and silica-dependent lymphocytic reactivity is positively associated with symptomatology in SAD patients (Ojo-Amaize et al., 1994);
- histopathological findings link cellular mediators of autoimmunity to the distribution of silicone (Raso, 1994);
- the symptoms of SAD resemble those of other disorders in which extrinsic agents trigger cytokine-mediated, autoimmune-like disease;
- silicone has been isolated from the synovium in patients who have experienced arthralgia (Silver et al., 1993);
- patients with silicone breast implants tend to have more rheumatic symptomatology than do appropriate controls (Giltay et al., 1994);
- patients with significant exposure to silicone (e.g., through rupture) develop autoantibodies to silicone (Wolf et al., 1993); and
- partial or complete reversal of symptoms and serological signs of immune dysfunction occurs in some patients following removal of silicone through explantation (Kaiser and Zagornik, 1992; Campbell et al., 1994; Spiera et al. 1994).

Many contemporary studies, including those listed above, show that silicone behaves as an immunologically active material, increasing the plausibility that it participates in the pathogenesis of autoimmune illnesses. Silicone gel has both adjuvant and immunostimulating properties (Naim et al., 1993). The recently completed 180-day mouse study of silicone conducted by the National Toxicology Program demonstrated that silicone gel can provoke clonal proliferation of macrophage precursors in the bone marrow, stimulate hepatic macrophages, depress natural killer (NK) cell levels, and, in the instance of elastomer, augment plaque-forming units in the spleen (NTP, 1994).

The fact that silicone is found in the synovial spaces where active rheumatologic disease occurs puts it "at the scene of the crime" (Silver et al., 1993) and provides further inferential evidence for a direct association between joint disease symptoms and silicone or its breakdown products (e.g., silica).

Support for a causal role of silicone in SAD can also be inferred from the similarities between SAD and autoimmune conditions with *proven* extrinsic causes, notably eosinophilia myalgia (EM) and toxic oil syndrome (TOS). In EM, the suspected agent is a contaminant of L-tryptophan, while in TOS (also known as the Spanish oil syndrome) it is a contaminant of adulterated cooking oil. Like SAD, these two disorders are characterized by myalgia, fatigue,

weight loss, sicca syndrome, Raynaud's phenomenon, central nervous system involvement, and evidence suggesting autoimmune involvement (Silver et al., 1992; Yoshida et al., 1994). A reasonable inference is that the common symptoms seen in TOS, EM, and SAD reflect the existence of a common pathophysiological substrate that is activated by components or breakdown products of the three respective inducing agents.

Reversibility of autoimmune symptoms after removal of a presumptive provocative agent (e.g., captopril or penicillamine) is widely taken as proof of a causal association between that agent and a given autoimmune process. In the instance of silicone, symptomatic and clinical improvement (including restoration of near normal numbers of NK cells) is seen in 40–60% of patients (Campbell et al., 1994; Vasey et al., 1995).

The possibility that such reversal following explantation surgery can be a placebo effect must also be considered. (See Chaput de Saintogne and Herxheimer, 1994.) However, surgery-related placebo effects, like those from drug treatment, usually last less than three months (Johnson, 1994) and at least some of the observed reversals following explantation appear to be persistent (see Kaiser and Zagornik, 1992; Spiera et al., 1994) and specific to removal of a silicone source (Vasey et al., 1995). The recent finding of an apparent association between HLA markers and susceptibility to developing SAD (Young et al., 1995) strengthens the likelihood that there is a subpopulation genetically predisposed to react to silicone.

The fact that both mice (NTP, 1994) and SAD patients (Vojdani, et al., 1992) show depression in NK cell numbers after exposure to silicone provides direct evidence of an immunologic effect attributable to silicone. The observation that NK cell depression is wholly or partially reversible in half the affected patients following explantation of the silicone source further corroborates this suggestion (Campbell et al. 1994). Taken in concert with findings of anticollagen antibodies in symptomatic breast implant patients (Teuber et al., 1993), the ability of silicone-collagen injections to induce an autoimmune condition in experimental animals (Naim, 1995) provides a cogent causal mechanism for SAD.

These new observations make silicone's contribution to the amalgam of immunologically mediated and chronic symptomatology in SAD patients both reasonable and biologically plausible. While psychogenic factors may play a role in accentuating illness, they fail to explain the full gamut of objective findings in patients who get sick after silicone gel implantation. Prospective, properly designed epidemiologic studies that focus on the SAD symptom complex will help to establish the extent of its occurrence and the degree to which silicone plays a role in its genesis.

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# MAGNETIC RESONANCE MAMMOGRAPHY OF PATIENTS WITH SILICONE BREAST IMPLANTS: PROSPECTIVES FOR THE FUTURE

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*In view of the large number of women having silicone gel–filled breast implants (one to two hundred thousand in Canada), and considering the complications related to bleeding and migration of silicone gel from both ruptured and intact devices, techniques to detect silicone noninvasively must be developed. Current clinical techniques for visualizing structures in the breast include computed tomography (CT), X-ray mammography, and magnetic resonance imaging (MRI). Among these techniques, proton MRI alone can provide three-dimensional structural information, can easily distinguish breast tissue from silicone, and does not require the use of ionizing radiation. Moreover, by employing relaxation time–weighted imaging techniques, MRI can be used to distinguish healthy breast tissues from breast pathology.*

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2. Abbreviations: ANA, antinuclear antibodies; ATP, adenosine triphosphate; CT, computed tomography; Gd-DTPA, gadolinium diethylenetriaminepentaacetic acid; MR, magnetic resonance; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; PCr, phosphocreatine; PDMS, polydimethylsiloxane; Pi, inorganic phosphate; PM, phosphomonoester; RA, rheumatoid arthritis; RF, radio-frequency; SLE, systemic lupus erythematosus; SS, systemic sclerosis; $T_1$, longitudinal relaxation time; $T_2$, transverse relaxation time; TDA, 2,4 toluene diamine; UCTD, undifferentiated connective tissue diseases.

3. Key Words: Magnetic resonance, MRI, MRS, silicon, silicone, breast prostheses.

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*Proton magnetic resonance spectroscopy (MRS) has also been used to detect silicones (PDMS) in the body, and $^{31}P$ MRS can detect the local changes in high-energy phosphate metabolite levels that are associated with many pathological processes (ischemic disease, necrosis, tumor metabolism). As a result, we propose that the combined use of $^{29}Si$ MR spectroscopy with $^{1}H$ and $^{31}P$ MRS will provide clues to the origin of prosthesis failure, will identify the processes of silicone degradation in the body, and will help us to define further the interactions between the body and silicone-based biomaterials. Moreover, it is our hope that $^{29}Si$ MR imaging techniques for monitoring PDMS and its break-down products in the body will be employed clinically in the not-too-distant future.*

*We anticipate that $^{1}H$, $^{31}P$, and $^{31}Si$ MR techniques will enable us to investigate noninvasively the fate of silicone-based biomaterials in the body. These techniques may provide a breakthrough in mammographic investigations, particularly for women with dense breasts, scarring, or silicone breast implants, i.e., in cases where CT and X-ray mammography are particularly limited.*

## INTRODUCTION

In the Province of Québec alone, more than ten thousand breast prostheses were implanted annually prior to the new regulations by Health and Welfare Canada which restricted the use of gel-filled devices on January 13, 1993 (Bueckert, 1993). In the United States, the Food and Drug Administration had previously imposed strict restrictions on the use of silicone breast implants on April 16, 1992. Such implantations are now restricted to women after cancer surgery and to a few thousand women who wish to have breast augmentation, but only on the condition that they agree to take part in clinical studies (Painter, 1992). Prior to these limitations, a great number of women had already received implants. In Canada, between one and two hundred thousand women have received silicone breast implants, while in the United States there are between one and two million women with implants (Baines et al., 1992).

For those women who currently have implants, the long-term biocompatibility of such devices is still very much in question. The ability of these implants to maintain their biofunctionality, in terms of volume, softness, and shape, and their biostability, in terms of maintaining their chemical and physical characteristics as well as an appropriate biological response, have yet to be demonstrated (Guidoin et al., 1991).

The biostability of a permanent implant should obviously exceed the life expectancy of the patient. If the mean age of the patient in this case is about 34 years at implantation, and her life expectancy is greater than 70 years, then the biostability of the device should be maintained over more than 40 years *in vivo*.

In view of the considerable challenge in developing new products that will meet these demanding requirements, it is essential that new noninvasive methods are established to evaluate and follow *in vivo* the behavior of existing breast prostheses which have already been implanted in patients.

## BREAST IMPLANTS

*Designs*

The various types of breast implants that until recently were in common use include:

- **silicone gel–filled implants,** made with a silicone elastomer envelope enclosing a viscous and oily silicone gel (Figure 1A). These implants were available in different sizes and morphological designs (round, oval, low or high profile, with or without Dacron® fixation patches). The envelope of some of these models was covered with a layer of polyurethane foam;
- **saline-filled implants,** made with a thicker and less flexible silicone elastomer envelope containing saline that was added at the time of implantation (Figure 1B);
- **double-lumen implants** made from two silicone elastomer envelopes, one inside the other, the inner one containing silicone gel, while the outer envelope contained saline (Figure 1C);
- **expandable implants,** similar in design to the saline-filled model, except that additional saline could be added after implantation (Figure 1D). This was sometimes required after reconstructive surgery to expand the surface area of the skin. This implant usually was implanted only temporarily and was later replaced with a permanent device (Artz et al., 1988); and
- **autologous implants**, generally proposed for mastectomized patients who, for different reasons, could not receive a silicone prosthesis. These implants usually involved several operations over an extended length of time, and required considerable experience on the part of the surgeon. Two more common techniques were the **latissimus dorsi reconstruction** that used a muscle from the back, and the **transverse rectus abdominus myocutaneous flap** that used tissue and muscle from the abdomen (Vasconez et al., 1984).

*Patients*

Two different populations of women are involved with breast implant surgery. There are those who undergo cosmetic augmentation, usually under 35 years of age, and those who have reconstruction following a mastectomy, usually at least 35 years old (Baines et al., 1992).

Procedures for cosmetic augmentation represent about 80% of all operations, while reconstructions following a mastectomy for breast cancer represent only about 20%. Other reasons for surgery, such as correcting congenital defects, represent only a very small percentage (Guidoin et al., 1991; Baines et al., 1992).

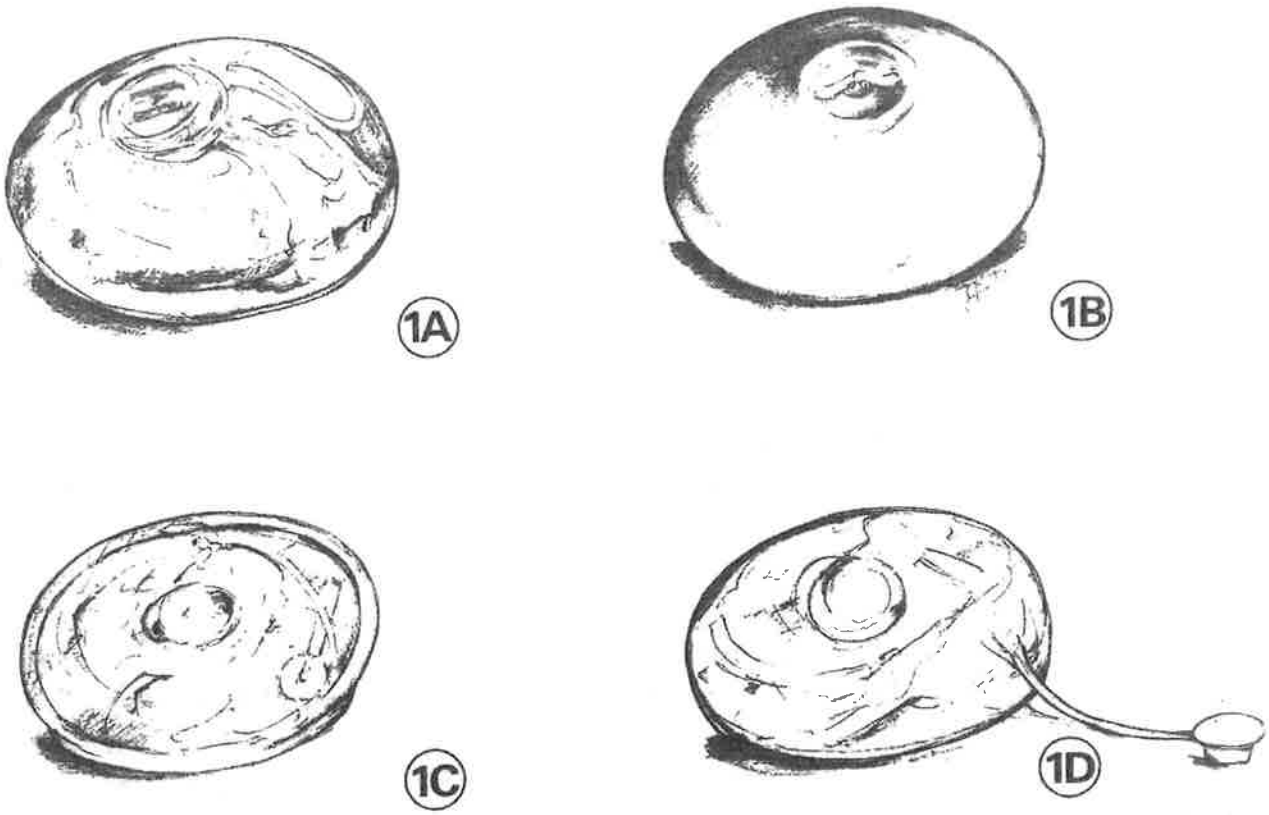


**FIGURE 1.** A: Silicone gel–filled prosthesis. B: Saline-filled prosthesis. C: Double-lumen prosthesis. D: Expandable prosthesis.

*Fate*

Recently, the Food and Drug Administration (Bright et al., 1993) reported the first national estimate of the prevalence of breast implants among adult women in the United States. Within the total female adult population, there are 33 implant recipients per 10,000 women, and nearly three quarters of these recipients have two implants. In the 35–44-year age group, the incidence is higher than the average, with 85 implanted per 10,000 women. The typical patient is a white woman, a resident of the south or west; she has a higher-than-average family income and more education than the average woman; she works and is slim.

