■ **ELISA/ACT Biotechnologies LLC** ■

LRA by ELISA/ACT® CLINICAL UPDATE #11

Silicone Hypersensitivity

What is silicone?

When people think of silicone they often confuse it with silicon, but *they are not the same!* Silicon (Si) is the second most abundant element on the earth's crust and has an atomic number and weight of 14 and 28.086, respectively. In humans, Si is an important constituent of our skeleton and a biological cross-linking agent for glycoproteins, such as osteonectin. In the environment, Si is a component of glass, sand, clay, and steel (24). Si is rarely found in nature as free Si, but rather as the oxide or silicate. Although Si and carbon (C) have many similar chemical characteristics, including their ability to polymerize, Si forms covalent bonds naturally with only oxygen (O), not itself (24). However, compounds containing C-Si bonds, or silicones, can be synthesized, and are similar to organic materials from a biologic and chemical perspective.

The term silicone, therefore, refers to a family of polymers synthesized from the heating of silicone dioxide (SiO_2) in the presence of C (Figure 1.) Next, Si is reacted with methyl-chloride, a process that results in the formation of methylchloro-silanes. After hydrolysis, low weight linear and cyclic prepolymers are formed; the primary polymer is reacted with catalysts to form the high molecular weight polydimethylsiloxane or PDMS. These inorganic polymers have elastomeric properties and exist in liquid, gel, and solid forms, depending on the polymer length and the degree of cross-linking.

Medical grade silicone elastomers were first used during World War II, when silicone was used to lubricate glass syringes (8).Today, silicone is used in many medical products, including dialysis and cardiac-bypass technologies (8) and prostheses for reconstructive and cosmetic surgery. For example, silicone is widely used in prostheses for the correction of hand deformities and for breast reconstruction or augmentation. Early implants were filled with either saline or silicone oil, but more recent implants are filled with a silicone gel. The manufacturing process is regulated, and the implants must pass several quality control tests, including measurements of heavy metals and volatile compounds (24).

What are the clinical and immunological manifestation of silicone hypersensitivity, and how widespread are the problems?

Silicone was believed to be inert for many years, despite brief case reports in the literature suggesting otherwise (2,5,10,21). The earlier complications reported in the United States were primarily related to silicone elastomer finger prostheses. In 1974 Aptekar et al (2) described a woman who developed a foreign body reaction with detritic synovitis following fracture of her metacarpophalangeal joint prosthesis. Osteolysis and lymphadenopathy have also been reported in association with finger implants (5,10,11). In fact, based on past and current data, it appears that 25% of hand prostheses develop fractures with the subsequent release of silicone particles and resultant foreign body reactions (5) and/or other silicone-related complications. In addition to hand prostheses, silicone-induced lympha-denopathies have been noted 5 to 9 years following implantation of silicone prostheses of the toe, hip, and wrist (24).

Silicone breast implants are, however, the leading cause of silicone-related complaints. Breast implants are prepared by repeatedly plunging a prosthesis mold into a silicone rubber mixture until the desired thickness is achieved; the implant is then filled with either saline or silicone gel. The literature now shows that a significant number of women with gel-filled implants have presented with a multitude of medical symptoms. Specific complaints have included swollen joints, morning stiffness, early afternoon fatigue, pain in selected joints and limbs, breast discomfort, lymphadenopathy, and scleroder-matous skin (3,4,6,7,13,16, 17,20-24). Less frequently, hair loss, dry eyes and mouth, chronic fever, Raynaud's phenomenon, and selected neuro- logic symptoms have been reported (7,22). Currently, many patients with silicone breast implants have been diagnosed as having connective tissue autoimmune (AI)

