

On the safety of breast implants

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SUMMARY. Recent media attention and controversy coupled with the FDA's product review have prompted a reappraisal of the potential health risks of silicone breast implants. The pertinent literature on this subject is reviewed and it is concluded that:

1. There is no evidence, clinical or otherwise, of carcinogenesis resulting from their use.
2. At present there is no conclusive evidence that they cause autoimmune disease but the increasing number of anecdotal reports of connective tissue disease in women who have been the recipients of such implants merits further investigation.
3. Postoperative technical and mechanical problems such as implant deflation, perforation, rupture, creasing or palpable folds may occasionally be encountered. Other complications of such surgery include capsular contracture and rarely, infection. These complications may require surgical revision, explantation, or implant exchange but do not in themselves make breast implants dangerous.
4. Silicone implants can safely be used in humans.

INTRODUCTION

A great deal of media attention has recently been given to the question of the safety of silicone-gel breast implants, both in Europe and America. The recent ITV *World in Action* programmes (23 September 1991, and 27 January 1992) have been notable UK examples. Recent FDA statements (26 November 1991, 14 January, and 19 February 1992) on the subject have served to rekindle media and public interest in the subject. Understandably the media publicity has caused considerable alarm and concern to patients and doctors alike and has provided the impetus for this review. In this article we review the available scientific and clinical information on this subject, and also provide key literature references concerning the supposed potential health risks of silicone breast implants.

Silicone has a wide variety of clinical applications finding use in orthopaedics (artificial joints, tendon grafting), cardiothoracic surgery (pacemakers, extracorporeal circulation equipment), neurology (CSF shunts), ophthalmology (lens implants), urology (penile implants), internal medicine (diabetic silicone-lubricated syringes, low friction coating of capsules) and,

of course, in many areas of plastic and reconstructive surgery. Consequently these devices have been pivotal in improving the quality and duration of life for millions of patients worldwide. Of all the surgical aspects it is perhaps the field of plastic and reconstructive surgery where criticism of their use has been focused.

The main areas of concern have been the safety of breast implants including the relationship to breast neoplasia, silicone gel leakage and the possible adverse effects on the immune system. The controversy surrounding the relationship between silicone implants and connective tissue disease deserves special mention. Each of these areas will be considered individually. Additional comments are made on the special types of breast implants like polyurethane foam covered prostheses, saline-filled and double lumen devices.

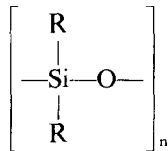
SILICONE CHEMISTRY AND THE BIOCOMPATIBILITY OF SILICONE BREAST IMPLANTS

Physicochemical aspects

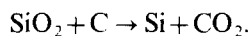
Silicone gel bag breast implants were first introduced in 1962 by Cronin and his resident Gerow.¹ Since then they have been extensively used for cosmetic augmentation mammoplasty, breast reconstruction and correction of congenital breast deformities. Their

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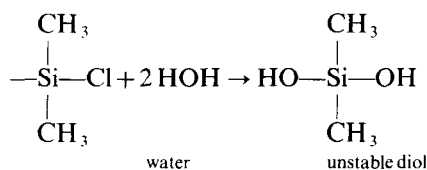
popularity has stemmed from their ability to maintain smooth-shaped augmentation of the female breast. Since 1965 virtually all breast augmentations in the USA have used gel bag implants based on silicone elastomer technology.² The technological and physicochemical aspects of silicone implants have been reviewed by Blais (1981)² and others.³ Silicones are a class of completely synthetic polymers containing silicon (Si), oxygen (O) and organic groups (R) and can be represented in the simplest form by the structure:



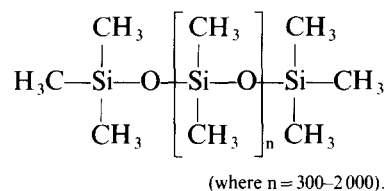
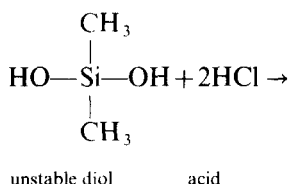
However silica or silicone dioxide (SiO_2) is an ubiquitous material present in sand, quartz, drinking water, body fluids etc. The first step in the production of silicone is the reduction of silica to the element (metal) silicon:



The silicon then reacts with methylchloride and in contact with water forms an unstable diol:



The diol in the presence of acid spontaneously polymerises:



The open ended chains so formed are then end blocked to form the stable polymer, polydimethylsiloxane (PDMS).

Silicone breast prostheses consist of a thin outer shell (or envelope) surrounding a gel or fluid.

The prosthesis envelope is made of a copolymer (the silicone elastomer) and a nonpolymer component (a filler and its coupling agent).

1. The starting material for the prosthesis envelope is a copolymer consisting of PDMS as the primary chain component. This PDMS is polymerized into long chains to form the elastomer. One of the methyl groups on the constituent units can be substituted with a bulky side group (e.g., phenyl or butyl) for improved elasticity and compliance of the finished article. It is also substituted in a few units with a vinyl or allyl side group (as sites of potential inter- and intra-molecular crosslinking) in order to achieve adequate mechanical properties and dimensional stability. The crosslinking or 'vulcanization' which takes place through the vinyl or allyl groups requires a thermally activated free radical initiator. The preferred initiator is 2,4 dichlorobenzoyl peroxide which thermally decomposes to initiate a sequence of events where crosslinking will be formed across activated vinyl and methyl groups in proximity. The silicone elastomer envelopes can absorb and are demonstrably permeable to many substances including silicone oil, gas, water, saline solution, dextrose, lipophilic drugs and endogenous products.^{2,4,5}
2. 30% of the shell of a present day prosthesis consists of a silicone dioxide or silica filler. This filler with a particle size of $30 \mu\text{m}$ is used to impart added hardness to the polymer⁶ and also helps to achieve adequate tear strength. It is fused to the polymer by a chemical reaction.