A study conducted by the Angus Reid Group for Health and Welfare Canada, on Canadian patients, showed that women who have received breast prostheses are primarily between 35 and 54 years old. The average level of education of women in this group is slightly higher than that of women in the overall population, and the proportion of women in this group with a high annual familial income is much greater than the proportion in the Canadian population (Angus Reid Group Inc., 1992). About one quarter of all current implants are reported to be associated with complications.

From the statistics collected by the Food and Drug Administration under their "Mandatory Manufacturer Reporting" requirement up until August 1993, these complications fell into the following categories (Command Trust Network, 1993):

- injuries 39,161
- malfunctions 365
- deaths 30
- other 6

Another edition of these reports, from July 1, 1992, to September 30, 1993, indicated that 32,832 women with silicone breast implants had experienced complications resulting from injuries (American Silicone Implant Survivors Inc., 1994). These cases involved silicone breast implants manufactured by:

- Dow Corning 19,668
- Surgitek 6,378
- Baxter 2,444
- McGhan 2,128
- Mentor 1,383
- Cox-Uphoff 639
- Unknown 192

*Complications*

While the reasons for implantation fall into two very distinct categories, the prostheses themselves are all made from the same material, and their chemical, physical, and mechanical behavior in a biological environment is very similar. Regardless of the reasons for the implantation, the complications associated with the implants are common to the two types of patients. The principal complications associated with silicone breast implants are summarized in Table 1. They can be divided into two main types of problems:

**TABLE 1. Complications Associated with Silicone Breast Implants**

| | Due to: | Complication: |
|---|---|---|
| Problems due to the device itself | Permeability of the envelope | Silicone oil bleeding and/or gel migrating |
| | Presence of Dacron® fixation patches | Mineralization of the capsule |
| | Inadequate tearing strength of the envelope | Damaged prosthesis, rupture and gel migration |
| Problems due to biological reaction of patients | Implantation of a foreign material | Contracture of fibrous capsule<br>Inflammatory reaction<br>Foreign-body reaction |
| | Presence of silicone material | Human adjuvant disease |

*Problems due to the device itself.* It has been observed that due to an initial permeability of the silicone elastomer, there is a tendency for silicone oil to bleed or migrate through the envelope (Barker et al., 1978) (Figure 2, see color plate 1). After implantation, this tendency has been found to be more pronounced. Within our own research group we have observed an

additional problem, namely that some of the chemical components of certain devices induce mineralization once implanted. Prostheses with Dacron® fixation patches are more likely to induce mineralization of the capsule (Rolland et al., 1991) (Figure 3, see color plate 2). Also, the tearing strength of the outer envelope being inadequate leads to puncture, rupture, and failure (Peters, 1981) (Figure 4, see color plate 3).

*Problems due to the biological reaction of patients.* The normal response of the body to the implantation of a foreign material is the formation of a surrounding sac of connective tissue, called a fibrous capsule, principally composed of collagen and myofibroblasts (Smahel, 1978) (Figure 5, see color plate 4). As long as this capsule remains thin, soft, and flexible, the prosthesis is likely to maintain its biofunctionality. However, in a sizeable number of patients, the capsule becomes hard and rigid, and undergoes contracture. This not only puts the prosthesis under excessive pressure, but also causes the patient severe discomfort, pain, and disfigurement (Vinnik, 1976). To resolve this type of complication, surgeons will attempt to break the fibrous capsule by external manipulation; alternatively, it may be necessary surgically to excise the implant and its capsule.

A second type of biological reaction suggests the possibility that the device may generate an inappropriate inflammatory response. This response is known to be induced by the presence of a foreign material in the body because lymphocytes and macrophages are mobilized against vacuoles containing silicone gel (Vistnes et al., 1977) (Figure 6, see color plate 5). A stronger response, called a granulomatous foreign-body reaction, has been observed to be associated with polyurethane foam and sometimes with silicone materials as well. This response is characterized by granuloma-containing multinucleated giant cells attempting to phagocytize the foreign material (Smahel, 1978) (Figure 7, see color plate 6).

A third type of host reaction is the migration of blood components across the prosthesis envelope into the silicone gel. The penetration of cholesterol across the envelope was identified as early as 1972 (Lange, 1972), and we have demonstrated that several other materials are able to migrate into a prosthesis as well (Guidoin et al., 1991). It is evident that the envelope of a breast implant can behave as a dialysis membrane.

A fourth type of problem involves a variety of autoimmune disorders that has long been associated with the injection of silicone or paraffin for cosmetic purposes and is now linked to the implantation of gel-filled silicone prostheses. These disorders have been grouped under the name "human adjuvant disease," and may be caused by prolonged hypersensitization in response to the foreign material which acts as an adjuvant, i.e., a nonspecific stimulating agent of the immune system (Baldwin and Kaplan, 1983). These diseases include:

- Rheumatoid Arthritis (RA), a chronic inflammatory disease involving most connective tissues of the body, primarily finger joints. It is characterized by proliferative inflammation of the synovial membranes, leading to deformity, ankylosis, and invalidism.

- Systemic Sclerosis (SS), which manifests by an increasing tightness and thickening of the skin with hyperpigmentation that can affect the entire body. Often associated with rheumatoid arthritis and systemic sclerosis is Raynaud's phenomenon, which is primarily characterized by blanching of the fingers and toes in cold conditions.
- Systemic Lupus Erythematosus (SLE), which is a chronic disease characterized by an erythematous rash on the face and other areas exposed to sunlight. It also involves the vascular and connective tissues of many organs, manifesting itself through a multiplicity of local and systemic signs.
- Undifferentiated Connective Tissue Diseases (UCTD), a group of diseases which have in common such histologic features as inflammatory damage to connective tissue and blood vessels with deposition of fibrinoid material. This group includes the diseases cited above as RA, SS, and SLE (Dox et al., 1979).

Patients with human adjuvant diseases often have additional symptoms such as fever, sleep disturbance, memory loss, chronic fatigue, arthralgia, myalgia, dry eyes, dry mouth, hair loss, etc.

Most publications which discuss autoimmune diseases in patients who have had breast implantation surgery are case reports or series of case reports. At a recent meeting of the American Federation for Clinical Research, however, Claman reported the results of a study indicating that women with silicone breast implants may be at an increased risk of autoimmune diseases (Charbonneau, 1993). Press et al. (1992) have demonstrated that antinuclear antibodies (ANAs) are associated with the development of autoimmune complications in women with silicone breast implants. Observing patients who underwent silicone breast augmentation and who developed significant clinical symptomatology, Vojdani et al. (1992) have shown definite and significant abnormalities of the T-helper/suppressor ratio, increased autoimmunity, and increased production of immune complexes. In addition, Goldblum et al. (1992) have shown that polydimethylsiloxane elastomers used in ventriculoperitoneal shunts can be responsible for the development of specific immune reactivity in humans.

Whether or not breast implants are associated with cancer has not been demonstrated yet. A study concerned with the incidence of cancer among young women (median age at implant: 31.4 years) who had had implants for cosmetic reasons, failed to demonstrate a link between breast cancer and the prostheses for postoperative periods ranging from 0.1 to 31.7 years (median: 10.6 years) (Deapen and Brody, 1992). Another study based on women who underwent cosmetic breast augmentation in Alberta from 1973 through 1986 showed that these women had a lower risk of breast cancer than the general population (Berkel et al., 1992). These results have been severely criticized due to the fact that the cohort of women seeking breast augmentation does not represent the population as a whole and the first author was later fired by the Alberta Cancer Board (Modan, 1993; Walker and Troscli, 1993).

As regards prostheses covered by polyurethane foam, the consequences may be very different, due to impurities or degradation of the foam, as well as the presence of 2,4 toluene diamine (TDA). The 2,4 TDA isomer is listed by the International Agency for Research on Cancer (IARC) as a possible carcinogen for humans. Its carcinogenicity in animals has been confirmed (IARC, 1978). As early as 1964, Hueper described a direct causation between polymers, particularly polyurethanes of different chemical compositions, and carcinomas in rats, and warned against exposing humans to these products (Hueper, 1964).

*Migration of Silicone*

The earlier practice of injecting silicone oil and silicone gel into the body for whatever reason is now prohibited in North America, but may still be used in some countries. The consequences of such a primitive approach are dramatic and have been well documented. Ellenbogen reported silicone migration, hepatic disease manifested as granulomatous hepatitis, and hypopigmentation, following silicone injections in three patients, and the same symptoms plus death in a fourth (Ellenbogen and Rubin, 1975). The manufacturing company, Dow Corning Inc., disapproved of the injection of silicone fluids for cosmetic purposes as early as 1971 (Braley, 1971).

With respect to gel-filled breast prostheses, the result of rupture of the envelope or bleeding of the silicone oil through the envelope will result in silicone migration within the capsule, beyond the capsule into the breast tissue, and sometimes to more distant locations. The migration of silicone has been found to be associated with both ruptured and intact breast implants. The location of migrated silicone gel and oil has been observed clinically in axillary lymph nodes (Hausner et al., 1978; Wintsch et al., 1978; Truong et al., 1988) (Figure 8, see color plate 7), in the abdomen and groin (Cappozi et al., 1978), in the arm (antecubital fossa) (Huang et al., 1978) and upper arm (Edmond, 1980), in the chest and shoulder (Mason and Apisarnthanarax, 1981), and, more recently, has been identified by magnetic resonance spectroscopy (MRS) in the blood and liver (Garrido et al., 1994). Moreover, Levine and Ilowite (1994) described a link between a rare digestive ailment in children and silicone breast implants in mothers who breast-fed them.

Migration of small particles of silicone has also been observed with other implants and devices containing silicone elastomers. Particles of silicone have been found in the inguinal lymph node after silicone rubber was used in hip arthroplasty (Travis et al., 1985), in the lymph nodes of patients with silicone elastomeric finger joint prostheses (Kircher, 1980), in the spleen of a patient with chronic renal failure following periodic hemodialysis (Gosselin et al., 1985), and in the liver, kidneys, lung, brain, adrenal, pancreas, and bone marrow of other patients (Travis et al., 1985). Silicone rubber is also believed to induce endocarditis, a complication associated with transvenous cardiac-pacing catheterization (Travis et al., 1986).

At the present time, there is a limited number of means that can be used to detect and identify silicone *in vivo* (Garrido et al., 1994). In fact, the techniques most commonly used are applied to explanted tissue only. These include gas-liquid chromatography (Baker et al., 1982) and

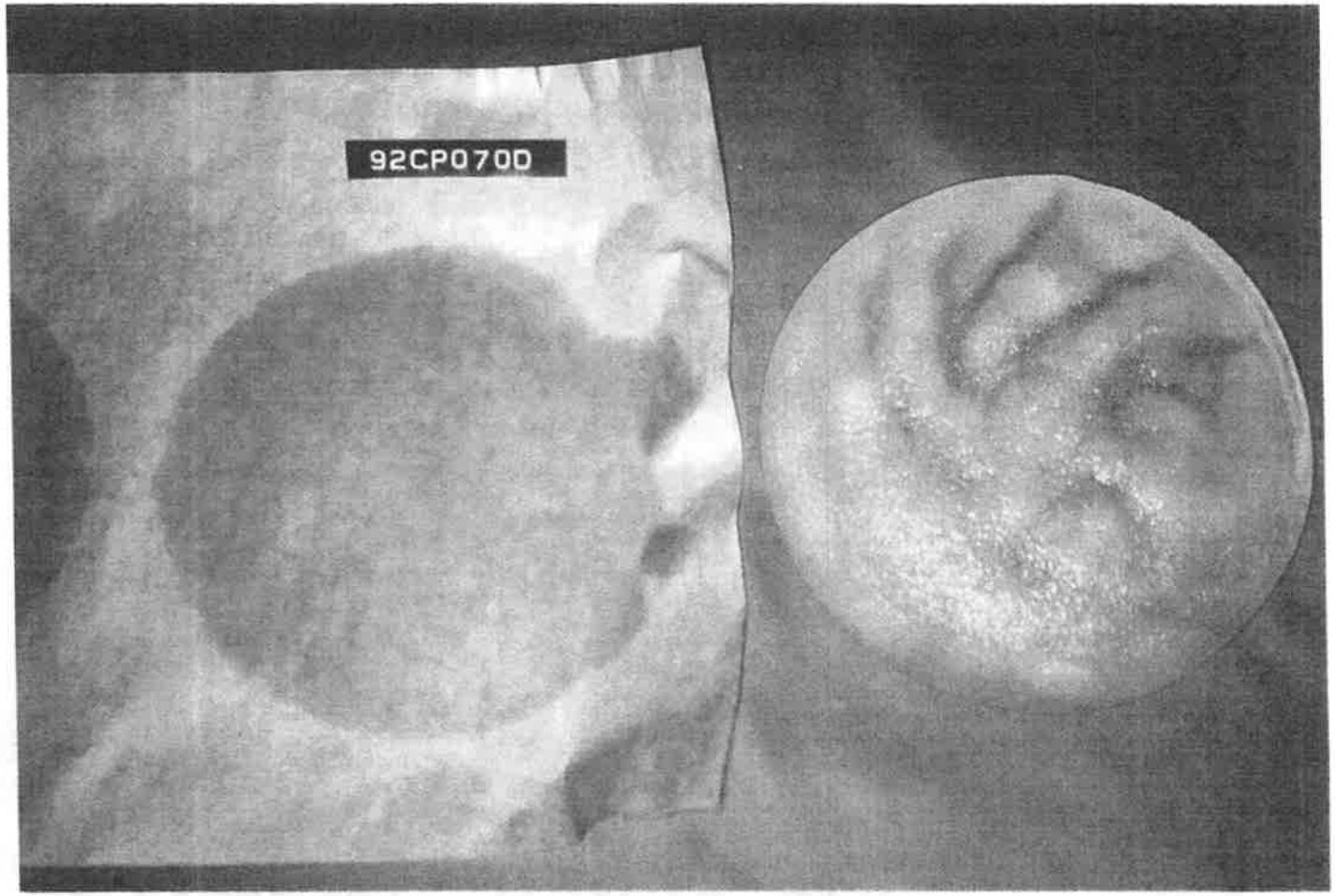


**FIGURE 2.** Explanted breast prosthesis and a sheet of brown wrapping paper showing oily stain resulting from only 14 days of direct contact (Même prosthesis; implantation time: six years).