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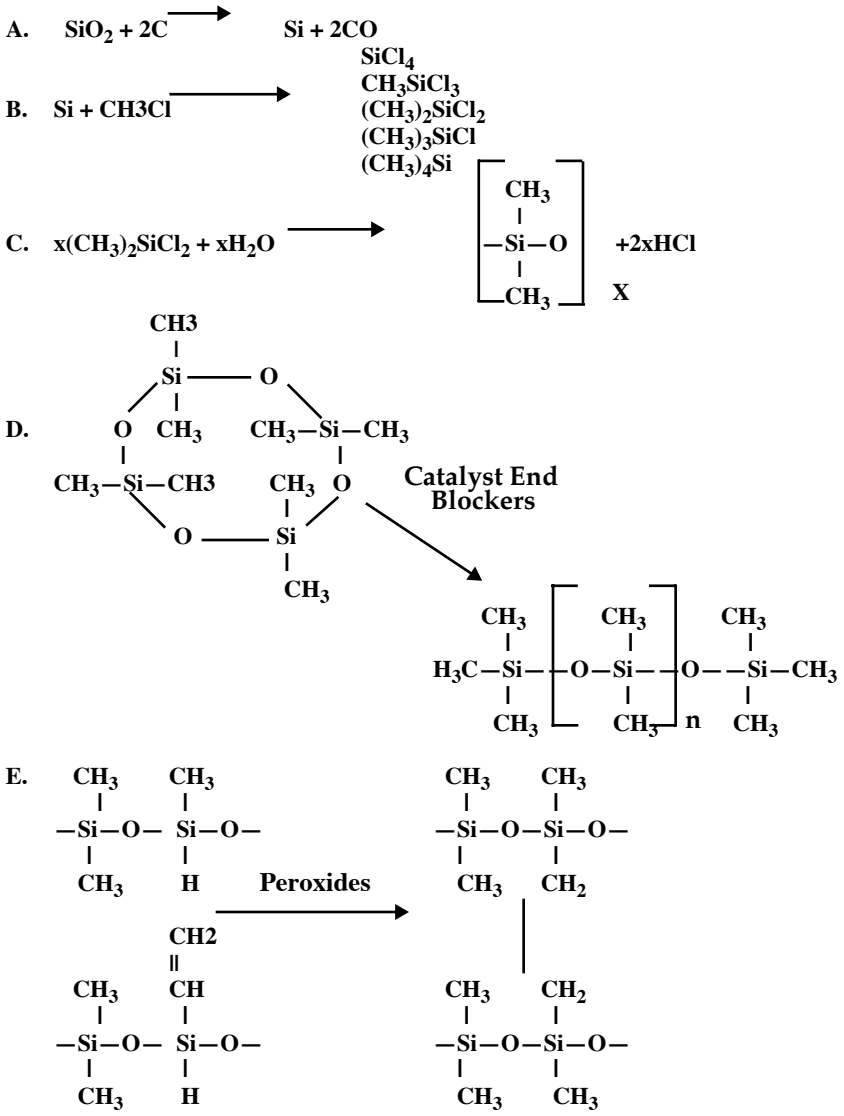

Figure 1. Overview of polydimethylsiloxane (PDMS) synthesis.
(A) Production of elemental silicon.
(B) Methylchloride treatment to produce methylchlorosilanes.
(C) Synthesis of prepolymers.
(D) Production of high molecular weight PDMS from prepolymers.
(E) "Curing" of silicone rubber by the use of cross-linking agents, such as peroxides.
Adapted from reference 24.

diseases such as progressive systemic sclerosis, systemic lupus erythematosus, Sjogren's syndrome, Hashimoto's thyroiditis, and rheumatoid arthritis (6,16,24). Thus, the spectrum of medical complications and symptoms with silicone implants is broad. Interestingly, progressive systemic sclerosis has also been demonstrated in South African gold miners who were exposed to silica during mining service (18). Thus, silicone and silica are not inert.

Only a few investigators have attempted to assess the immunologic aberrations of individuals with well-defined silicone-induced reactions. Immune markers in women with breast implants have included the presence of antinuclear auto-antibodies (ANA) (7,16), elevated rheumatoid factor and immune complexes, alterations in the T-helper/T-suppressor ratio, decreased natural killer cell activity, and antibodies to a wide range of tissue proteins (3,23). In addition, women with breast implants and dermato-myositis appear to have a significantly higher prevalence of human leukocyte antigen (HLA) as compared to control subjects (14). Most recently, the presence of silicone antibodies has been demonstrated in children with elastomeric shunts (9). Finally, high titers for rheumatoid factor and ANA and depression of T-cell function have been reported in South African gold miners previously exposed to silica (18). These findings provide strong evidence for an immunologic response to both silicone devices and silica.

What immunologic mechanisms are involved in silicone hypersensitivity?

Provocation of an immune response typically requires several factors. These include the recognition of something as foreign by the host; a foreign substance of a particular size and complexity; and the host must be able to recognize and respond to the foreign substance. Because of silicone's chemical structure many investigators deny it is capable of eliciting an immune response alone. However, PDMS has several properties that may confer or enhance immunogenicity (24), including:

- *many oxygen atoms which increase electrostatic forces*
- *side groups that allow for hydrogen bond interactions*
- *PDMS is hydrophobic*

Silicone appears to induce both local and systemic reactions, depending on where the prosthesis is located. For example, joint and bone prostheses seem to be associated with local immune reactions (2,5,10,11). One likely explanation for the chronic inflammation with these silicone prostheses is the shedding of silicone. Several studies have shown that small silicone particles are shed over time, and these "wear particles" can cause nonspecific foreign body reactions (2,5,21).

In contrast to joint prostheses, the medical complications induced by breast implants are typically generalized immune responses. Silicone gels may have adjuvant properties and/or act as a specific immunogen. Such processes would activate "cross-reacting immune responses toward self tissues and/or host autoreactive systems" (24), and result in

connective tissue disease. The presence of silicone antibodies in children with elastomeric shunts supports a "specific immunogenic effect" (9). However, adjuvant properties are also likely given that Naim et al (15) recently demonstrated silicone gel has greater immuno-potentiating effects than complete Freund's adjuvant and silicone oil in rats.

Alternatively, the AI diseases currently recognized in association with PDMS may be induced by other compounds used to prepare the implants. For example, polyurethane is a polymer often used to encapsulate breast implants. Studies have shown that small amounts of a carcinogenic substance can be released by implants treated with polyurethane (19). Sabine Rehm has theorized that in mice such implants provoke inflammation by macrophage infiltration, T-cell activation, and other cellular actions (Figure 2) that result in subsequent connective tissue damage similar to that seen in women with implants (19). It is likely more investigations will be required before the mechanisms of silicone hypersensitivity are conclusively demonstrated.