The material enclosed by the shell can be an oil or a gel or a physiological fluid. It is known that the nature of the filling fluid strongly influences the shape and tactile properties of the implant and of the reconstructed breast.

1. Oils: conventional silicone fluids or oils consist of linear PDMS's. These are oligomers of relatively low viscosity. They are the closest to being inert and are easily purified.
2. Gels: these are made of different intermediates and are more difficult to purify. The primary component is a vinyl and phenyl-substituted PDMS similar to the prepolymer used for the envelope. The ideal gel polymer has a molecular weight lower than that of the envelope material i.e. relatively short chain length ($n = 50-500$). In addition a second reactive component is added, the hydrogenosiloxane ($n = 3-200$). The gel polymer occludes within its networks a large amount of PDMS oils (i.e. diluent). By altering the relative amounts of diluent and of the hydrogenosiloxane the physical properties can be altered. The viscosity of the gel polymer is related to the degree of polymerization and cross-linking. Gels have an open mesh type of polymer networks with

long cross-links consisting of many dimethylsiloxane units. They occlude large amounts of PDMS oils (i.e., diluent) within these networks. The PDMS oils they occlude within these networks allow the gel to exhibit visco-elastic properties and, if the cross-linking is sufficient enough, gives it both dimensional and form stability i.e., 'shape memory'.

3. Blended gels: are made of linear silicone fluids mixed with separately prepared microgel particles.

Today there are 2 basic classes of implants on the market namely:

1. The pre-sealed silicone gel containing versions.
2. The 'inflatable' devices designed to be filled with physiological aqueous media intra or post-operatively. This is almost exclusively isotonic saline although dextrose, dextrans, were used in the past and newer implants may contain 'bio-oncotic' gel (Misti gold).

Subcategories of these 2 basic types depend on:

1. properties of the high molecular weight (silicone) envelope namely compliance, shape, and surface (smooth or textured)
2. presence of internal compartments e.g., double lumen prostheses which possess a gel-prefilled compartment and an outer inflatable compartment
3. presence of tissue fixation appendages
4. different inlet valve designs.

Biocompatibility of silicone implants

Traditionally silicone has been considered 'inert' and this had made it popular in reconstruction. But inertness has to be considered at 3 levels; chemical, biological, and immunological. For a long time silicone has been known to be relatively inert chemically⁵⁻⁹ but this does not equate with biological inactivity. Additionally silicone implants, as opposed to silicone fluid injections, have historically been considered to be biologically inert. However, as a 'foreign' material silicone is encapsulated by fibrous tissue. In addition an inflammatory reaction may occur in response to silicone fluid or gel. Injections of medical-grade silicone fluid in albino mice in the first 72 h elicits a response characterized by neutrophils, plasma cells and macrophages. Thereafter for up to 18 months lymphocytes, fibroblasts and plasma cells predominate.¹⁰ Injections of PDMS in mice generate granulomatous lesions with an acute inflammatory infiltrate histologically.¹⁰ The injected silicone can be found in macrophages, regional nodes, and throughout the reticuloendothelial system of such animals.⁶ Other reports have subsequently confirmed that silicone has the capacity to migrate to remote areas.¹¹⁻¹³ The histological reaction of soft tissues to silicone particles has been described in other clinical and experimental studies.¹³⁻¹⁶ Essen-

tially it is a foreign body reaction but also contains chronic inflammatory cells (lymphocytes, plasma cells, and macrophages). Localized responses taking the form of granulomas have been named 'siliconomas'.^{11,17} However a granuloma is not indicative of an immunological response but is a focal chronic inflammatory response to tissue injury evoked by a poorly soluble substance. Systemic responses to silicone have also been reported (these are discussed in the section on connective tissue diseases). Because of the occurrence of these local and systemic responses, silicone can no longer be considered either chemically or biologically inert.¹⁸

Immunologically, it is known that silicone (injected or otherwise) does not induce or elicit an antibody response.¹⁹ However the histological picture at the injection sites is compatible with a cell mediated response. In 1983 Heggers and colleagues showed that silicone is capable of eliciting such a response as demonstrated by macrophage migration inhibition (MMI) in previously sensitised female guinea pigs.²⁰ The in vitro MMI assay is a well known and accepted model of in vivo cellular immune response. Using electron microscopy and X-ray energy dispersive diffraction analysis they also showed that silicone is capable of being transferred intracytoplasmically from macrophages to lymphocytes via a cytoplasmic bridge (thereby providing a possible avenue for antigen processing and presentation). They concluded that because this cellular immune response is similar to that elicited by purified protein derivative (PPD) (as in tuberculin testing), silicone may act as a hapten-like incomplete antigen. It should however be noted that the MMI caused by the silicone injection was only 44.5% compared to 90% elicited by a standard antigen, PPD. The immunological reactivity of silicone has been disputed. Of interest, crystalline silica (different from silicone) can serve as an immunological adjuvant i.e. capable of stimulating the immune system.

Biohandling of silicone

Silicone compounds are ubiquitous in the human body and have been documented in almost every organ which has been analysed in people who do not have implants.²¹ The amount of silicone compounds present in drinking water is significant in some major American cities where an individual ingests 1-2g of silicone compounds per year.^{22,23} Silicone compounds are digested and absorbed from the GI tract, circulated systemically, and excreted in urine.²⁴ At the present time there is no indication that the body can breakdown medical grade silicone that has been correctly synthesised. There are few known toxic compounds of silicone in contrast to silica and asbestos and there is little evidence in the literature to support the concept that silicone is deleterious to health.