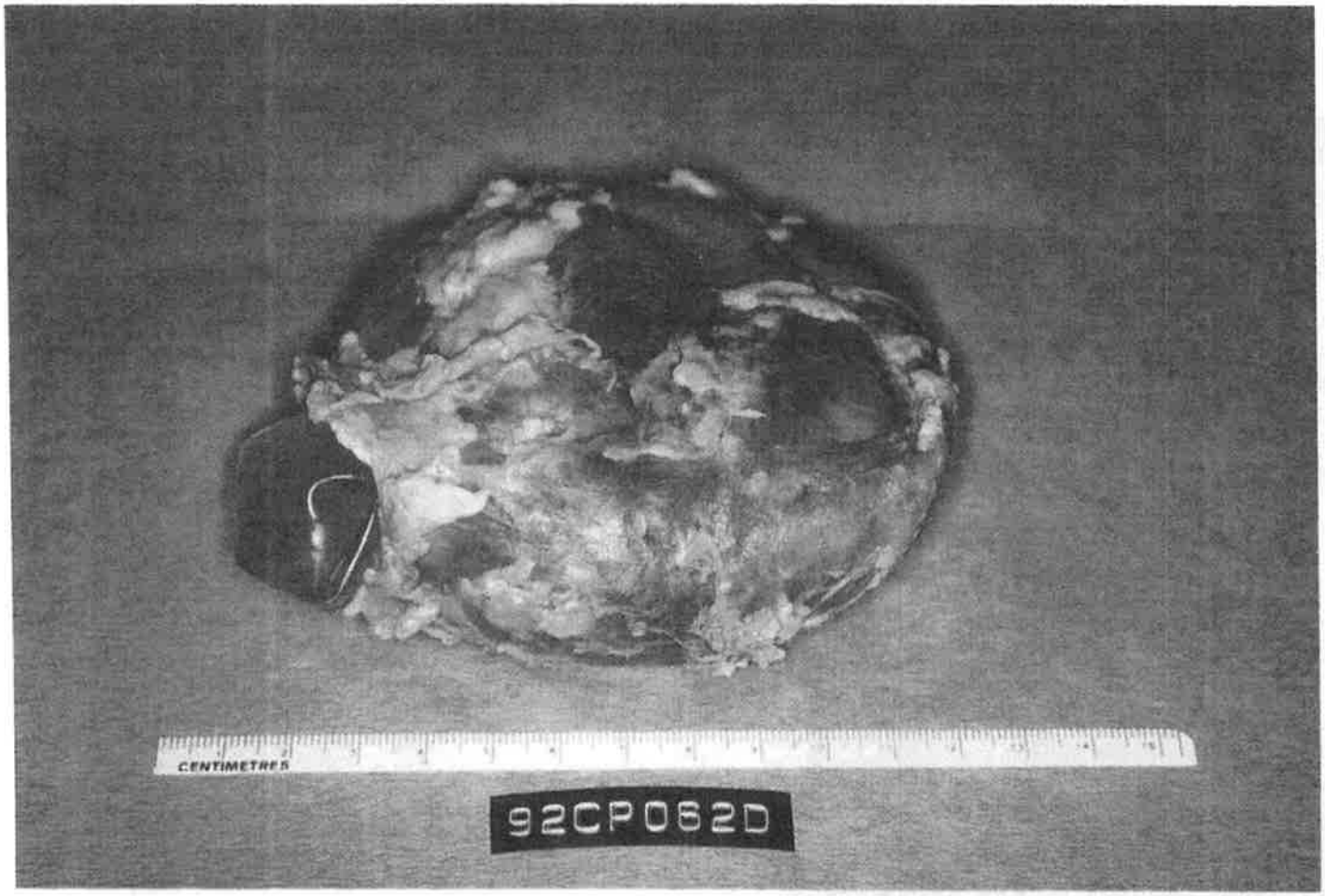


**FIGURE 5.** Explanted breast implant enclosed and contracted by its fibrous capsule (gel-filled prosthesis; implantation time unknown).

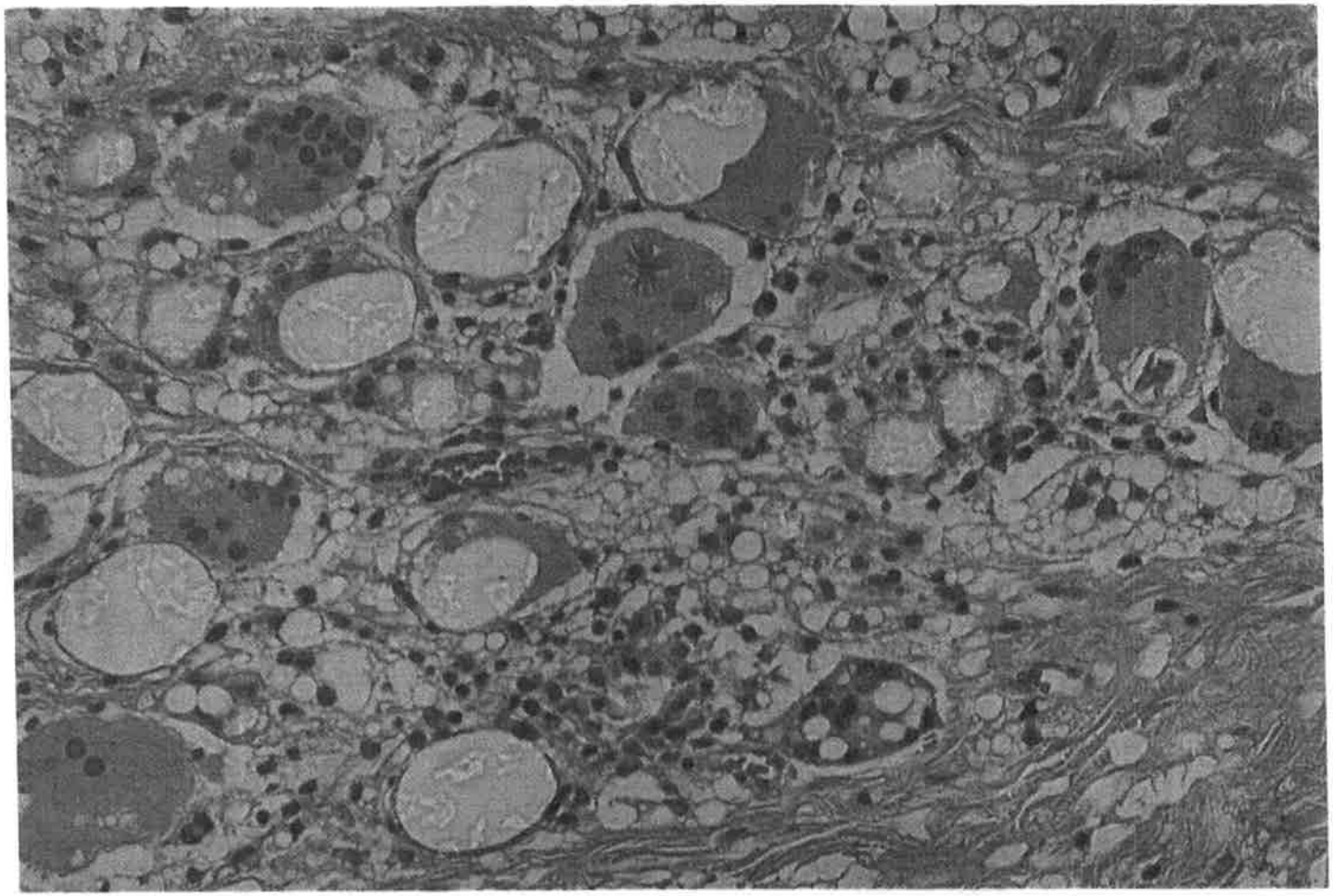

**FIGURE 6.** Section of a fibrous capsule showing large vacuoles containing silicone material identified by Energy-Dispersive X-ray Analysis. Inflammatory cells present are: lymphocytes, multinucleated giant cells, and plasmocytes (gel-filled prosthesis; implantation time: 16 years).

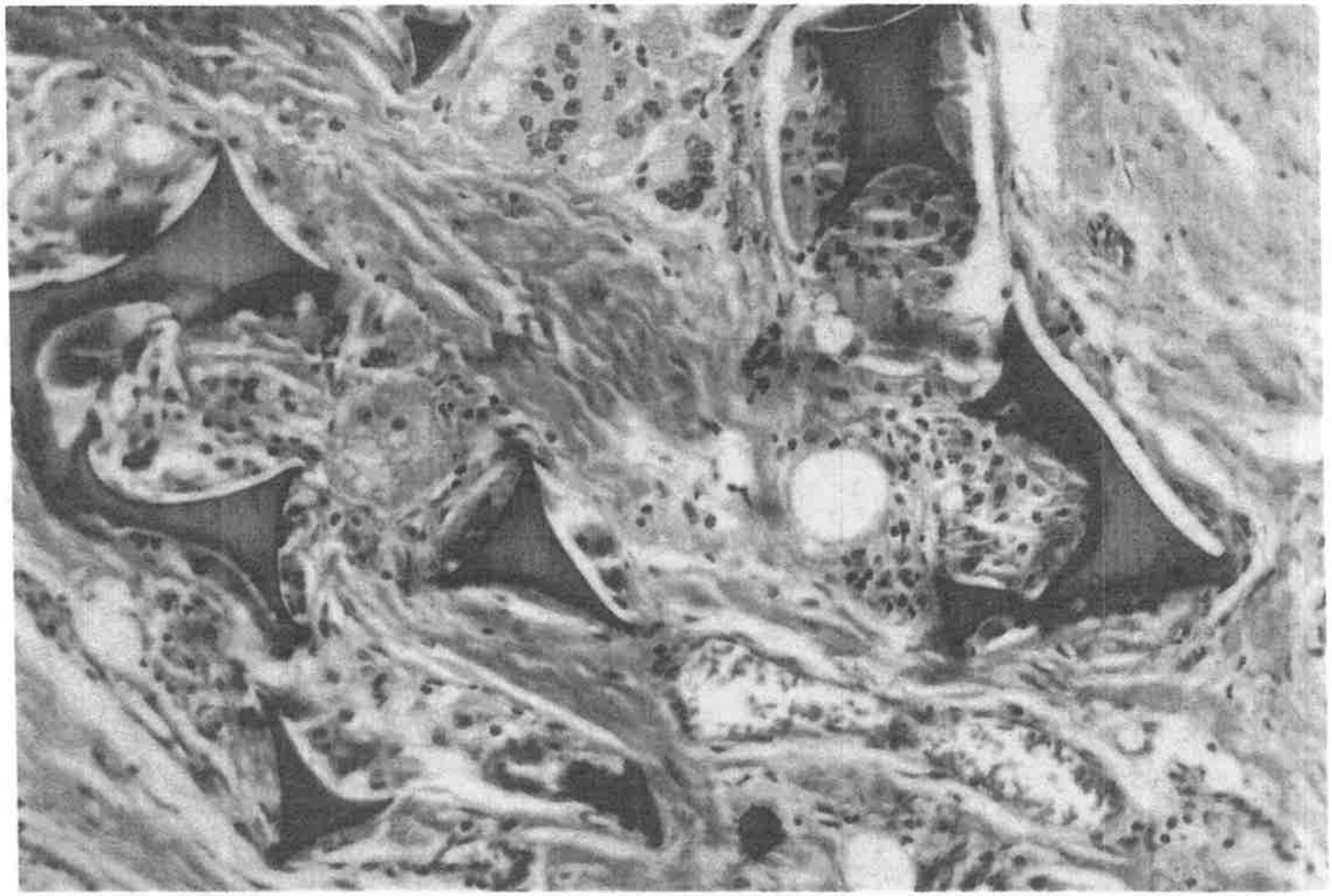

**FIGURE 7.** Section of a fibrous capsule showing fragments of polyurethane foam inducing a granulomatous foreign-body reaction (gel-filled prosthesis covered with polyurethane foam; implantation time: 2 months, 11 days).

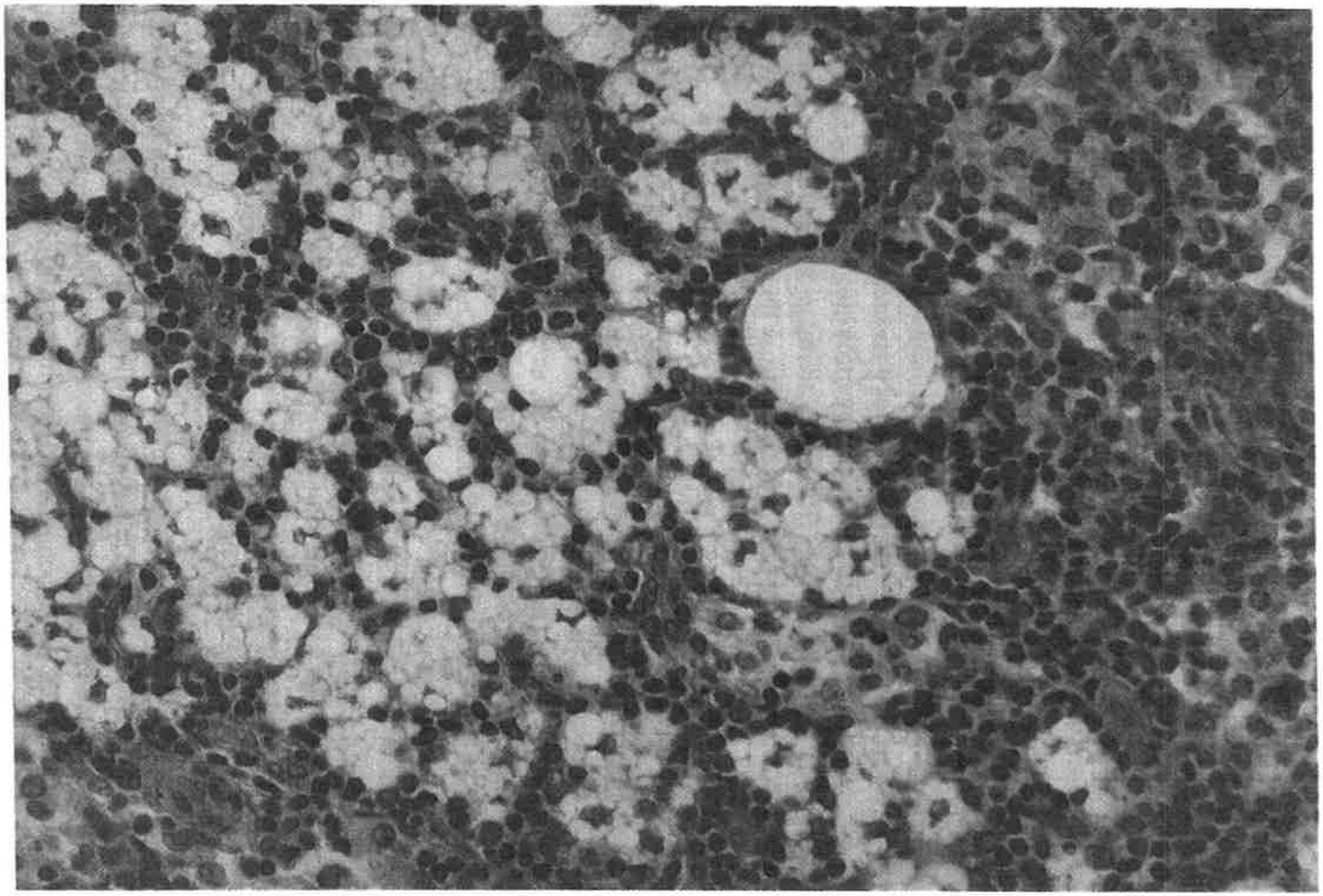

**FIGURE 8.** Section of a fragment of lymph node showing vacuoles containing silicone (gel-filled prosthesis; implantation time: three years).

scanning electron microscopy with an elemental detection X-ray analysis probe (Winding et al., 1988).