What is the current status of silicone breast implants?

It is estimated that between 1 and 2 million woman have breast implants (17,19), and that 150,000 women receive implants each year (1). Thus, it natural that controversy erupted when numerous reports associating these implants with connective tissue disease began proliferating. On April 16, 1992 after a review of the literature, the Food and Drug Administration (FDA) announced that breast implants filled with silicone gel would be accessible to women requiring reconstructive surgery *only* if they participated in controlled clinical trials (12). This decision polarized certain women's groups who believed the action was patronizing and abdicating their right to make a decision (1). Other women viewed the FDA decision as protecting them from risks that might otherwise bring about ill health. Some medical groups believe the available scientific evidence relating silicone to immune-related disorders and systemic diseases is weak (8), whereas others applaud the decision as scientifically justified. Many respected organizations, including the AMA, the American College of Physicians, and the American College of Rheumatology, to name a few, believe the benefits of implants have not been adequately weighted (8). Clearly, it is an emotional issue that will continue to arouse heated arguments and cause emotional turmoil.

Ideally, silicone breast implants would be available to all women, but tests would be conducted first to identify those women who would later develop immune reactions to silicone. For example, a genetic predilection for silicone hypersensitivity has been proposed since abnormalities in the HLA serotype have been found in connection with AI disease (14). In addition, women who suffer from a variety of biochemical deficits or an immuno-logic overload from chronic exposure to foreign antigens or toxicants may be most susceptible to developing hypersensitivity to silicone. These women would need to be identified, and we believe that methodology to do so is already available.

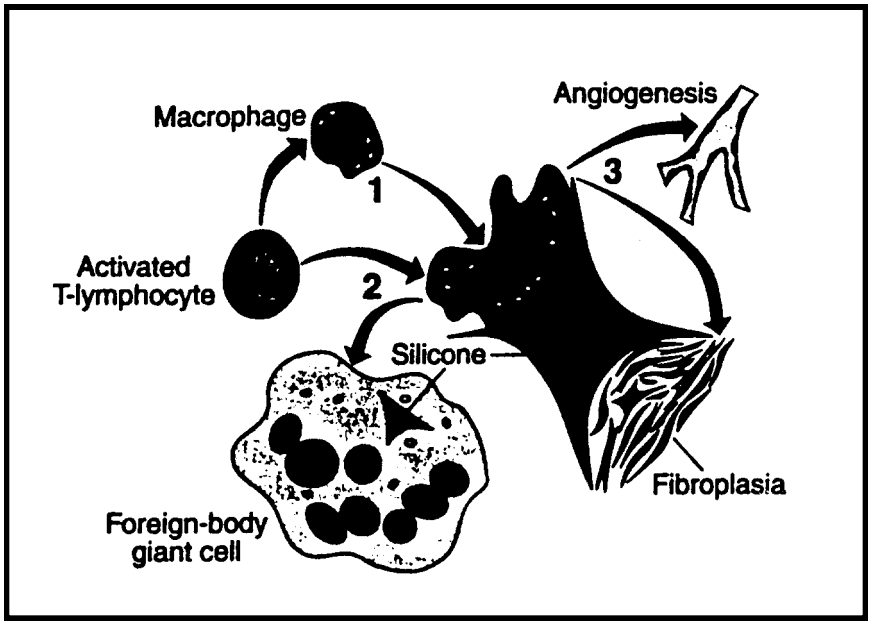

Figure 2. One theory on how silicone-filled breast implants may invoke an inflammatory response. 1) Macrophages gather over the surface of the implant; 2) Activated T-lymphocytes stimulate macrophages to fuse and form foreign body giant cells that engulf beads of silicone gel; 3) Angiogenesis and fibroplasia occur around implant in response to factors released by macrophages. *From Stone who adapted from Sabine Rehm.*

Are there currently any procedures to diagnose a hypersensitivity to silicone?

No clinical procedures to assess silicone hypersensitivity have been used in any studies conducted to date, but one is currently available. The ELISA/ACT® LRA test, an immunological test used to indicate toxic burden and hypersensitivities, is one of the only clinical procedures that can be used to test for reactivity to silicone.

Silicone is a recent addition to the LRA by ELISA/ACT® panel of over 400 foods, food additives, and environmental chemicals and toxins. This is the most comprehensive assessment of the human immune system by any laboratory in the world. In a sample of 100 randomly selected autoimmune disease treatment resistant patients, 3% had a strong reaction, and 3% had an intermediate reaction. In a repeat study of 108 randomly selected autoimmune disease patients, 1% had a strong reaction, and 3% had intermediate reactions. Although testing continues, it appears that silicone hypersensitivity may occur in approximately 3% of the population.

These intriguing results may allow state-of-the-art testing, either to prevent or assist in the **diagnosis of silicone-induced immune dys-regulation**.

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Contact

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