CAPSULAR CONTRACTURE AND SILICONE BREAST IMPLANTS

Definition

The commonest postoperative complication of augmentation and reconstructive mammoplasty using silicone prostheses is the formation of and the subsequent contraction of fibrous capsules around implants.²⁵⁻²⁷ The nature of the soft tissue response which results in capsule formation has been reviewed by Vistnes & Ksander.²⁸

Incidence

Capsule formation itself is universal and it has been reported with all types, shapes, surfaces and sizes of prostheses.^{1,29} The reported incidence of clinically significant capsular contracture ranges from 3-74%.^{4,30-32} This variation reflecting different methods of measurements used, a lack of objectivity in some studies, the types of implants used, and their location (submammary or submuscular). It appears less commonly with saline filled implants than gel filled ones.³³ The use of polyurethane foam-covered, and textured surface implants have greatly reduced the incidence of capsular contracture. In the world's only prospective randomized double blind control study, Coleman et al elegantly showed that texturing decreased the incidence of capsular contracture at one year from 58% to only 8%.²⁹

Time scale and manifestations

Capsule formation and contraction may occur either weeks or even years after implantation.^{26,27,31} Cosmetically the breast becomes spherical, firm and distorted and it often causes pain, discomfort, and embarrassment.

Aetiology and mechanisms

Despite several decades of research the cause of capsular contracture remains unknown.³⁴ The underlying mechanism is shrinkage of the granulation tissue forming around the implant mediated by the contraction of the myofibroblasts and appears to be caused by multiple factors. Research suggests several different explanations including infection,³⁵⁻³⁹ haematoma,⁴⁰ surgical trauma,⁴¹ migration of silicon oxide (silicate filler) from the prosthesis wall, or diffusion of silicone through the device wall.⁴² Silicon (either as silicone dioxide or PDMS) has been identified in the fibrous capsule and the surrounding tissue by various methods (histology, electron microscopy, energy dispersive X-ray analysis, infra-red spectral analysis, atomic absorption spectroscopy and electron microprobe).^{16,34,43-45} All silicone prostheses (regard-

less of the manufacturer) induce the formation of collagenous capsules around them which contain myofibroblasts, and giant cells, the latter being characteristic of a large scale foreign body response.^{43,46-51} Capsule formation and contracture has been thought to represent a foreign body reaction to the presence of a large amount of indigestible material.^{48,49,52} This foreign body reaction is a response to 'irritation' and is dependent (in terms of incidence, rapidity of onset and severity) on the properties of the implanted material⁵³ and its interaction with the host tissue.

Mechanical theory

Wilflingseder's hypothesis is that the contractive fibrosis is commonly a result of the 'grazing' of silicone particles away from the elastomer shell causing a phagocytic response that in some way leads to contraction of the tissue.⁵¹ Kossovsky and colleagues also believe that the fibrosis and capsular contracture is attributable partly to the small grazed particles the 'microirritants'.⁵⁴ They are said to be generated as the muscle rubs against the surfaces of the prosthesis.

Infection hypothesis

Another theory of causation is low grade infection.^{26,55,56} Support for this hypothesis is not uniform.

Immune theory

Immunological factors have been implicated in capsular formation and contracture. They are thought to act by means of an antigen consisting of a silicone-protein complex.^{54,57}

Silicone gel 'bleed'

The minute amounts of silicone gel which leak or bleed through the envelope of the prostheses have at one time been thought to be responsible for causing or increasing capsular contracture. This mechanism is today known not to be important.

Diagnosis

The diagnosis of capsular contracture is largely clinical. The only consistent and totally safe diagnostic aid is breast ultrasound, although if the capsule is calcified it can be detected radiologically. Calcification of the fibrous capsule is extremely rare⁵⁸ therefore X-ray diagnosis of calcification is not useful as a diagnostic tool for capsular contracture.

Most cases of calcification of the capsule in the literature have followed direct injections of silicone into the breasts.^{59,60,61} The material used may also determine the incidence of calcification. What seems

apparent is that the incidence of calcified capsular contracture is related to the presence of free silicone in the tissue as evidenced by the Japanese experience where large numbers of direct injections of silicone gel, paraffin and paraffin like substances were made culminating in a high incidence of calcification.⁵⁹ Calcification may also be related to Dacron patches as there is no reported case of a calcified capsule with a silicone gel filled prosthesis in the absence of a dacron patch.⁵⁸ There are also no reports of calcification of capsules surrounding submuscular implants.⁵⁸ Although calcification may exacerbate the symptoms of capsular contracture its clinical significance lies in the possible diagnostic problems it may pose (on X-ray screening mammography) as the calcium deposits could simulate or obscure calcification due to breast carcinoma.

Treatment and prevention

Various methods have been devised to minimise capsular contracture after implantation of breast prostheses. They include prophylactic antibiotics,³⁸ intraluminal antibiotics,^{35,56} intrapocket irrigation with bactericidal and antibiotic solutions.³⁶ Modifications in implant design have had as their aim the reduction of this problem. Saline filled prostheses have been used^{33,62} as have been textured surface implants.²⁹ Polyurethane foam covered prostheses certainly reduce capsular contracture to low levels.^{55,63-65} All the above techniques and variations have resulted in the reduction of capsular contracture but none has completely eliminated it.

The treatment of established capsular contracture can be by closed or open methods.

1. Closed compression capsulotomy is a forceful manual rupture of the encasing fibrous envelope. Though simple and easy to learn it is not devoid of complications.⁶⁶ The most notable is implant rupture occurring in 0.93%.^{30,67,68}
2. Open procedures used in the treatment are anterior discectomy, capsulectomy and the exchange for textured surface or polyurethane foam covered implants.