## MAGNETIC RESONANCE MAMMOGRAPHY TODAY

*MR versus Alternative Imaging Methods*

The first and most obvious advantage of MR techniques over CT or X-ray mammography is that ionizing radiation is not required to visualize the breast. It has been estimated that if 75% of the five hundred thousand women in Quebec who are 40 to 49 years old were to undergo two-view mammography one time each year for ten years, the radiation dose delivered could be expected to cause 15 additional breast cancer deaths over the lifetime of these women (Caro and O'Brien, 1993). To date, no long-term adverse health effects have been demonstrated for MR techniques. The second immediate advantage of MR over CT or X-ray mammography is that with MR any number of thin-slice regions of interest can be visualized, from virtually any orientation. Current MR imaging (MRI) equipment also can acquire and reconstruct three-dimensional image data. Whereas CT can also image thin slices of interest, it is limited to axial views, and X-ray mammography provides only two-dimensional projectional views (Schneider and Chan, 1993). The ability to image in three dimensions is an obvious asset when visualizing structures of the body that are as highly heterogeneous as the breast.

The presence of a silicone prosthesis in the breast can provide a considerable obstacle to X-ray mammography and ultrasound imaging, particularly if silicone gel has escaped from the prosthesis. Because silicone gel is radiopaque, such a prosthesis can obscure part of the breast in mammographic images. Also, the prosthesis itself, as well as the surrounding fibrous capsule, are additional complications to X-ray mammography which requires compression of the breast (Eklund et al., 1988; Hawes, 1990; Schneider and Chan, 1993). In sonographic images, silicone gel which has leaked from the prosthesis often manifests itself as a low-level homogeneous echogenic noise which obscures the structures beyond it (Rosculet et al., 1988). In contrast, MRI has been shown to be useful for visualizing breasts which are dense or have silicone injections or implants, scar formation from previous surgery, or fat necrosis; MRI can also be used to visualize regions adjacent to the breast such as the chest wall (Pierce et al., 1991).

One drawback of MRI is that a typical patient examination requires more time than do other imaging techniques (CT, ultrasound, X-ray). A typical MR exam, which includes several series of images to visualize a region of interest in the body, takes 45 to 60 minutes, including patient preparation and setup of MR exam parameters. For a typical two-view X-ray mammography exam, this time is approximately 15 minutes. Similarly, ultrasound imaging of the breast is normally limited to visualizing small regions of the breast to determine whether a previously detected lesion is solid or cystic, which requires 10 to 15 minutes. Another factor which limits the use of MR techniques is that the intense magnetic field required makes MRI unsuitable for patients with some types of aneurysmal and hemostatic clips, some dental

implants, some types of artificial heart valves, and for all patients with pacemakers or artificial hearts (Shellock and Swengros, 1991). Moreover, claustrophobic patients may not tolerate being placed within the bore of the MR magnet.

*Proton MRI of Breasts without Prostheses*

The sensitivity of proton MRI for visualizing lesions in the breast is illustrated by the case in which MR images identified a breast tumor only 3 mm in diameter (Turner et al., 1988). Examples of MRI images of breasts, acquired with a 1.5 T GE Signa® system, are shown in Figures 9A and 9B. Moreover, the shape of a breast lesion and its change in signal intensity with different MR radio-frequency (RF) pulse sequences allows differentiation between benign and malignant processes in the breast (El Yousef et al., 1985). Breast pathology can also be characterized by the administration of intravenous MR contrast agents such as Gd-DTPA (gadolinium diethylenetriaminepentaacetic acid) which enhance the MR signal intensity of areas of high tissue perfusion. In this manner, breast carcinomas can be consistently enhanced over normal tissue or benign lesions, such as fibroadenomas (Pierce et al., 1991). Also, sequential MRI of the time course of this tissue signal enhancement, after administration of a contrast agent, can demonstrate differences between benign and malignant tumors in the breast (Debruhl et al., 1992; Smith, 1992). This finding has been verified clinically by Stack et al. in a study of 18 patients with palpable breast masses (1990).

*Proton MRI of Breasts with Prostheses*

The presence of a silicone gel prosthesis in a breast exhibiting a clinically detectable change from its normal condition, i.e. change in shape, palpable masses, patient discomfort, etc., places additional demands on the imaging technique which is chosen to visualize the breast. The published results of one study show that X-ray mammograms detected signs suggestive of prosthesis rupture in only 16 of 24 patients with ruptured implants (Andersen et al., 1989). The conclusion of this study was that mammograms accurately detect ruptures only if the silicone gel is released and has migrated away from the implant, provided it has not migrated out of the breast. In another case, a false positive result was obtained when the X-ray image of a hematoma was interpreted as a ruptured implant (Andersen et al., 1989). Another limitation of traditional mammography is associated with the detection of silicone granulomas which may be formed when silicone has escaped from a prosthesis. Clinically, these granulomas may be indistinguishable from malignant breast disease (Brandt et al., 1984).

The sensitivity of the MR techniques to the different chemical environments experienced by protons in tissue, fat, and silicone gel provides a means of discriminating between these compounds in the breast. Proton MR images with appropriate relaxation time ($T_1$ and $T_2$) weighting can provide contrast between fatty tissue, ductal tissue, lesions, cysts, and silicone gel in the breast (Table 2). Moreover, the sensitivity of proton MRI is well demonstrated by one case in which an intracapsular rupture of a silicone prosthesis was identified (Sinha et al., 1993). One MR technique known as the Three-Point Dixon Technique exploits the differences between the proton chemical shift frequencies in water, fat, and silicone gel in order to obtain separate water/fat and silicone images of the breast (Schneider and Chan,

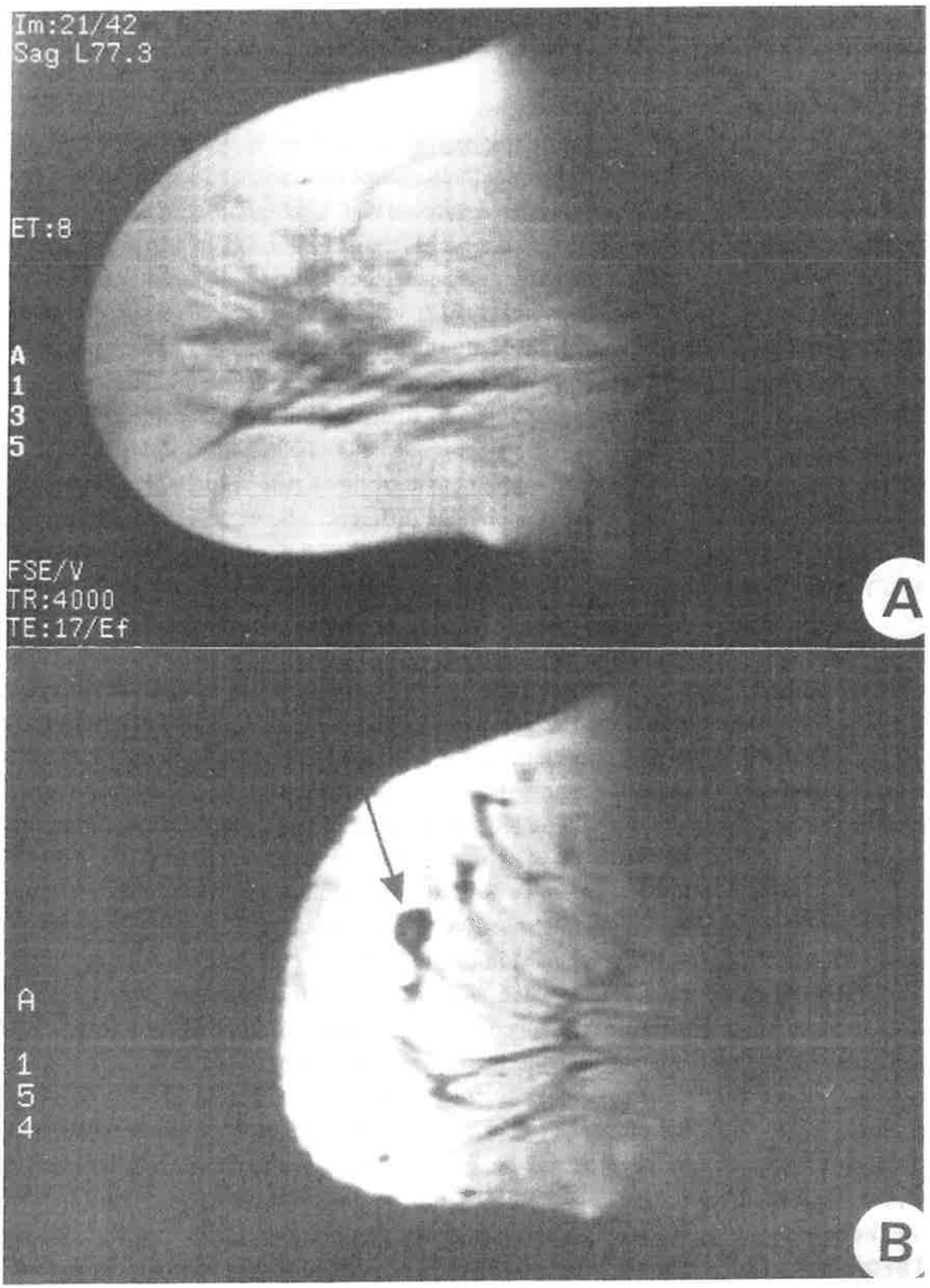


**FIGURE 9.** MRI breast examination of a middle-aged patient. A. $T_2$-weighted MR image of a normal involuted breast (right), acquired with a fast spin–echo sequence (sagittal view, TR = 4000 msec, TE = 17 msec); B. MR image of the left breast of the same patient, demonstrating a nonspecific nodule in an involuted breast (arrow). This image was acquired with a gradient-recalled echo sequence (SPGR) (sagittal view, TR = 150 msec, TE = 3.3 msec).

1993). Proton MR images obtained with this technique have positively identified a normal prosthesis envelope, a ruptured prosthesis envelope, a fibrous capsule, and a fluid collection not containing silicone which was outside the envelope (Schneider and Chan, 1993). It is notable that these images were obtained with the current commercially available 1.5 Tesla General Electric Signa® imaging system. Proton MR images, obtained in our lab, of breasts with silicone gel–filled prostheses are shown in Figures 10A and B, and 11A and B. Chemical shift selective imaging techniques (with water and fat MR signals suppressed) have also been developed, and have yielded highly sensitive *in vivo* images of the distribution of implanted silicone in an experimental animal (Pfleiderer et al., 1993a). Furthermore, these techniques have been combined with an echo-planar imaging technique; $^{1}H$ MR images of the silicone distribution in a patient can be acquired in as little as eight seconds (Garrido et al., 1993a).

**TABLE 2. Proton Relaxation Times of Normal and Pathological Breast Tissue**

| Tissue | | $T_1$ (msec) | $T_2$ (msec) |
|---|---|---|---|
| Fatty tissue | | 174 | 57 |
| Ductal tissue | | 286 | 53 |
| Ductal hyperplasia | | 302 | 46+ |
| Carcinoma | > 2 cm diam | 532+ | 56 |
| | < 2 cm diam | 258 | |
| Fibroadenoma | noncalcified | 526+ | 58 |
| | calcified | 253 | 47 |
| Fibrocystic disease | predominantly fibrous | 378 | 50 |
| | predominantly cystic | 954+ | 83+ |

Relaxation times measured at 0.3 Tesla.
+readily distinguishable from both normal fatty and ductal tissue.
Source: El Yousef et al., 1985.