IMPLANT FATIGUE AND RUPTURE

The possible deterioration of the physical and biological properties of the implanted silicone, as a result of interaction with the biological environment of the body, is another concern about the safety of breast implants. The envelopes of breast implants recovered during autopsy are said to 'often exhibit signs of deterioration such as loss of tear and tensile strength, deep staining, microporosity, and local changes in the surface characteristics'.² Kossovsky and colleagues

(1983) have reported that an immune mediated phagocytic attack (based on the silicone-protein antigenic complex) of the surface of the implant does occur leading to pits on the silicone surface with cellular aggregates embedded in it.⁵⁴

The rupture of a breast implant is an uncommon complication although there are a number of case reports in the literature.^{52,67,69-79} It would appear that up to 1% of all implants, particularly of the early varieties with thinner envelopes are liable to rupture. It is universally accepted that the diagnosis of a ruptured breast prosthesis can be difficult both for surgeons and radiologists alike. In fact at times it is completely missed preoperatively.⁸⁰ It is thought that many broken implants are undiagnosed because they are asymptomatic and the silicone is maintained in the fibrous capsule. Ruptured implants however appear to cause minimal morbidity.⁷⁹

Aetiology

There may be a history of trauma in the preceding several months. In Andersen's series⁷⁹ 10 of the 18 patients gave a history of trauma in the previous year. It may follow closed capsulotomy (closed manual compression treatment of capsular contracture),³⁰ and has been reported to occur during a mammogram.⁷⁹ Rupture may be due to faulty manufacture or fatiguability of creases that form as a result of capsular contracture.

Diagnosis

An antecedent history of trauma is not necessary for diagnosis. One half of the patients had had prior closed capsulotomy in one series.⁸⁰ The symptoms and signs include a nodule in axilla, breast, or chest wall, an alteration in the size, shape (distortion), symmetry, and consistency (firm or soft) of the breast, and the occurrence of pain and tenderness. Diagnosis by physical examination can be difficult. The condition is often asymptomatic being discovered on routine mammography, mastectomy, or revisional surgery (such as open capsulotomy for contracture). Mammography has been advocated as an aid in the diagnosis of rupture.⁷⁸ It is a good screening test for this purpose with a 67% sensitivity⁷⁹ and is very accurate if the silicone has migrated outside the implant capsule giving a 90% pickup rate in Andersen's series.⁷⁹ False negatives are due to the silicone being contained within the fibrous capsule making mammography inaccurate in these circumstances. False positives, in which patients diagnosed as having implant rupture both clinically and radiologically are found to have intact implants at operation may occur.^{78,79,81} The number of false positives is however low and may be due to haematoma or even a diverticulum of the fibrous capsule.⁷⁸

The radiological signs of breast implant rupture

have been summarized by Andersen and colleagues (1989) and Theophilis and Stevenson (1981).^{78,79} They are:

1. a decrease in size of the implant
2. an ill-defined border or irregular density of the implant
3. multiple lobular or spherical densities adjacent to or separate from the implant
4. a tapered, nonspherical appearance of the gel.

Mammography can be technically demanding because the augmented breast cannot be compressed to the same extent as the normal breast tissue.⁸² Moreover a definite increase in the incidence of breast cancer following breast irradiation has been reported⁸³ and this persists for the patient's lifetime and is greatest in those exposed to radiation at younger ages.⁸⁴

Breast ultrasound has proved reliable in the diagnosis of augmented breasts and has been especially valuable in the differential diagnosis of capsular contracture, implant rupture or periprosthetic haematoma in subpectoral breast augmentations with gel-filled implants.⁸² Pre-operative diagnosis helps to prepare the patient for surgery appropriately and avoids unnecessary surgery if the diagnosis is a liquid haematoma or seroma. Some authors⁸⁵ have drained these under ultrasonic guidance but there is a risk of damaging the implant and extreme caution has to be exercised if this procedure is considered at all. Ultrasound can clearly distinguish between silicone gel, muscle, haematoma and fluid collections.⁸² The prosthesis itself is said to be completely echofree (transonic) with a well defined and clearly demarcated outline. Rupture on ultrasound is suggested by:⁸²

1. A decrease in the anteroposterior diameter of the implant compared to the normal size.
2. Dense linear echoes representing invagination of the prosthesis, creating the image of deep folds in the prosthesis.
3. Migrating echo-free implant material in the form of lobules.
4. Also the direction of the rupture is usually traceable in the direction of the original implant passage.

Ultrasound is considered by some to be the investigation of choice in evaluating prosthesis related complications.⁸²

Treatment of implant rupture entails removal of the implant and any surrounding silicone. The techniques which have been used to remove silicone from soft tissues include:

1. suction assisted removal - usually not effective
2. wide local excisions of soft tissue
3. excision biopsy of any silicone granuloma
4. open capsulectomy and implant exchange.

The residual silicone in the soft tissues causes minimal morbidity⁷⁹ but may result in intermittent ten-

derness and inflammation of the skin and subcutaneous tissue.

SILICONE GEL LEAKAGE AND CONNECTIVE TISSUE DISEASES (HUMAN ADJUVANT DISEASE)

Of the concerns about the safety of breast implants it is the possible systemic effects of silicone gel bleed which have attracted the most controversy and media attention. These include effects on the immune system and the so called 'human adjuvant disease'. The first association between augmentation mammoplasty and connective tissue disease was made by Miyoshi and colleagues in Japan in 1964.⁸⁶ They described two cases of arthritis and hypergammaglobulinaemia in women following the injection of paraffin oil. The term 'human adjuvant disease' (HAD) was coined by Miyoshi to describe this condition because of its supposed similarity to adjuvant arthritis in rats. Adjuvant arthritis in rats is thought to be due to cell mediated immunity (CMI).⁸⁷⁻⁸⁹