## POTENTIAL FOR MONITORING HEALING AND/OR TISSUE REACTION TO IMPLANTS WITH $^{1}H$ NUCLEAR RELAXATION TIME MEASUREMENTS AND $^{31}P$ MRS

### *$^{1}H$ Relaxation Times of Lesions*

In addition to providing image contrast, the variation of proton nuclear magnetization relaxation times between different tissues can provide information about breast pathology. As discussed previously, there are both longitudinal ($T_1$) and transverse ($T_2$) relaxation time differences between normal tissues and lesions in the breast (Turner et al., 1988) (Table 2). For example, ductal hyperplasia has a lower $T_2$ than normal ductal tissue and the $T_2$ of cysts is markedly elevated (El Yousef et al., 1985). Lesions such as carcinomas larger than 2 cm in diameter, noncalcified fibroadenomas, and cysts demonstrate elevated longitudinal relaxation times ($T_1$) over ductal hyperplasia, predominantly fibrous fibrocystic disease, calcified fibroadenomas, normal ductal tissue, and fatty tissue (El Yousef et al., 1985). As a result, localized relaxation time measurements of the breast to supplement MR images with various

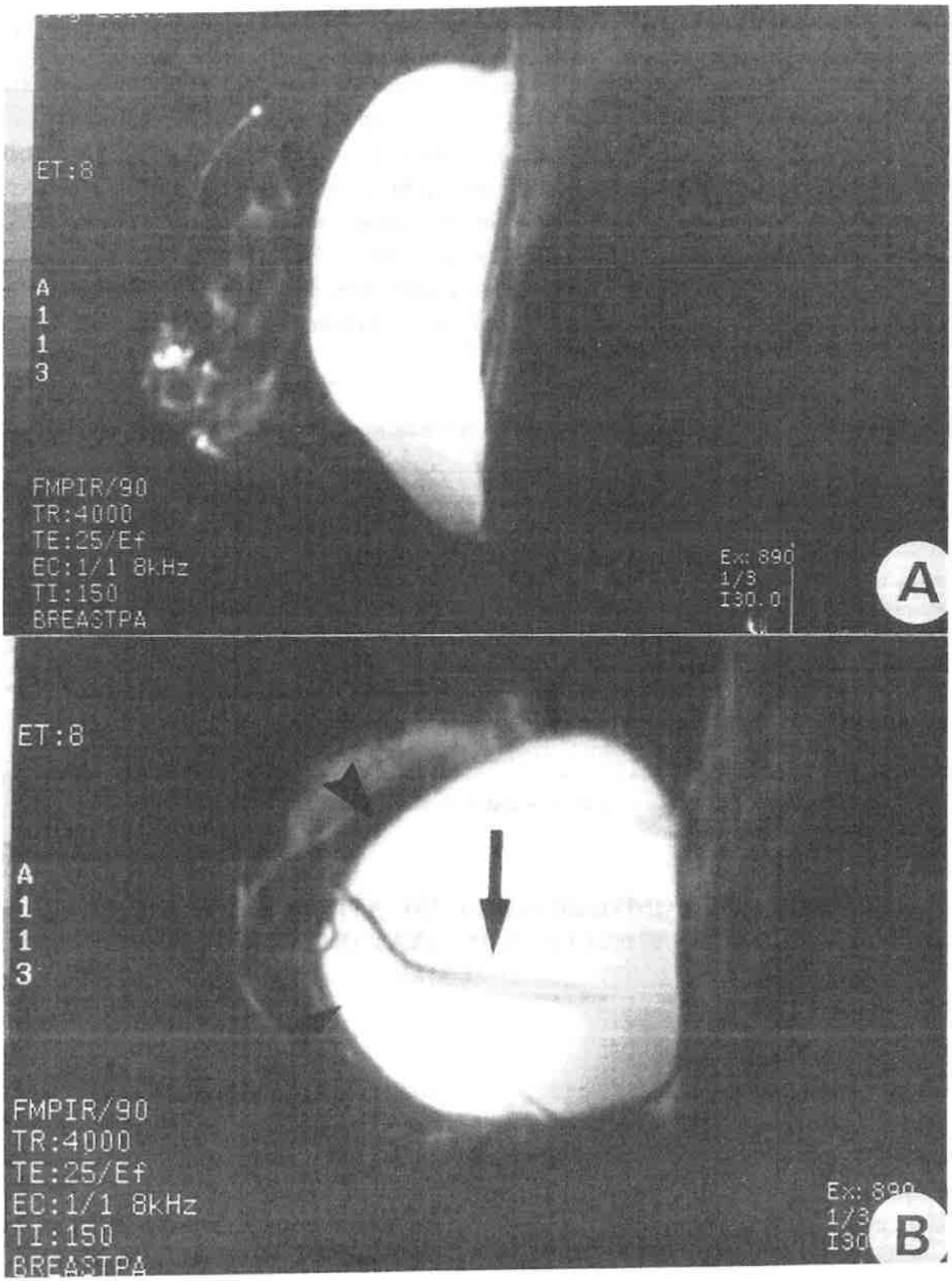


**FIGURE 10.** MRI breast examination of a middle-aged patient. A. $T_1$-weighted MR image of a normal oval-shaped saline-filled silicone prosthesis implanted six months earlier in the right breast, acquired with an inversion-recovery sequence (FMPIR) (sagittal view, TR = 4000 msec, TE = 25 msec, TI = 150 msec). B. $T_1$-weighted MR image of the implant in the left breast of the same patient. This image demonstrates a rounded prosthesis suggesting capsular contraction (arrowheads), and the structure within the prosthesis (arrow) appears to be a portion of the prosthesis envelope, suggesting intracapsular fold of the prosthesis (FMPIR sequence, sagittal view, TR = 400 msec, TE = 25 msec, TI = 150 msec).

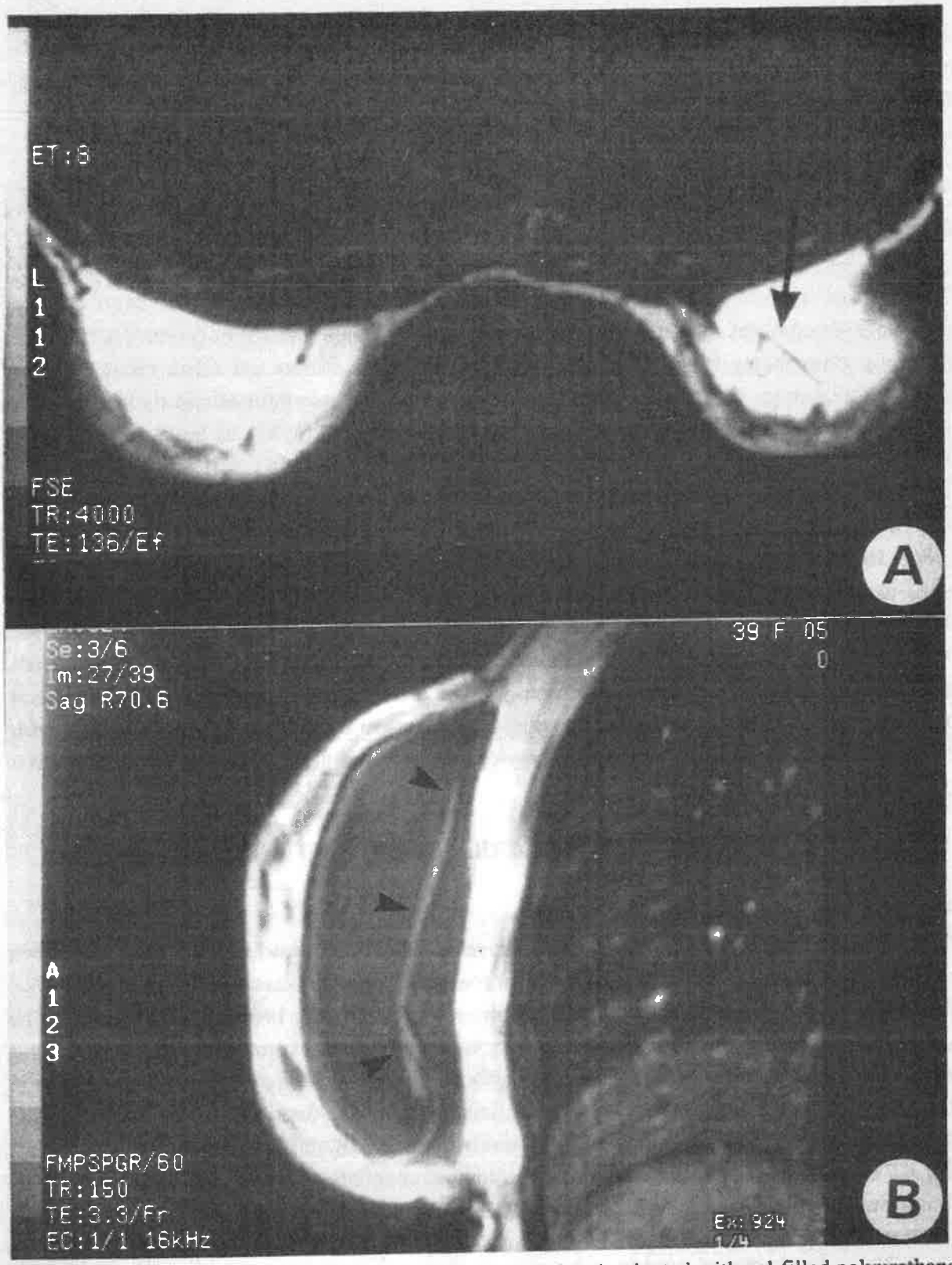


**FIGURE 11.** MRI breast examination of a middle-aged patient implanted with gel-filled polyurethane-coated breast prostheses for five years. A. An axial view of both breasts acquired with a fast spin–echo sequence. The left breast is contracted and an intracapsular fold of the left prosthesis is indicated (arrow), whereas the contralateral breast appears normal (TR = 4000 msec, TE = 136 msec). B. A gradient-echo MR image of the left breast of the same patient. Again, the folded prosthesis envelope is apparent (TR = 150 msec, TE = 3.3 msec).

informed selections of $T_1$- and $T_2$-weighting can further aid in the noninvasive characterization of breast pathology.

### *$^{31}P$ Magnetic Resonance Spectroscopy*

The presence of an implanted prosthesis in a breast provokes a certain amount of tissue reaction and healing, as evidenced by the formation of a fibrous capsule around each breast implant. Characterization of this tissue reaction may be provided noninvasively by $^{31}P$ MRS. Phosphorous spectra provide measures of the relative concentrations of high energy phosphate metabolites such as phosphocreatine (PCr), adenosine triphosphate (ATP), and inorganic phosphates (Pi). They also indicate the intracellular pH (Bottomley, 1989). Abnormalities in processes affecting high-energy phosphate metabolites and their responses to various stresses have been shown to be detectable with $^{31}P$ MRS, as have the effects of ischemic disease, necrosis, and tumor metabolism (Bottomley, 1989). Of particular interest for $^{31}P$ MRS studies of the breast is the fact that $^{31}P$ spectra of normal breast tissue cannot be obtained because of the low concentration of phosphorous metabolites (Oberhaensli et al., 1986). However, in a study of six breast cancer patients, total phosphate metabolite contents were measured at three to four times higher than normal (Bottomley, 1989). Also, in a separate study, $^{31}P$ spectra of a breast tumor contained a prominent phosphomonoester (PM) peak and demonstrated a pH higher than that of normal brain and muscle tissue (Oberhaensli et al., 1986). Thus, if a silicone implant provokes a tissue reaction which involves a local increase in phosphate metabolite levels, this, like tumors in the breast, will be detectable with $^{31}P$ MRS. Moreover, the discrimination between the affected tissues and any adjacent normal tissue should be excellent.

## FUTURE PROSPECTS: $^{29}$SI MRI AND MRS

### *$^{29}Si$ MRI of Breasts with Silicone Implants*

Silicone granulomas resulting from the leakage of silicone gel into breast tissue have been shown to be clinically indistinguishable from malignant breast disease (Debruhl et al., 1992). Moreover, complete removal of this free silicone gel from the breast parenchyma can be difficult because it may be impossible to determine at the time of surgery if all of the gel has been removed (Argenta, 1983). The sensitivity of $^{29}Si$ MR techniques to the silicon nuclei in the gel provides a means of selectively visualizing the silicone distribution in a breast and can thereby potentially alleviate both of these problems. The MR sensitive nucleus $^{29}Si$ accounts for 4.7% of all Si atoms. As a result, the estimated concentration of $^{29}Si$ in the silicone gel found in breast implants is 660 mM (Goldstein et al., 1987). In comparison, the intracellular skeletal muscle concentration of ATP is 5 mM (Guyton, 1976). Each ATP molecule contains three $^{31}P$ nuclei and each of these contributes to a unique MR spectral peak. Considering the different concentrations of $^{29}Si$ and $^{31}P$ in these two systems, and their relative MR sensitivities (Table 3), the $^{29}Si$ MR signal from silicone gel is expected to be 16 times more intense than the $^{31}P$ MR signal from intramuscular ATP. The normal tissue $^{29}Si$ concentration is estimated to be less than 10 μm and is undetectable by $^{29}Si$ MR *in vivo* (Dobbie and Smith, 1982). This negligible background signal ensures high contrast between silicone and tissue in

$^{29}Si$ MR images obtained *in vivo*, and is thus reasonably expected to be a sensitive means of mapping not only the distribution of silicone but also the migration of silicone gel throughout the body.

**TABLE 3. Relative Sensitivities of Various Nuclei for MR**

| Nucleus | Natural abundance | I | γ (MHz/T) | $S/S_{Proton}$ |
|---|---|---|---|---|
| $^{1}H$ | 100% | 1/2 | 42.6 | 1 |
| $^{2}H$ | 0.015% | 1 | 6.5 | 0.0095 |
| $^{29}Si$ | 4.7% | 1/2 | 8.5 | 0.0079 |
| $^{31}P$ | 100% | 1/2 | 17.1 | 0.065 |

Sensitivity, S, is proportional to the product $I(I+1)\gamma^3$
I = the nuclear spin
γ = the nuclear gyromagnetic ratio

*$^{29}Si$ MRS of Breasts with Silicone Implants*

The MR chemical shift frequency of $^{29}Si$ in siloxane-based compounds is highly dependent on the Si-O-Si bond angle (Sternberg and Priess, 1993). Moreover, for silicon nuclei in one of the three siloxane units nearest the end of a siloxane chain, the $^{29}Si$ chemical shift increases with proximity to the chain end (Harris and Robins, 1978). As a result, $^{29}Si$ MR spectra can be used to characterize the chemical environment experienced by silicon in silicone gel (Garrido et al., 1991). For example, the broad chemical shift spectrum of $^{29}Si$ allows easy discrimination between polysiloxanes, silica gel, hydrolyzed silicone, and highly coordinated silicone complexes (Table 4) (Garrido et al., 1993b). This sensitivity to chemical changes in the silicone gel and the noninvasiveness of MR techniques enable one to monitor any changes that may occur in implanted silicone *in vivo* over time (Pfleiderer et al., 1993b). The fact that silicone prostheses often deteriorate because of the absorption of body fluid components suggests that there may be some chemical changes occurring in the silicone elastomer of the prosthesis envelope prior to rupture, and in the silicone gel after it has escaped from the prosthesis (Allwork and Norton, 1976; Pfleiderer et al., 1993b). Monitoring the chemical environment of silicon in the body with $^{29}Si$ MR spectroscopy may therefore provide us with clues to the origin of prosthesis failure, as well as demonstrate the degradation of silicone gel as a result of interactions with the body.