This was followed by a number of case reports of connective tissue diseases occurring in women who had previously undergone augmentation mammoplasty. These early cases appeared first in the Japanese literature and followed injections of paraffin or silicone for breast augmentation, a practice which is now obsolete. More recently additional case reports have appeared mainly in the American journals. Consequently there is, today, a growing body of medical literature reporting a relationship between silicone implants and auto-immune phenomena. This consists mainly of anecdotal reports of connective tissue diseases in women who have previously undergone augmentation mammoplasty.^{18,90 100}

Observations on 18 patients and the first review of the literature were made by Kumagai and associates in 1984.⁹⁷ Their patients had received paraffin (7) or silicone (8) or unknown substances (3). Spiera (1988) observed that 4.4% (5) of his patients who had silicone breast implants 2-21 years previously developed scleroderma compared to only 0.3% of his patients with rheumatoid arthritis who had breast augmentation.¹⁰¹ In some of these patients there was partial remission of disease after removal of the implants. This, Spiera noted, did not establish any causal relationship between silicone and connective tissue diseases. Brozena et al (1978) reported 2 patients with a progressive systemic sclerosis-like illness which developed several years after augmentation and recovered completely after removal of the implants (by way of bilateral mastectomy) in one of the patients.¹⁰² The only reported epidemiological study to date is that of Weisman et al (1988).¹⁰⁰ In a follow-up of 125 subjects they found that a third (38) has musculoskeletal complaints but found no evidence that aug-

mentation mammoplasty induced inflammatory connective tissue disorders during the 6.8 years of follow up. Although a causal relationship has been suggested by the regression of the symptoms in a number of patients following the removal of the implants,^{95,101,102} the epidemiological evidence is not conclusive.

More recently the subject has been reviewed by Sergott et al (1986)¹⁰³ and others.^{95,104} Considering the implants which are in common use today, systemic disease with or without serological abnormalities has been reported mainly in relation to silicone gel-filled implants, the association with saline-filled devices being very rare.⁹⁵ The connective tissue diseases which have been reported following breast implants include scleroderma, rheumatoid arthritis, mixed connective tissue disease (MCTD), systemic lupus erythematosus (SLE), Sjogren's syndrome, Raynaud's phenomenon, haemolytic anaemia, Hashimoto's thyroiditis and others. The most commonly reported condition is scleroderma.¹⁰⁴ The incidence of the common collagen diseases per million per year is as follows: SLE 10–70; scleroderma 2–12; rheumatoid arthritis 5000–10 000; MCTD 5–10; polymyositis/dermatomyositis 2.¹⁰⁵ Although many of the above reports are anecdotal, they cannot be ignored and it is reasonable to suggest that silicone implants could precipitate autoimmune phenomena in a genetically susceptible host.¹⁰³

Possible underlying mechanisms which have been postulated to explain systemic immunological disease¹⁰⁶ include:

1. Interaction of host macromolecules with the hydrophobic silicone surface leading to denaturing of native proteins thus rendering them immunogenic.¹⁰⁷
2. Possible breakdown of silicone to silica, a known immunopathogen.
3. Silicone acting as a hapten or adjuvant to existing immunogens. This is highly unlikely because its chemical structure renders it difficult to bind covalently to a protein (to become immunogenic).
4. Gel bleed through the elastomeric membrane of the implant which could cause both the systemic, and local effects (like capsular contracture).
5. Shearing of silicone dioxide molecules from the implant shell.⁵¹

This (5) occurs whether the implant is gel- or saline-filled and it has been suggested to explain a report of systemic disease occurring in association with saline filled implants inserted 8 years before.⁹⁵ The external surface of the implant presents a surface that has sharp projections of silicone dioxide (SiO₂) which may be sheared off.^{44,103} The sheared off molecules can act as hapten-like substances and combine with other molecules (carriers) to form an antigenic complex.^{20,108} This complex could then act as an adjuvant with subsequent development of systemic disease.

The postulated action of silicone as a hapten or

hapten-like substance has been disputed by other workers,^{22,104} who have stated that 'there is absolutely no evidence either clinically or experimentally that silicone dioxide acts as an adjuvant or that it separates from the implant'.²²

Electron dispersive X-ray analysis and scanning electron microscopy have demonstrated that silicone compounds do exist in the capsule around almost all implants (probably in the form of macromolecular 'bleed').³⁴ The amount of silicone found around saline implants is very much less than that found around standard gel-filled implants and is largely confined to the first several mm of the capsule.³⁴

The most authoritative review highlights the absence of positive results from experimental studies and the absence of any reliable epidemiological data¹⁰⁴ and casts doubt as to the existence of 'HAD' as an entity and cautions against the use of the term as it implies an immunological process for which there is, as yet, no proof.

The individual case reports of connective tissue disease following silicone breast implants have certainly drawn attention to this potential association and the possible immunogenicity of silicone. One way to resolve this would be to set up National Implant Registries and also to encourage every surgeon, physician, rheumatologist, dermatologist or general practitioner to report any post implant patient with symptoms suggestive of connective tissue disease to the Departments of Health and/or Implant Registries. Alternatively, or in addition to the aforementioned, there is a need to design and set up proper scientific studies to define the extent of the association, the specific patient population, and collect and analyse the epidemiological data. Specifically the baseline incidence of connective tissue diseases in the population receiving breast implants, and post-implant incidence have to be determined to see if indeed there is an increase. The prevalence and incidence rates of these diseases also have to be considered.¹⁰⁹

The FDA in a statement on the subject on 18 December 1990¹¹⁰ concluded that 'there is no convincing evidence that the tiny amounts of silicone which leak and go to the rest of the body leads people to develop autoimmune diseases or affect a developing foetus'. The FDA 'dismissed' all clinical reports as more or less pure coincidence. This is borne out by numerous authors reporting the above who have stressed that no definite connection or no objective evidence of a causal relationship between silicone implants and 'HAD' has ever been demonstrated.^{18,90–93,95–100}

In summary the evidence relating silicone and connective tissue is:

1. Initial reports from Japan suggesting an epidemiological linkage were after injections of paraffin or liquid silicone which are potentially more hazardous and associated with many complications.

This practice has largely been abandoned at least in the West.

2. The systemic symptoms reported or attributed to breast implants are ubiquitous and nonspecific. They often develop in individuals after the age at which most women request breast implants. The diagnosis of HAD is poorly defined clinically.
3. The number of patients in whom symptoms resolve after removal of implants is approximately equal to those in whom they do not.¹¹¹
4. To date more than 3 million breast implants worldwide have been inserted but less than 100 cases of the so-called HAD have been reported. Figuratively speaking this is the world's largest prospective cohort study of any medical procedure or device and if there was any problems they should have come to light by now.
5. There is no evidence that the prevalence of CTD is greater among women who have received silicone breast implants than the age matched female population.¹⁰⁴ It should be noted that not every patient with such vaguely defined symptoms is likely to be reported in the literature and low-grade, subclinical association cannot be completely ruled out.
6. 'Common things are common'. It is always taught in medical schools that common diseases occur more frequently with a given constellation of symptoms and that the unusual manifestations of common diseases occur more frequently than rare diseases. It is therefore more likely that a woman with a breast implant will develop a common collagen disease rather than a rare new disease.²²
7. There is no reports of CTDs occurring in patients who have been exposed to similar amounts of silicone¹⁰⁸ such as silastic finger joints, siliconized A-V shunts, silicone containing heart valves, polyurethane foam-covered implants, multiple injections using siliconised needles (diabetics) or liquid used after vitrectomy.¹¹²
8. Epidemiological data aside, the absence of positive experimental results (i.e. lack of adjuvant arthritis with other adjuvants other than complete Freund's adjuvant and the lack of evidence that silicone not silica acts as adjuvant) is one of the strongest arguments yet against the association.
9. If the silicone gel bleed (shed into and found in the capsule) or SiO₂ (putatively sheared from the shell) is the cause of the HAD then simply removing the prosthesis probably would not do much²² to resolve the symptoms of HAD as one would also need to remove the silicone which is in actual contact with the body tissues i.e. in the capsule and in the adjacent lymph nodes.

SILICONE AND THE IMMUNE SYSTEM

Although there have been reports showing macrophage ingestion of silicone, inhibition of macrophage

migration by silicone,²⁰ and of silicone transfer intracytoplasmically from a macrophage to a lymphocyte via intracellular bridges,²⁰ there is no evidence that silicone affects antibody response or cell mediated immunity.^{113,114} Kossovsky et al (1987) demonstrated the ability of silicone-protein complexes to induce delayed hypersensitivity reaction in guinea pigs.¹⁰⁷ No dose response information was given making this study difficult to interpret. Additionally the MMI elicited by the silicone mixed with complete Freund's adjuvant is not comparable to silicone breast implants because it could be due to impurity or contamination.¹⁰⁴ Also the inhibition was only marginal 44.5% compared to the 90% with a standard antigen (PPD). Brantley^{113,114} found no evidence of host sensitization to silicone either by the lymphocyte transformation assay or by changes in lymphocyte subpopulations in rats. Also there is no measurable lymphocyte recognition or memory expressed with respect to silicone. The silicone from the gel leakage or from molecular shearing from the shells is phagocytosed by macrophages. They are however unable to digest it but transport it to the lymph nodes where it probably stays forever.¹⁰⁹ The body's response to silicone is a non-specific one and does not involve antigenic recognition by lymphocytes.^{113,114} Some authors have considered silicone to be a non-specific stimulating agent of the immune system i.e. an immunological or antigenic adjuvant⁹⁵ but there is no proof for this.¹⁰⁴ Silica and not silicone can serve as an adjuvant and there is no evidence to indicate that the silicone in the body is converted (oxidised) to silica. To elucidate this problem specific studies of the genetic and immunological implications of silicone exposure both in animals and humans are needed. There is no known case occurring in the UK in which silicone has interfered with the body's immune defence mechanism.¹¹⁵

SILICONE IMPLANTS AND THE DEVELOPMENT OF BREAST CANCER

There is understandable concern about the uncertainty of placing a foreign material next to an organ which has the propensity for developing cancer of the female breast. No evidence however exists that breast prostheses cause breast cancer or that breast cancer occurs at a greater frequency among augmented women than in women without implants.¹¹⁶⁻¹²⁰ Deapen and colleagues in an 11 year retrospective analysis of more than 3100 women who had received silicone gel prostheses found no excess of breast cancer or of local soft tissue sarcomas after a median follow-up of 6.2 years.¹¹⁶

Although there have been sporadic case reports of malignancy after breast augmentation with different materials,^{118,120,121} no causal relationship has ever

been established. These carcinomas are likely to be coincidental because of the high risk of developing carcinoma of the breast in the normal population (1 in 9 women in the USA, 1 in 13 women in the UK) and as the population of women who have undergone augmentation mammoplasty becomes older.¹²² Morgenstern et al reviewed 12 women with carcinoma of the breast and co-existent silicone mastopathy and found that 'there was no evidence that silicone is implicated in the aetiology of breast cancer'.¹¹⁸ It is important to note that 9 of these had injections of liquid silicone for cosmetic breast augmentation, and 3 had leaking silicone gel prostheses.