**TABLE 4. Relative $^{29}Si$ Chemical Shift Frequencies of Various Silicone Species**

| Species | Frequency shift (ppm)* |
|---|---|
| tetramethylsilane | 0 |
| polysiloxane | -20 |
| hydrolyzed silicone | -40 to -85 |
| silica gel | -90 to -115 |
| highly coordinated complexes | -120 to -150 |

* Frequency shifts are expressed as fractions of the Si resonant frequency, in parts per million (ppm), and so do not depend on the magnetic field strength used for the measurement.
Source: Garrido et al., 1993b.

## CONCLUSIONS

The current controversy over the stability and biocompatibility of silicone gel–filled mammary prostheses has created a need for a sensitive means of monitoring silicone gels *in vivo*. Different types of MRI and MRS can complement each other in determining noninvasively the location, distribution, and chemical changes in silicon compounds, as well as monitoring the tissue reaction to the implant *in vivo*. Proton MRI has been demonstrated to yield sensitive three-dimensional images of anatomical structures in the body. Differences in nuclear relaxation times between silicone gel and normal and pathological tissues in the breast provide contrast between these structures. Moreover, differences in the chemical shift frequency between protons in silicone gel, tissue, water, and fat enable the acquisition of separate silicone images, and water/fat images of the breast containing a prosthesis. Images constructed from $^{29}Si$ MR signals will identify the spatial distribution of only the silicone-containing compounds in the body, while $^{29}Si$ MRS will monitor changes in the chemical structure of these compounds as a result of interactions within the body. In addition, $^{31}P$ MR spectroscopy can be expected to detect any changes in high energy phosphate metabolite levels that may occur as a result of tissue reaction to implanted materials in the breast. Thus, MRI and MRS techniques have the potential to enable noninvasive monitoring of the fate of silicone-based prostheses in the body. Due to limitations of cost and availability, however, it is not proposed at the present time that these techniques replace X-ray mammography for the purpose of routine screening for lesions. MR techniques, however, can be a sensitive supplement to current mammographic screening techniques, particularly for patients with dense breast tissue, scar tissue from previous surgery, or implanted prostheses.

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# HIGHLIGHTS OF THE RECENT IMMUNOLOGY OF SILICONE WORKSHOP, NATIONAL CANCER INSTITUTE MARCH 13–14, 1995

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This workshop started with a discussion about the chemistry of silicon and silicon dioxide; it addressed the question of how material from nature (silicon) is used for manufacturing silicone gels (Lane and Burns, 1995) and continued with different presentations to cover the following issues:

## SILICONE MIGRATION TO DISTANT TISSUES

By nuclear magnetic resonance (NMR) and histopathology, it was shown that silicone migrates from the implant site to adjacent tissues and distant organs, such as the liver and spleen (Garrido et al., 1995; Karjoo and Vojdani, 1995; Puszkin et al., 1995; Wolf et al., 1995). It was also shown that silicone is not an inert material but that it undergoes chemical transformation in a biological environment. Through NMR spectroscopy using $^{29}Si$, it was confirmed that silicone, partially hydrolyzed silicone, silica, and other silicon compounds were present in animal tissues exposed to silicone and in blood samples from women with gel- filled breast implants. By contrast, tests done on the blood of nonimplanted patients were completely negative for silica, silicon, and silicon dioxide. The reaction of monomer to polymer can go both ways and, as a result of the aging of material, polymer is broken down to monomer.

$$\text{MONOMER} \rightleftharpoons \text{POLYMER}$$

Therefore, if polymer is placed into the body, its breakdown products will be detectable in the blood and tissues a few years later (Baitch, 1995; Garrido et al., 1995; Karjoo and Vojdani, 1995; Puszkin et al., 1995; Shanklin and Smalley, 1995; Wolf et al., 1995).

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2. This manuscript was prepared from the point of view of laboratory and immunological diagnosis and may not reflect all the material presented.

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## BINDING OR ADSORPTION OF PROTEINS TO SILICONE

Polydimethylsiloxane, like other hydrophobic polymers (polystyrene, polypropylene, nitrocellulose), adsorbs soluble proteins with high avidity under physiological conditions (Butler et al., 1995). Through atomic force microscopy, it was revealed that the potential adsorptive surface of polydimethylsiloxane is much greater than that of polystyrene, used in the manufacturing of ELISA plates. Therefore, the data presented raised a philosophical concern as to why hydrophobic substances are used for medical prostheses in an environment in which cell surfaces and soluble proteins are typically negatively charged and repel adherence. Adherence or binding of polydimethylsiloxane or other silicone byproducts to body proteins changes the self material to nonself material; consequently immunological reaction to this complex occurs, especially in an individual having genetic predisposition to autoimmune diseases (Brautbar et al., 1995; Kossovsky, 1995; Vojdani and Karjoo, 1995; Young et al., 1995). Moreover, through the observation of macrophage-like cells and fibroblast cell lines, it was shown that inclusion complexes of α-cyclodextrin and silicone compounds have a cytotoxic effect as well as DNA-membrane damaging properties. Thus, in addition to the autoimmune properties of silicone complexes, the lethal effect on cells also was demonstrated (Felix et al., 1995).

## GENETIC PREDISPOSITION TO SILICONE-INDUCED IMMUNOLOGIC DISORDER

HLA typing was performed in order to examine a connection between the symptoms seen in implant patients and the HLA antigen. Data from this study did suggest that symptomatic patients with implants share important genetic characteristics (primarily HLA-DR53 positivity) which make them different from their asymptomatic counterparts. Therefore DR53 may be a marker for women who are predisposed by their HLA genotype to develop an immune-mediated reaction following exposure to some component of silicone gel breast implants (Young et al., 1995).

This genetic predisposition issue was further confirmed by the study of T-cell proliferation; in this study, the effect of silicone on different strains of mice was observed. It was demonstrated that injected silicone gel induces an *in vitro* T-cell proliferative response in certain strains of mice (BALB/C, C57), but not in DBA. This response is mediated by silicone-induced peritoneal cells which stimulate spleen, lymph, and mesenteric lymph node cells in syngeneic mice injected subcutaneously with silicone gel, but not with saline (McDonald et al., 1995). Environmental factors such as housing and the amount of fat in the diet affect the degree of T-cell proliferative response due to silicone injection. With a low-fat diet, a much lower T-cell response was detected (McDonald et al., 1995).

## SILICONE GEL ACTS LIKE AN ADJUVANT

One of the properties of adjuvants is the enhancement of immunologic responses to conventional antigens. A comparison of silicone gel with classical adjuvants again showed that silicone gel has the ability to enhance immunological responses to different antigens. Furthermore, it was demonstrated that the occurrence of collagen-induced arthritis in dark agouti (DA) rats was more frequent in the control saline-injected group. It was concluded that silicone gel taken from a commercial breast implant is capable of mediating collagen-induced arthritis in susceptible strains of rat (Naim et al., 1995). Thus, it may be concluded that the different autoreactive antibodies detected in the sera of patients with silicone breast implants are caused by what different investigators have described as the adjuvant characteristics of silicone gel implants. These include: ANA, thyroid antibodies, phospholipid antibodies, other tissue antibodies, myelin basic protein antibodies, myelin-associated glycoprotein, and ganglioside and sulfatide antibodies with low levels of C3 and C4 complement (Brautbar et al., 1995; Lewy, 1995; Silverman et al., 1995b; Tan et al., 1995; Vojdani and Karjoo, 1995). Immune complexes and immunoglobulin levels were also reported to be elevated in 23% of the examined patients, especially when serum electrophoresis and immunofixation for kappa and lambda chains were performed (Potter and Morrison, 1995). This elevation of immunoglobulin levels led to the possible development of plasmacytoma and multiple myeloma, due to silicone gel implants. In genetically susceptible mice (BALB/C), it was shown that silicone gel, but not silicone oil, induced plasmacytoma, a cancer of the plasma cell (Silverman at al., 1995a).

And finally, according to the reports and presentations of several investigators to the National Cancer Institute, 18 cases of multiple myeloma (especially of immunoglobulin-G) have been detected so far in patients with silicone breast implants. This excessive number of multiple myeloma among patients with silicone breast implants certainly warrants further investigation and may justify that tests of immunoglobulin levels and kappa-lambda monoclonal measurements be included in the silicone implant patient's yearly checkup.

In summary, as we have hypothesized in earlier publications (Vojdani et al., 1993, 1994), silicone, after it is released from its bag, will reach distant tissues and organs where body proteins adsorb it or adhere to it. This complex of silicone and human body proteins will then initiate host reactivity against silicone and macromolecules within the microenvironment of the implant. As a result, autoreactive antibodies are produced which may in turn cause atypical connective tissue disease, atypical neurological disorder, immunologic disorders, and possible cancer (at least multiple myeloma).

On the basis of the results presented in this workshop, as well as the results of earlier studies, it can be concluded that patients who complain of silicone-induced immune dysfunction syndrome (SIIDS) deserve objective evaluation. However, because of the multiorgan effects of silicone and the detected presence of different abnormalities in different patients, there is no single test that may help in the diagnosis of this complex disease. Therefore, quantitative

evaluation of both cellular and humoral immunity is needed to diagnose atypical connective tissue disease or atypical neurological disorders, the most common disorders among these patients. Major emphasis should be put on detection, by Western Blot assay, of nonspecific tissue antibodies, myelin-associated glycoprotein antibodies (MAG), and ganglioside, sulfatide and silicone surface-associated antibodies (Baldwin and Kaplan, 1983; Varga et al., 1989; Varga and Jimenez, 1990; Benveniste, 1992; Bridges et al., 1993; Teuber et al., 1993; Vojdani et al., 1993, 1994; Campbell et al., 1994; Claman and Robertson, 1994; Silverman et al., 1995a). Because of the incidences of multiple myeloma in patients with silicone implants, measurement of immunoglobulin levels by immunofixation test for the kappa and lambda chains of IgG, IgM, and IgA, and HLA typing should be added to the long list of laboratory tests.

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# A RHEUMATOLOGIST'S VIEW OF SILICONE

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The debate over silicone breast implants began in earnest in December 1990. Congressman Ted Weiss, concerned about the quality of monitoring by the Food and Drug Administration (FDA) of the manufacture and use of silicone breast implants (Committee, 1992), convened hearings of a subcommittee of the House Government Operation's Committee. Among those testifying were an internist, Norman Anderson, M.D., a pathologist, Nir Kossovsky, M.D., a chemist, Pierre Blais, Ph.D., an engineer, Tom Talcott, who had worked for Dow Corning, and myself, a rheumatologist.

Media interest was further heightened when two of my patients and two women from California appeared on the program entitled, *Eye to Eye with Connie Chung*. During this broadcast, which aired a week previous to the hearings, the four women reported that their breast implants were making them ill.

The drama unfolded in multiple stages. The FDA imposed a moratorium on the use of gel-filled breast implants, not because of proven toxicity, but because of insufficient safety data. Director Kessler said, "We know more about the life of a tire than a breast implant" (Kessler, 1992).

Manufacturers presented flawed safety data. Most follow-up studies lasted two years or less. The majority of study subjects were lost to follow-up. No questions were asked about symptoms of connective tissue disease or cancer (Subcommittee, 1992).

The American Society of Plastic and Reconstructive surgeons billed members $1,050.00. Lobbyists were hired. Satisfied women were flown to Washington. Two hundred thousand letters were written to members of Congress, and $60,000 contributed to key Congressmen (Subcommittee, 1992).

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Women with signs and symptoms of rheumatic disease sued manufacturers and, at times, surgeons, forcing the judicial system to address the problem. Jury decisions were split, but some patients won multimillion dollar verdicts that withstood the appeals process.

A group of attorneys formed the plaintiff's steering committee. They consulted with physicians experienced with these patients. A class-action settlement was agreed upon which was available to women who wished to join. What remains unclear is the amount of settlement that the symptomatic women will receive and when they will receive it.

Investigators with diverse backgrounds attempted to understand the interaction between silicone and the living organism. Rheumatologists, pathologists, allergists, toxicologists, hematologists, neurologists, and others with an interest in immunology studied the problem. Ultimately, principles of disease causation and epidemiology were applied.

Animal studies of injected gel showed clearly that silicone caused not only local inflammation but was also migratory (Bridges and Vasey, 1993). Although short-term studies demonstrated that hard silicone appeared inert, it is now clear that even hard silicone slowly disintegrates, causing local and potentially distant inflammation (Peimer et al., 1986). Naim showed that experimentally emulsified 50% silicone gel is an adjuvant (Naim and Lanzafame, 1993).

Why did I agree to take the controversial position that silicone was causing human disease? Having been alerted by a 1984 paper (Kumagai et al., 1984) describing connective tissue disease in Japanese women with silicone exposure, Luis Espinoza, M.D., and I recognized that many of our patients had presented with similar symptoms. We saw and reported women with defined connective tissue disease, including scleroderma (Brozena et al., 1988), systemic lupus erythematosus (Walsh et al., 1989), and rheumatoid arthritis (Martinez-Osuna et al., 1990). Nonetheless, it was clear from the beginning that most symptomatic women had only chronic fatigue and muscle and joint pain (Vasey et al., 1994).

Desperate implanted women recognized they were steadily worsening. The coauthor of my book (Vasey and Feldstein, 1993) on this subject interviewed symptomatic women; he told me they thought they were dying, but I could not find any major organ system failure. Many women were forced to make the difficult decision to remove the implants. It was gratifying that symptomatic women, both with and without defined connective tissue disease, improved after implant removal. Sclerodermatous skin softened, swollen lymph nodes disappeared, pleural effusions resolved, pain lessened, and patients slowly regained their energy.

After the testimony, my phone rang continuously and appointments backed up for a year. We summarized the first 50 patients, the majority of whom were seen before the publicity (Vasey et al., 1994). As more and more symptomatic women were evaluated, it became clear that the consistent clinical picture was one of chronic fatigue, muscle and joint pain. Most symptomatic women had local problems, but some, usually with the implants under the pectoralis muscle, did not. We did not foresee that most implants would eventually rupture

(deCamara et al., 1993). Markers of immune-mediated inflammation, including IL-2 and hyluron, were noted in the breast capsule around the implant (Wells et al., 1994a).

Other investigators made important observations. Bernard Patten, M.D., a neurologist, best characterized the neurological manifestations (Ostermeyer Shoaib et al., 1994). Peripheral neuritis is most common, but neurocognitive dysfunction is also frequent. Multiple sclerosis–like and amyotrophic lateral sclerosis–like syndromes have also been described in women with silicone breast implants.