The concern about carcinogenicity has largely arisen from misinterpretation of studies in rodents which linked implanted silicone gel to the development of cancer. These results have been questionably extrapolated to the risk of developing breast cancer in humans.¹²³ The background to this is worthy of detailed comment. On 2 November 1988, Dow Corning Corporation, the originator of silicone medical devices, presented their long-term animal study data to the US Food and Drug Administration (FDA). These data showed that 25% of rodents developed sarcomas (predominantly fibrosarcomas) at the site of silicone gel implantation 7 months–2.5 years after implantation.^{20,124} This effect is nonspecific since it is a phenomenon seen in both mice and rats and occurs even after injection of inert substances such as cellophane, nylon, glass, metal and indeed silicone provided the size of the implant is sufficiently large but is clearly independent of chemical composition. First coined in 1984, it is now known as 'solid state tumorigenesis' or the 'Oppenheimer effect'¹²⁵ first described in 1941. Brand (1988) demonstrated that rodents have a species specific inherent genetic instability which results in the formation of sarcomas. As no comparable instability exists in humans, sarcomas related to these materials should be extremely rare. Of importance, there is no single documented case of sarcoma developing in response to breast implants in humans since the introduction of silicone as a medical implant in 1962.

It is generally accepted that minute quantities of silicone gel do 'bleed' from a breast implant over a period of time but the use of silicone lubricated syringes by insulin dependent diabetics results in a similar amount of silicone being deposited into their subcutaneous tissues. Consequently over a lifetime the diabetic may be exposed to as much silicone as a woman with breast implants and there is no higher incidence of sarcomas in diabetics or in patients with pacemakers or artificial joints made with silicone.

In contrast to the suggestion of an increased risk of developing carcinoma there are two reports which draw attention to the reduced risk of developing breast carcinoma post augmentation mammoplasty. McGrath and Burkhardt (1984) refer to 'many isolated reports in the literature that there may be significantly fewer

patients developing breast cancer after augmentation mammoplasty'.¹²⁷ Deapen and co-workers (1986) found a statistically significant decreased risk of developing breast cancer in women under the age of 40 compared to the general population. This apparent lower breast cancer rate in women having augmentation mammoplasty 'suggests that many such women may have a reduced amount of breast tissue'.¹¹⁶ The logic behind this is not clear but there is certainly no increase in the incidence of breast cancer associated with the use of silicone gel implants. In Alberta (Canada) a 16 year follow-up of 11 991 patients who received breast implants in the period 1970–1986 found fewer than expected cases of breast cancer in this group compared to the control population (unpublished).

IMPLANTS AND INTERFERENCE WITH EARLY TUMOUR DETECTION

In addition to the potential direct effect of inducing carcinoma, concern has been voiced that the technique may prevent tumours from being detected early in patients with breast implants. This is because of uncertainty about the amount of breast tissue that may be obscured by the implant. Morgenstein (1985) thought that the interpretation of physical findings might be rendered difficult by silicone induced mastopathy thereby obscuring early diagnosis.¹¹⁸ This is an unlikely occurrence because silicone is now not injected for breast augmentation and additionally many implants lie behind the breast and lumps in the breast should still be easily felt by examination, either by the patient or by the doctor.¹¹⁵ Sometimes physical examination of the augmented breast is easier than before augmentation.¹²⁸

Mammography is the best method available for breast screening.¹²⁹ It is theoretically possible that the value of film mammography for the diagnosis of breast cancer may be compromised in the patient with breast implants.^{118,127} The possible mechanisms by which prostheses may interfere with screening mammography are:

1. Obscuration of the breast tissue.
2. Compression of the tissue making it more dense thus tending to obscure tiny lesions.
3. Rendering mammography more difficult because the breast is less compressible.⁸²

It has been suggested that mammography may not be as reliable because the implant may obscure a variable portion of the gland tissue.¹²² Gel implants have been reported to obscure a portion of the breast, whereas saline-inflatable devices can result in good 3-dimensional visualisation.¹³⁰ Not all agree with this conclusion and it has been stated that 'an area of consolidation or calcification which is suggestive of

malignancy can be seen by the many views of xero-radiography (or mammography) in the presence of a gel-filled or saline filled prosthesis'.¹³¹ The valve of an inflatable implant could obscure the presence of malignancy in its vicinity.¹³¹ Although Synder¹³² noted that they could not see through either a saline filled or a gel filled prosthesis, they could visualise the breast tissue surrounding the prosthesis making mammography worthwhile. In Wolfe's opinion (1978) the compression of breast tissue by any implant (saline or gel filled) makes it difficult to identify some of the early changes caused by carcinoma (such as distortion of the architectural pattern)¹³³ although others dispute this.¹²² Wolfe made the first quantitative estimate of the amount of breast tissue that might be obscured by the implant putting this at 75%.¹³³ Silverstein and colleagues found, in a review of 35 patients with prior augmentation mammoplasty whom they treated for breast cancer, that 'compared with nonaugmented women whose cancers were found with screening mammography, augmented patients with breast cancer present with a higher percentage of invasive lesions and involved axillary lymph nodes resulting in a poorer prognosis'.¹³⁴ Other authors have noted that portions of the breast parenchyma may be obscured in each projection by silicone prostheses¹³⁵ although in Jansen and Mackey's review of 30 patients this was much less with saline filled implants.¹³⁶ A number of factors should be considered:

1. To date there is no reported case of delayed diagnosis solely due to the presence of implants.
2. In some instances a deep-seated carcinoma may be more easily visualised by mammography after augmentation because the implant pushes it forward.¹²⁷
3. The accuracy of X-ray interpretation depends on the skills of the radiographer and radiologist.
4. There are special X-ray techniques for imaging augmented breasts. Hayes and co-workers¹²² concluded, from their calculations of the percentage of breast tissue in patients who had previously undergone breast implant surgery that two film mammography was not a reliable screening procedure for women who had undergone augmentation mammoplasty and called for a more reliable breast screening method for this group of women. Possible improvements include:
 - a. the use of a 90 degree lateral view rather than the oblique view in order to increase the amount of tissue visualised¹²⁸
 - b. the use of manual exposures.
5. The subpectoral position used in most implants reduces the obliteration of breast tissue detail that may be noted on mammography.
6. Mammography may be facilitated in patients with severe hypoplasia, when, because of the post-operative protrusion of the mammary gland, the

glandular tissue proper is more clearly visible anterior to the prosthesis.