Aristo Vojdani, Ph.D., an immunologist, found evidence of humeral and cellular immune perturbation in symptomatic women. He noted that antinuclear antibodies, lymphocyte subsets, mitogenic responses, and antibodies to myelin were different from controls (Vojdani et al., 1992). Antibodies to silicone by solid phase enzyme–linked immunosorbent assay were noted in several studies (Goldblum et al., 1992; Wolf et al., 1993). Silicon was found at higher levels in the circulatory system of women with implants than in controls (Teuber et al., 1994). Bridges showed unusual immunoblots, even in symptomatic women who did not have defined connective tissue disease (Bridges et al., 1993). Most recently, Smalley et al. (1995) showed heightened mitogenic responses to amorphous silica in women with breast implants. Young has shown an immunogenetic predisposition to developing constitutional symptoms in the form of DRW 53 (Young et al., 1995).

The typical clinical syndrome is as follows: pain develops around the implants, spreads around to the back in a bra-strap-distribution as far as the interscapular area, up to the shoulder, and gradually down the arms and into the neck. Regional lymph nodes in axillary and cervical areas became swollen and tender. Other symptoms include: dry eyes and mouth, hair loss, dyspnea, chest tightness, paresthesia, crampy abdominal pain, urinary frequency, chronic fever of 100° (rarely higher), and erythematous rashes which are more pronounced on the trunk than the face and extremities.

As the pain spreads, the fatigue gradually worsens. Productive women working 16-hour days require a 2-hour nap in the afternoon. They sleep poorly and awake exhausted. When they consult their physicians, the workup is unrewarding, causing physicians to suggest a psychological basis for the symptoms. The affected women blame old age, menopause, and depression.

We recognized that only a controlled epidemiological study showing an increase in rheumatic diseases or signs and symptoms would satisfy those who insist on epidemiology and are not willing to accept other scientific criteria of medical causation. We conducted the first such study beginning in 1988 (Wells et al., 1994b). We sent questionnaires to women with and without breast implants in a busy private plastic surgery practice. We asked the right questions, but asked too many of them. The chronic fatigue and muscle and joint pain were greater in younger women with breast implants (15% vs. 10%), but not to a statistically significant degree. The prevalence of lymphadenopathy as swollen (8% vs. 1%) and tender

(12% vs. 3%) lymph nodes was significant, but only in the absence of a multiple comparison (Bonferroni) correction.

A major weakness of the study was the short duration of implantation (five years). In our retrospective study, it took an average of five years to become symptomatic. There is great individual variability, from immediate symptoms (as in the first North American patient reported in 1979) (Uretsky et al., 1979), to decades without symptoms.

The next study documenting a statistically increased symptom, but not a disease. was a case-controlled study from Olmstedt County, Minnesota (Gabriel et al., 1994). Trends were noted in any arthritis (1.35 x increased over controls) and sicca symptoms (dry eyes and mouth) (1.39 x over controls). Morning stiffness (1.81 x increased over controls) was statistically significant. The authors constructed a new control group (women with cancer) to explain it, but women with mastectomy for fibrocystic disease (no cancer) had a higher rate than women with implants for cancer. Cancer does not typically cause morning stiffness. The importance of this study relates to risk of symptoms rather than disease causation. Other groups have also been unable to document an increased prevalence of a defined connective tissue disease (scleroderma ) in controlled studies (Sanchez-Guerrero, 1994).

Most recently, a Dutch group, in a questionnaire study similar to ours in a plastic surgery clinic, found statistically significantly increased painful joints (2.6 x increased over controls) "regularly burning eyes" (2.43 x increased over controls), and skin abnormalities worsened by sun exposure (5.05 x increased over controls) (Giltay et al., 1994). Patients and controls had the same number of complaints before surgery, but women with breast implants developed twice as many complaints after implants were placed ($p < 0.001$).

While controlled epidemiological studies are documenting both statistically increased prevalence of symptoms (morning stiffness, arthritis, photosensitive rash, and irritated eyes) and strong trends toward significance (chronic fatigue, myalgias, arthralgia, arthritis, sicca symptoms, and lymphadenopathy), not all agree that causation should be determined solely by epidemiology. Epidemiology may be hampered by lack of appropriate case definition and difficulty in achieving an adequate sample size to detect small differences. Clinicians cannot delay patient diagnoses and treatment to wait until adequate sample size is achieved. Traditionally, epidemiology addresses risk assessment and disease spread rather than causation.

Hill (1965) has argued that consistent clinical observations, temporal relationship with exacerbation after placement and remission after removal, and dose-response curve coupled with experimental plausibility, are sufficient to establish causation. All of Hill's criteria have been satisfied in the above-cited studies, and recently have been discussed in detail (Brautbar et al., 1994). The difficult problem is how to advise patients in the absence of an absolutely definitive epidemiological study or a diagnostic laboratory study. Increasingly, in difficult

circumstances, the reasonable trend in medicine is to explain the options and allow the patient to decide.

Even severely affected women struggle with the decision to remove the implants and not replace them because of the adverse cosmetic result. For women who had them placed for cosmetic reasons, a simple mastopexy uplifting the breast is helpful. Tissue transplant procedures also can be helpful. Previously mastectomized women have an even more difficult decision. Clearly, many women gain great personal satisfaction and have immune toleration to the silicone debris slipping into their bodies. For those women who have unexplained chronic fatigue and muscle and joint pain despite careful medical evaluations, consideration should be given to implant removal without replacement.

The lack of epidemiological demonstration of an increased incidence in scleroderma, systemic lupus erythematosus, and rheumatoid arthritis does not mean women with these conditions and breast implants should not remove them. The ample evidence of silicone/silica acting as an adjuvant argues that naturally occurring rheumatic diseases would be aggravated.

Our early patients with scleroderma all improved post–implant removal (Brozena et al., 1988). One woman with apparent severe systemic lupus had a clinical return to normalcy, including a reversion of a positive antinuclear antibody test to negative (Walsh et al., 1989).

We recently reviewed our preliminary experience with symptomatic women who replaced gel-filled implants with saline-filled implants. The silicone/silica envelope is the same in both sets of implants. Our data on 32 women who made the exchange suggested they did not do as well as those who removed and did not replace the implants.

The serendipity of geography cast the rheumatology group at the University of South Florida into the limelight and the glare of publicity. Our controls were the women in our practice without implants. It was clear the array of signs and symptoms, and the clinical course in women with breast implants, differed from our other patients. In rheumatology, small battles in the course of each patients' illness continue, but few wars are won. In this regard, symptomatic women with breast implants are no exception.

The struggle to understand the complex interaction of the human body with silicone continues. The recent meeting in Washington, D.C., addressing the small or nonexistent risk of multiple myeloma in women with breast implants, is an example. Still, clinical observations to date are hopeful, with the stabilization and improvement of most symptomatic women who remove and do not replace their breast implants. It remains for each treating physician to establish a diagnosis, disease causation, and treatment based on his or her knowledge of medicine, differential diagnosis, and absence of evidence of other diseases.

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SPECIAL ARTICLE

# Women with silicone breast implants and unexplained systemic symptoms: a descriptive cohort study

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## ABSTRACT

Background: Since their introduction, the safety of silicone breast implants has been under debate. Although an association with systemic diseases was never established, women continuously blamed implants for their unexplained systemic symptoms. In 2011, a pattern of symptoms caused by systemic reactions to adjuvants (e.g. vaccines, silicone) was identified: 'autoimmune syndrome induced by adjuvants' (ASIA). Our aim was to collect a cohort of women with silicone breast implants and unexplained systemic symptoms to identify a possible pattern and compare this with ASIA.

Methods: Women with silicone breast implants and unexplained systemic symptoms were invited through national media to visit a special outpatient clinic in Amsterdam. All were examined by experienced consultant physicians and interviewed. Chest X-ray and laboratory tests were performed.

Results: Between March 2012 and 2013, 80 women were included, of which 75% reported pre-existent allergies. After a symptom-free period of years, a pattern of systemic symptoms developed, which included fatigue, neurasthenia, myalgia, arthralgia and morning stiffness in more than 65% of women. All had at least two major ASIA criteria and 79% fulfilled ≥3 typical clinical ASIA manifestations. After explantation, 36 out of 52 women experienced a significant reduction of symptoms.

Conclusions: After excluding alternative explanations, a clear pattern of signs and symptoms was recognised. Most women had pre-existent allergies, suggesting that intolerance to silicone or other substances in the implants might cause their symptoms. In 69% of women, explantation of implants reduced symptoms. Therefore, physicians should recognise this pattern and consider referring patients for explantation.

## KEYWORDS

Allergy, autoimmune induced adjuvant disease (ASIA), explantation; silicone breast implants, systemic symptoms

## BACKGROUND

Since their introduction to the market in 1962, silicone breast implants have been the subject of international debate. From 1992 to 2006, the Food and Drug Administration (FDA) restricted the use of silicone breast implants due to controversy about their safety and concerns about their association with systemic symptoms and alleged autoimmune diseases.[1,2] Currently, over four million women worldwide have been augmented or reconstructed with silicone breast implants.[3] The vast majority of these women seem satisfied with their implants and do not experience any local or systemic symptoms.[4]

The question whether silicone breast implants can cause serious systemic health problems has often been posed but seldom thoroughly answered.[5] Local complications described are breast pain, capsular contraction, implant rupture, asymmetry, and infection.[6,7] In addition, breast implants have been associated with a very rare type of lymphoma.[8] Although often suggested,[9,10] no studies could confirm strong associations between silicone breast implants and atypical systemic symptoms or well-defined autoimmune diseases.[11,12]

Alternatively, some authors have reported a pattern of symptoms in patients with silicone breast implants that mimic autoimmune diseases.[10,13] In the early 1990s, this even led to the introduction of a new 'disease' called 'siliconosis' or 'silicone reactive disorder' with symptoms such as memory loss, fever, morning stiffness, paraesthesia, hair loss, sweating, and joint pain. These 'diseases' were

introduced by lawyers in lawsuits against breast implant manufacturers.[10,13] In 2004, a causal relationship between these symptoms and silicone breast implants was still not confirmed.[14] In 2011, immunologists, however, discovered similarities with systemic symptoms and immunological reactions to other adjuvants, such as vaccines. A syndrome called 'autoimmune (autoinflammatory) syndrome induced by adjuvants' (ASIA) was introduced and defined by several major and minor criteria (*table 1*).[15] According to two Dutch authors at least two major criteria or one major and two minor criteria are required for the diagnosis of ASIA.[16] Until now, only a few case series have reported women with silicone implants who fulfil the criteria of ASIA.[17,18]

The recent recall of silicone breast implants of the French manufacturer Poly Implant Prothèse (PIP), due to fraudulent usage of industrial silicone gel, has reignited the debate on the safety of silicone implants.[19,20] As a result, worried patients with implants from different manufacturers presented to their GPs, plastic surgeons, and other physicians with unexplained systemic symptoms. Most of these women felt ignored, as physicians tend to deny any association between silicone implants and their complaints. In addition, several of these women even went to court to get recognition for their health problems, which they believe to be caused by their silicone breast implants. Therefore, Dutch health authorities in association with the Netherlands Society of Internal Medicine and Netherlands Society of Plastic Surgery introduced a special outpatient clinic for women with silicone breast implants and unexplained systemic symptoms, which resulted in the present inventory.

The aim of this descriptive cohort study was to identify a possible pattern of symptoms in a cohort of women with silicone breast implants and unexplained systemic symptoms. In addition, similarities between these symptoms and the so-called ASIA syndrome were explored.

**Table 1.** *Suggested criteria for diagnosis of ASIA*

| |
|---|
| **MAJOR CRITERIA** |
| 1. Exposure to an external stimuli (infection, vaccine, silicone, adjuvant) prior to clinical manifestations. |
| 2. The appearance of 'typical' clinical manifestations: |
| • Myalgia, myositis or muscle weakness |
| • Arthralgia and/or arthritis |
| • Chronic fatigue, unrefreshing sleep or sleep disturbances |
| • Neurological manifestations (especially associated with demyelination) |
| • Cognitive impairment, memory loss |
| • Pyrexia, dry mouth |
| 3. Removal of inciting agent induces improvement |
| 4. Typical biopsy of involved organs |
| **MINOR CRITERIA** |
| 1. The appearance of autoantibodies or antibodies directed at the suspected adjuvant |
| 2. Other clinical manifestations (i.e. irritable bowel syndrome) |
| 3. Specific HLA (i.e. HLA DRB1, HLA DQB1) |
| 4. Evolvement of an autoimmune disease (i.e. MS, SSc) |

**ASIA = autoimmune (auto inflammatory) syndrome induced by adjuvants; HLA = human leukocyte antigen; MS = multiple sclerosis; SSc = systemic sclerosis.**

## PATIENTS AND METHODS

In December 2011, Dutch women with silicone breast implants and systemic symptoms were invited by the national media (e.g. television and internet) to attend a specialised outpatient clinic at VU University Medical Center in Amsterdam. This descriptive cohort study was approved by the Medical Ethics Review Committee of the VU University Medical Center. All women visited the clinic on their own request and none were rejected for evaluation. Women with any type of silicone breast implants were accepted. At the outpatient clinic, medical history and physical examination were performed by an experienced internist to exclude any alternative explanation for the complaints.

A detailed medical history was taken with special attention to the characteristics of the implants (e.g. type of implant, reason for implantation) and experienced symptoms (e.g. time to symptoms, local complaints, and systemic symptoms). The physical examination consisted of a general examination with special attention for breast and axillary lymph nodes. All women underwent chest X-ray (to exclude sarcoidosis) and general laboratory blood tests, including C-reactive protein (CRP), haemoglobin, thrombocytes, leucocytes with differentiation, renal function and liver enzymes. On indication, with the aim of excluding alternative explanations for their complaints, additional imaging tests and immunological serology were performed (e.g. antinuclear factor (ANF)).

After the visit to the outpatient clinic, additional data were obtained using a structured questionnaire. To this end, all women were contacted by phone and interviewed by an independent researcher. According to the questionnaire, women were asked in detail about the implantation history and self-reported symptoms.

Finally, the collected data were analysed using SPSS software (SPSS for Windows 21.0, Inc., Chicago, IL, USA 2012). For the analysis, self-reported symptoms were compared with the ASIA criteria as mentioned in *table 1*. Data are presented as median with range.