Breast ultrasound

Ultrasonography has been suggested for routine use after mammography for the 'visualisation of all tissue surrounding the prosthesis'.¹³⁸ It should not, however, be used alone as it is not as sensitive as mammography, and requires special ultrasound equipment. Ultrasonography, does appear to be of value in augmented patients with palpable abnormalities which may be difficult to visualise on mammography.^{128,139}

It has been suggested that women should be informed pre-operatively that the prostheses will render screening mammography less reliable, and women at high risk of developing breast cancer should be discouraged from augmentation mammoplasty or at least be made aware of the fact explicitly and emphatically.¹²⁸

SILICONE GEL LEAKAGE ('GEL BLEED') AND CANCER ELSEWHERE

The diffusion of silicone through the envelope of gel-filled breast prostheses into the surrounding tissue has been recognised for several years.^{16,42} This is not associated with development of cancer elsewhere in sites other than the breast and there is no evidence that this poses a health risk. Silicone is known to cause lymphadenopathy and has been detected in lymph nodes draining the breast. This occurs as a foreign body reaction.^{13,140} It is usually asymptomatic being in most cases an incidental finding, occasionally tender, but of no clinical significance.¹⁴¹ In contrast rupture of a gel-filled prosthesis results in large quantities of silicone being released and can cause a granuloma in the vicinity of the breast and at distant sites such as the abdominal wall and the arm,^{71,73} although it should be appreciated that patients with ruptured breast implants have minimal morbidity.⁷⁹

POLYURETHANE FOAM-COVERED IMPLANTS

These implants have been used for over 20 years for breast reconstruction, primary augmentation, and revision after failure of uncoated silicone implants. There is no doubt that they have markedly reduced capsular contracture^{55,63,64,123,142,143} which is the commonest complication of uncoated implants. It is thought that this works by disorganizing the collagen in the capsule, which, although it may still contract, is not mechanically efficient to produce dramatic shrinkage. A number of concerns have been raised in the past regarding polyurethane (PU) covered

implants.¹⁴⁴ Firstly there is speculation that the porous nature of a microtextured implant could favour infection and septic inflammation. Secondly it does not guarantee that capsule contracture will not occur. Thirdly because there is fibrous tissue ingrowth into the foam it becomes firmly adherent to the tissues, rendering complete removal of a PU-covered breast prosthesis difficult, should its removal become necessary.¹⁴⁵ However, it is the question of carcinogenicity which is of paramount concern.

Polyurethane in the body of animals is gradually broken down to TDA (2,4 diaminotoluene) which is known to cause liver cancer in laboratory animals. It should be stressed that it needs a very high amount of TDA to cause cancer in animals. The FDA's position (April 1991)¹⁴⁶ is that even if TDA was formed in humans, the risk of its causing cancer would be very low. The FDA's estimate of the risk in the 'worst case' scenario is only 1 : 10 000 while that of the risk from the amounts of polyurethane which are normally broken down is 1 : 1 000 000. The risk therefore is extremely small - too small, in the assessment of the FDA, to warrant alarm on the part of patients and certainly too small to justify surgically removing them. The FDA's panel of experts concluded that there was no scientific evidence to justify removing silicone-gel implants from the market at that time.¹⁴⁶ The manufacturers of polyurethane foam-covered implants, Surgitek, have since ceased making them.

OTHER BREAST IMPLANTS

Saline-filled prostheses

Though these devices have been hailed in the past as causing less capsular contracture,^{5,62} and minimal interference with the radiological diagnosis of breast carcinoma,⁶² they are associated with a number of problems. Notable among these is the high rate (more than 15%) of saline leakage or spontaneous deflation^{5,62,147} which has thrown them into disfavour. Another problem is bacterial growth which may be caused by valve inadequacies. The incidence of capsular contracture in some cases is less than for silicone^{5,62,148} although this has not been the finding of other workers who contend that the incidence is similar but merely delayed.^{62,149} The aesthetics of breast reconstruction using saline filled implants are not ideal as underfilling of these implants can give rise to folds in the prostheses which may be visible and also be palpable by the patient and the physician.

Double lumen prostheses

These are difficult to fabricate and have a lot of potential problems.¹⁵⁰

CONCLUSIONS

1. Women who have had or are considering having breast implants face no significant risk of developing cancer as a result because no clinical evidence of carcinogenesis has been noted in more than 25 years of use of silicone implants. Breast implants have never been shown to cause any form of cancer in humans.
2. The large body of available evidence indicates that breast implants are 'as safe as any implantable medical device and are beneficial for the vast majority of properly selected patients'.¹⁵¹
3. Despite the concern about cancer distant from the breast, effects on the immune system, and effects on the foetus, these are at present only hypothetical considerations. The incidence of connective tissue disease in women with breast implants appears to be within the background incidence of connective tissue disease and human adjuvant disease may well be a myth.^{22,109} However, the case reports of connective tissue disorders after breast implants underscore the need for large controlled epidemiological studies of the incidence of these disorders among patients receiving silicone breast implants.
4. Patients need to be told about all possible risks no matter how small so that they can make an informed choice. For instance, they should know they run a 10% risk of developing capsular contracture, causing painful firm breasts over a period of 10 years.
5. The recent alarm and anxiety about the safety of breast implants is out of proportion with any scientific evidence that has been presented to date.
6. Used appropriately the risks associated with breast implant use are minimal. They have a continuing and important role to play in improving patient's quality of life and self-esteem.

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