## RESULTS

From March 2012 to March 2013, 84 women and two men presented to the specialised outpatient clinic. Four out

of the 84 women declined participation in the inventory. In addition, two male patients with silicone testes were excluded from the cohort. Finally, 80 women with silicone breast implants and systemic symptoms could be included in the analysis. Characteristics of these 80 women are summarised in *table 2*. The median age was 47 years (range 22-78 years). The majority of women (89%) had silicone breast implants for cosmetic reasons. The median total exposure time to silicone breast implants was 14.5 years (range 2-42 years). Although most women did not have a medical history besides breast augmentation, 60 out of 80 women (75%) reported pre-existent allergy (*table 2*) prior to implantation.

Of the 80 included women, 79% of them had local symptoms such as breast pain or capsular contraction (*table 3*). Besides local symptoms, all women reported systemic symptoms (*table 4*). The most frequently reported symptoms included fatigue (89%), neurasthenia (74%), joint pain (69%), muscle pain (65%), morning stiffness (65%), night sweats (63%), and dyspnoea (45%). In addition, women experienced cognitive problems (35%), dermatological symptoms (31%), gastrointestinal symptoms (30%), and alopecia (23%). Of note, only a minority of women reported psychological symptoms including sleeping disorders (19%) and depression (4%). While being exposed to silicone breast implants, 11 out of 80 women (14%) developed a total of 14 confirmed autoimmune diseases at a median time of seven years after first implantation (range 3-30 years; *table 5*). In the women who were not diagnosed with an autoimmune disease, routine blood tests, chest X-ray, and additional investigations did not show significant abnormalities, with the exception that ANF serology was positive in 20% of the women.

Following implantation of silicone breast implants, the women reported a symptom-free period with a median of 4.5 years (range 1 month to 30 years). In most women, the symptoms developed gradually or semi-acutely, but in 11 out of 80 women the onset of all their complaints was quite acute. Shortly before the onset of their symptoms, two women had undergone a mammography, one woman had a closed capsulotomy, and another woman had experienced a trauma with a ball on the thorax.

When classified according to the suggested ASIA criteria (*table 1*), as summarised in *table 6*, all women had at least two major ASIA criteria and 79% of the women even fulfilled ≥3 typical clinical ASIA criteria manifestations. Besides memory loss, other cognitive impairments (*table 1*) were noticed such as word finding problems, coordination and concentration problems.

Because of the unexplained symptoms a number of women decided to have the implant explanted. At the time of the analysis, 52 out of 80 women had had an explantation of

**Table 2.** *Characteristics of 80 women with silicone breast implants and unexplained systemic symptoms*

| | n | % |
|---|---|---|
| **Age (years)** | | |
| <30 | 4 | 5 |
| 30-40 | 11 | 14 |
| 40-50 | 29 | 36 |
| 50-60 | 21 | 26 |
| 60-70 | 14 | 18 |
| >70 | 1 | 1 |
| **Intoxications** | | |
| Nicotine | 25 | 31 |
| Alcohol | 45 | 56 |
| Other drugs | 1 | 1 |
| **Known allergy** | | |
| None | 20 | 25 |
| Metals | 3 | 4 |
| Food | 2 | 2 |
| Atopic constitution* | 19 | 24 |
| Medicines | 14 | 17 |
| Latex/rubber/plasters | 3 | 4 |
| Multiple | 19 | 24 |
| **Silicone exposure (years)** | | |
| <5 | 4 | 5 |
| 5-10 | 15 | 19 |
| 10-15 | 21 | 26 |
| 15-20 | 13 | 16 |
| 20-25 | 8 | 10 |
| >25 | 19 | 24 |
| **Implant replacements** | | |
| None | 35 | 44 |
| 1-2 | 31 | 39 |
| 3-5 | 13 | 16 |
| >5 | 1 | 1 |
| **Reason for implantation** | | |
| Augmentation | 71 | 89 |
| Reconstruction | 9 | 11 |

n = number of women; % = percentage of women; *eczema, hay fever, pollen and dust mites allergy.

**Table 3.** *Local symptoms in 80 women with silicone breast implants and unexplained systemic symptoms*

| | n | % |
|---|---|---|
| None | 17 | 21 |
| Pain | 41 | 51 |
| Capsular contraction | 40 | 50 |
| Lymphadenopathy* | 28 | 35 |
| Changed size, form or consistence | 20 | 25 |
| Lost sensibility | 9 | 11 |
| Infection | 5 | 6 |
| Local skin disorders | 3 | 4 |
| Rotation | 1 | 1 |

n = number of women affected; % = percentage of women affected *axillary (n= 16), neck (n = 10), thoracic wall (n= 2).

**Table 4.** *Pattern of unexplained systemic symptoms in 80 women with silicone breast implants*

| | n | % |
|---|---|---|
| Fatigue | 71 | 89 |
| Neurasthenia of the extremities* | 59 | 74 |
| Arthralgia** | 55 | 69 |
| Myalgia | 52 | 65 |
| Morning stiffness*** | 52 | 65 |
| Night sweats | 50 | 63 |
| Dyspnoea | 36 | 45 |
| Cognitive problems† | 28 | 35 |
| Dermatological symptoms‡ | 25 | 31 |
| Disorders of digestive tract | 24 | 30 |
| Alopecia | 18 | 23 |

n = number of women affected; % = percentage of women; *patients described pins and needles, tingling, feeling of numbness, a heavy feeling in the extremities; **mostly in the small joints of the hands and feet; ***severe stiffness for more than 30 minutes; †word finding problems, concentration and coordination problems and memory loss; ‡rash, eczema, urticaria and itch.

**Table 5.** *Confirmed autoimmune disease in 11 women with silicone breast implants and unexplained systemic symptoms*

| Confirmed disease* | n |
|---|---|
| Antiphospholipid syndrome | 1 |
| Scleroderma | 1 |
| Systemic lupus erythematosus | 1 |
| Sjögren's disease | 2 |
| Ulcerative colitis | 1 |
| Crohn's disease | 1 |
| Psoriatic arthritis | 2 |
| Autoimmune hepatitis | 1 |
| Perniciosa | 2 |
| Lichen sclerosis | 2 |

n = number of women; *some women have more than one confirmed diagnosis.

**Table 6.** *Eighty women with silicone breast implants and a pattern of unexplained systemic symptoms according to ASIA criteria*

| | n | % |
|---|---|---|
| **MAJOR CRITERIA OF ASIA** | | |
| **1. Exposure to external stimuli** | 80 | 100 |
| **2. Typical clinical manifestations** | | |
| Chronic fatigue or sleep disturbances | 72 | 90 |
| Neurological manifestations (demyelination)* | 59 | 74 |
| Arthralgia and/or arthritis | 55 | 69 |
| Myalgia | 52 | 65 |
| Cognitive impairment, memory loss** | 28 | 35 |
| Pyrexia, dry mouth | 25 | 31 |
| **3. Removal of stimuli leads to improvement** | | |
| Explantation or replacement not yet done | 30 | 38 |
| No improvement yet*** | 17 | 21 |
| Significant improvement | 33 | 41 |
| **4. Typical biopsy** | | |
| Pathology not done | 62 | 77 |
| Silicone in lymph node | 3 | 4 |
| Silicone found in capsular tissue | 12 | 15 |
| Histiocytic reaction | 3 | 4 |
| **MINOR CRITERIA OF ASIA** | | |
| **1. The appearance of autoantibodies: ANF serology** | | |
| Unknown | 10 | 12 |
| Weak positive | 16 | 20 |
| Doubtful | 11 | 14 |
| Negative | 43 | 54 |
| **2. Other clinical manifestations†** | . | . |
| **3. Specific HLA (i.e. HLA DRB1, HLA DQB1) ‡** | . | . |
| **4. Evolvement of an autoimmune disease** | 11 | 14 |

ASIA = autoimmune (autoinflammatory) syndrome induced by adjuvants; n = number of women affected; % = percentage of women; *neurasthenia was included; **memory loss, word finding disorders, coordination and concentration problems; ***limited follow-up; ANF = antinuclear factor; †to the authors it remains unclear which manifestations can be included; HLA = human leukocyte antigen; ‡not done.

their breast implants. Currently, the median follow-up after explantation is seven months (range 1 month to 18 years). Among the 52 women who underwent explantation, 36 women reported a significant decrease of their symptoms, whereas nine of these 36 women stated that their symptoms had completely disappeared.

## DISCUSSION

The present nationwide study shows a pattern of self-reported symptoms in 80 women with silicone breast implants and unexplained symptoms, which included fatigue, muscular and joint pain, morning stiffness, neurasthenia, pulmonary, cognitive and dermatological symptoms. The observed pattern of symptoms resembled the typical clinical manifestations of ASIA.[15] All women had at least two major criteria and 79% of them had more than three typical clinical manifestations. In addition, 79% of women had local symptoms such as breast pain or capsular contraction. Furthermore, 75% of women reported a history of allergy before implantation. Because of their unexplained symptoms, 52 women decided to explant the silicone implants and 36 of these women reported significant reduction of their symptoms.

In our population, we identified a clear pattern of self-reported symptoms, which resembled a newly introduced syndrome, known as ASIA. Although most studies could not confirm an association between silicone implants and connective tissues diseases,[11,21] a few studies demonstrated an association between implants and undefined symptoms such as fatigue, arthralgia, myalgia

and cognitive symptoms.[10,22,23] In the present cohort, most women reported semi-acute onset of their symptoms, which could be explained by implant rupture or silicone gel bleeding. Previously, it has been described that symptoms of chronic fatigue, impaired short-term memory and multi-joint pain can develop after implant rupture.[24]

Besides systemic symptoms, 79% of women experienced local symptoms such as breast pain or capsular contraction, suggesting an association between local and systemic symptoms in our population. In line with these clinical observations, associations between local breast symptoms and systemic symptoms as well as immune factors have been described earlier in women with silicone breast implants. For example, capsular contraction has been demonstrated to be associated with systemic symptoms and circulating immune complexes.[25,26] Women with silicone breast implants and autoimmune diseases have shown differences in human leukocyte antigen (HLA) typing as compared with asymptomatic women with implants.[27] HLA DR and HLA DQ positive haplotypes are overrepresented in women with silicone breast implants and systemic symptoms.[13] In a recent study, it has been demonstrated that in susceptible individuals a disturbance in the modulation of key cytokines might be responsible for a perpetuation of the inflammatory reaction, which locally causes capsular contracture and systemically may trigger autoimmune diseases.[28] When left in situ, capsular tissue may continue to provoke systemic symptoms even after explantation of the silicone implants.[29]

Prior to implantation, the majority of women (75%) reported a pre-existent allergy. Silicone is generally believed to be a biologically inert product and used in many medical devices including artificial valves, joints and needles.[30] However, recent case reports have described allergy-like reactions in patients with silicone in pacemakers, nasogastric tubes and cochlear implants.[31-33] More recently, Hajdu *et al.*[34] suggested that systemic symptoms following exposure to silicone, such as described in ASIA, may only appear in subjects with underlying diseases or high susceptibility. In addition, a study in 2008 demonstrated that women with silicone breast implants had a higher serum IgE than women without silicone breast implants.[35] The results of our study subscribe to the hypothesis that silicone or other chemical substances in the implants may cause systemic symptoms in women with atopy or a hyperimmune state.

After explantation of silicone implants, 36 out of 52 women experienced a significant reduction of their symptoms. In the literature, only a few studies have described the outcome of explantations in patients with silicone implants and unexplained systemic symptoms. In several studies, recovery of these symptoms has been described after explantation, but prospective studies are lacking.[36-38] Although the follow-up of the present cohort is too limited for definite conclusions, our findings suggest that explantation may be an adequate treatment for unexplained systemic symptoms in women with silicone breast implants. As capsular tissue can function as an adjuvant itself, capsulectomy should be considered as well. Although we noticed a significant improvement in many patients after explantation these results should be interpreted with caution because there was no control group. We will continue to include patients in this cohort in the future, with the aim of following them up for at least five years. We will start using a standardised questionnaire before and after explantation to gather information on systemic symptoms prospectively.

Another potential limitation of this study is the design, as women with silicone breast implants and unexplained symptoms visited the specialised clinic on their own request, leading to selection bias. In addition, as most of the signs and symptoms were subjective, recall bias or suggestion cannot be excluded. Although, it is worth mentioning that two experienced clinicians with vast experience examined these patients looking for alternative explanations for their symptoms, before including them in the present descriptive cohort study. Since radiology investigations were not performed routinely, due to financial limitations, it was not possible to investigate the relation between silicone leakage and unexplained symptoms. As the Netherlands is a relatively small country, enabling travelling from every region to our clinic, we expected a large number of women to visit the clinic. Although women came from all over the Netherlands, only 84 women visited the clinic within 12 months. As the women had easy access to the specialised clinic and their visits were paid by the Dutch insurance companies, we believe that a representative number of women visited this clinic. As a result, we may conclude that the prevalence of unexplained systemic symptoms in women with silicone breast implants is probably low.

Although questioned for decades, the safety of these implants has not been adequately investigated. Since the PIP debacle, the importance of large prospective registration studies and post-market surveillance for medical devices has been frequently emphasised.[39,40] As long as such studies are lacking, observational and retrospective studies may provide valuable information. We realise that the present study has several limitations, but believe that our preliminary findings may help physicians, such as general practitioners, plastic surgeons and internists, to recognise this pattern of systemic symptoms in women with silicone breast implants and unexplained symptoms. Although the prevalence of this pattern appears to be low it is of significant importance to recognise these symptoms and consider explantation as the unexplained symptoms may lead to unnecessary health care consumption in women with silicone breast implants.

## CONCLUSIONS

In the present descriptive cohort study in the Netherlands, the unexplained systemic symptoms in 80 women with silicone breast implants were evaluated. A clear pattern of symptoms was reported including fatigue, joint and muscle pain, morning stiffness, night sweats, cognitive and dermatological complaints. The observed pattern of symptoms was compatible with ASIA. Most women (75%) with silicone breast implants and unexplained systemic symptoms had pre-existent allergies, suggesting that intolerance to silicone or other substances in the implants might cause these symptoms. In these susceptible women, explantation of the implants may reduce the symptoms. Although the prevalence of this pattern appears to be low, it is of significant importance to recognise these symptoms and consider explantation of the silicone implants and capsulectomy. Therefore, this article's primary message is to recognise and treat this pattern in susceptible women with silicone breast implants. Especially, when the alternative explanations are unavailable, the probable association between the silicone implants and their complaints should be taken seriously.

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